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Potentials and controversies in open access publishing: a spotlight on medicine

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OPEN ACCESS

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Abstract:

The paper gives an overview of open access publishing (OAP) within the medical field. Tracing the evolution from traditional print to digital dissemination, the article highlights OAP's transformative impact on scholarly communication. Emphasizing the benefits of unrestricted access to scientific literature, the paper looks into diverse OAP models and examines supporting policies from political and academic bodies. The challenges such as article processing charges (APCs), potential erosion of peer-review credibility, and the proliferation of predatory journals are also addressed. The paper suggests that questions on future sustainability and dominance of OA scholarly publishing models still remain open.

Keywords: scholarly communication, open access publishing, article processing charges (APCs), peer-review credibility, predatory journals

Sažetak:

Otvoreni pristup u medicini: mogućnosti i prijepori

Rad daje pregled objavljivanja znanstvenih radova u otvorenom pristupu (OAP) u području medicine, prateći prijelaz s tradicionalnog tiskanog na digitalno objavljivanje. Članak naglašava transformativni utjecaj OAP-a na znanstvenu komunikaciju, izdvaja prednosti neometanog i slobodnog pristupa znanstvenoj literaturi te razmatra različite modele OAP-a i politiku potpore koju otvorenom pristupu pružaju politička tijela i akademske ustanove. U članku se opisuju i izazovi OAP-a, kao što su naknade za obradu članaka (APC), potencijalna erozija kredibiliteta recenzijskog postupka i proliferacija predatorskih časopisa. Zaključci sugeriraju da pitanja o budućoj održivosti i prevlasti modela znanstvenog objavljivanja u otvorenom pristupu još uvijek ostaju otvorena.

Ključne riječi: znanstvena komunikacija, objavljivanje u otvorenom pristupu, naknade za objavu članaka, kredibilitet recenzijskog postupka, predatorski časopisi

Introduction

The shift from conventional print communications to digital online dissemination was one of pivotal moments in the evolution of academic publishing. It brought profound changes, enabling restructuring of traditional models of scientific communication, and preparing the scientific community for the new paradigm. The emergence of open access publishing (OAP) played a key role in this evolution, introducing new publishing methods, revised access approaches, and increased public availability of scientific information. OAP represents a remarkable development in scholarly communication, contributing to a more accessible and collaborative scientific landscape.

A conference in Budapest (1) resulting in Budapest Open Access Initiative (BOAI), as well as the Bethesda Statement on Open Access (2) and Berlin Declaration on Open Access (3) that followed shortly after, marked the advent of new era in scholarly publishing aimed to achieve two major goals: the elimination of paywalls for articles published in peer-reviewed journals, thus making research results widely accessible without cost to readers, and a significant reduction in overall publishing and access costs for researchers, their institutions, and funding agencies, particularly the increasingly costs of major journal subscriptions for institutional libraries (4).

Over the course of two decades following the public announcement of those goals, the OA movement has gained strength, leading to a rise in the number of OA journals and development of various OAP outlets. However, this growth is accompanied with controversies that challenge its core principles.

The objective of this paper is to outline the evolution of open access publishing (OAP), with a particular focus on the field of medicine, and to highlight certain controversial issues addressed in recent medical literature.

Open access publishing (OAP)

According to Aronson (5) the phrase "open access" to scientific data, including gene sequence data, was first mentioned in the 1990s. The earliest reference to free online access to published articles in journals occurred in 2001, in the Budapest Open Access Initiative (BOAI). BOAI defines open access to peer-reviewed journal literature as "its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited" (1). BOAI recommends two complementary strategies, authors self-archiving their papers in open archives and a new generation of open-access journals.

The Bethesda Statement on Open Access Publishing was issued in April 2003 as a result of a meeting held at Howard Hughes Medical Institute. It defines open access publication as one which grants a "free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, transmit, and display the work publicly and to make and distribute derivative works, in any digital medium for any responsible purpose, subject to proper attribution of authorship" and from which every article is "deposited immediately upon initial publication in at least one online repository" (2).

Unrestricted access to scientific literature is the key benefit enabled by OAP, particularly for researchers in low-income countries. Beyond this, OAP accelerates the publication process, ensuring rapid dissemination of research. It amplifies the visibility and impact of publications, fostering a more interconnected global scientific community. Importantly, OAP contributes to building trust in science by promoting transparency and openness, and enhancing collaboration on an international scale (6).

OAP models

Contemporary scientific journals' publishing models include traditional subscription model, where access is paywalled (in order to read the paper scientist or their institutions have to pay a subscription), open access model, where all journals' content is free to readers, but the publisher may charge authors for article processing costs, and the hybrid model (subscription model with an open-access choice available).

Open access to scientific publications can be achieved through:

- Publishing in OA journals ("gold OA") or choosing the OA option in hybrid journals, providing immediate and unrestricted access to all content. These journals are registered in Directory of Open Access Journals (DOAJ), and the publishers usually charge article-processing fees (APCs) from the author. A worthy exception are so called Diamond/Platinum journals, which offer free and unrestricted access without charging either readers or authors.
- Self-archiving ("green OA") in which authors share a publisher-allowed version of their paper (submitted, accepted or published) by posting it in an institutional or subject repository, personal web pages and/or social media profile. Publishers usually apply embargo period (in STEM disciplines six to twelve months).
- Preprinting in which authors make their work public prior to official journal publication by sharing research results in the form of a preprint. A preprint is a version of a scientific manuscript posted on a public server prior to formal peer review, providing rapid feedback and dissemination of the results. With the surge of post-pandemic preprinting, journals are beginning to allow and even encourage its use (7).

Support to OA policy

During the last decade, increasing number of research institutions, international organizations, political entities, and funding bodies adopted the OA principles, proclaiming mandatory OA to scientific outputs resulting from publicly funded research. The recent document of the Council of the European Union (May, 2023) „RECALLS that scholarly publishing, through journals, is currently the primary academic means of disseminating research results and new scientific knowledge“, „HIGHLIGHTS that immediate and unrestricted open access should be the norm in publishing research involving public funds“ and „REITERATES the importance of accelerating the transition to open science to improve research quality, efficiency and impact by promoting transparency, accessibility, diversity, reusability, reproducibility and trustworthiness of research results, that open access to scholarly publications, including their reuse, is one of the core elements of an open science system (8).
In 2022, the US Office of Science and Technology Policy (OSTP) updated its previously existing OA policy (9) recommending that all federal agencies should adjust their public access policies as soon as possible, and no later than the end of 2025. The goal is „to make publications and their supporting data resulting from federally funded research publicly accessible without an embargo on their free and public release" (10).
In the communique issued in May 2023, G7 Science and Technology Ministers recognized that „openness, freedom, and inclusiveness should be enhanced globally for the sound development of scientific research" and that they will „collaborate in expanding open science with equitable dissemination of scientific knowledge and publicly funded research outputs including research data and scholarly publications in line with the Findable, Accessible, Interoperable, and Reusable (FAIR) principles“ (11).

OA in Croatia

Croatia still does not have an official OA policy, but the e-infrastructure that makes it possible is financed by state funds. This primarily refers to the Hrčak platform (12), which provides free access to articles published in Croatian professional and scientific journals, and Dabar, a nation-wide system of institutional digital repositories (13). Both infrastructures are open to journals, institutions and authors free of charge.

OAP in medicine

Initiatives aimed at enabling wider and faster access to medical information gained momentum in the early 1980s. At that time the US National Library of Medicine (NLM) had already been experimenting with the application of emerging technology to facilitate access to medical information. However, two key developments at the end of the century have permanently changed access to medical information. In 1996, NLM launched the Internet based PubMed, a free search engine accessing primarily the MEDLINE database of references and abstracts from biomedical journals (14). Then came PubMed Central (PMC), freely available online since 2000. Both resources are developed and maintained by the National Center for Biotechnology Information (NCBI) at NLM. Harold Varmus, Nobel Prize winner and then director of the US National Institutes of Health (NIH), said that he „was convinced that a radical restructuring of methods for publishing, transmitting, storing, and using biomedical research reports might be possible and beneficial" (15).
From comprising only two journals, *PNAS: Proceedings of the National Academy of Sciences* and *Molecular Biology of the Cell*, PMC has grown to an archive of articles from thousands of journals. Recently, PMC started to include authors' manuscripts deposited because of the research funding bodies' OA mandates, and preprints collected through the NIH Preprint Pilot (16).
In early 2000s, two big publishers of open access medical journals, Public Library of Science (PLOS) and Biomed Central (BMC), entered the publication arena, and the boom of OA publication models started around the year 2003. Today, in the field of (bio)medicine more than 60% of published papers are freely available. Figure 1 illustrates the annual growth of number of papers indexed in PubMed, emphasizing the escalating share of OA papers over time. Out of 1.774.478 papers published in 2022 and accessible at the PubMed platform, 1.063.183 are readily accessible as free full texts. In the same year, the percentage of OA among PubMed-indexed papers from Croatia exceeded 70%.

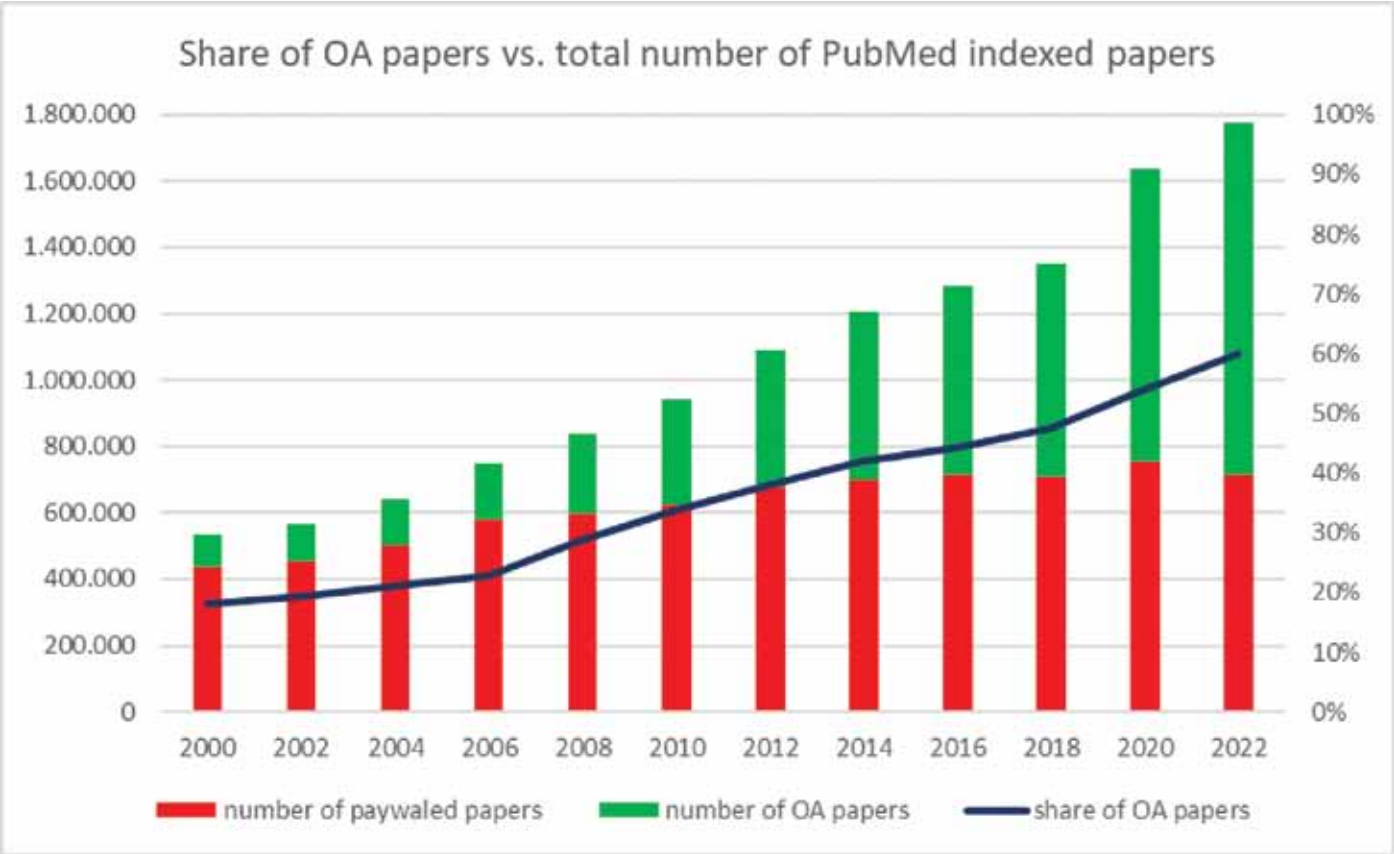

Figure 1. Share of OA papers vs. total number of PubMed indexed papers

There are numerous reasons explaining the upsurge of open access in the field of biomedicine. The OA principles in fact coincide with the main principles of access to health information. For example, the Healthcare Information For All (HIFA), a global campaign working closely with World Health Organization to improve the availability and use of reliable healthcare information worldwide, proclaimed a vision of „a world where every person and every health worker has access to the reliable healthcare information they need to protect their own health and the health of others, and is protected from misinformation" (17). Moreover, in 2019 the World Medical Association (WMA) adopted the *Statement on healthcare information for all* proclaiming that „Access to relevant, reliable, unbiased, up-to-date and evidence-based healthcare information is crucial for the public, patients and health personnel for every aspect of health, including (but not limited to) health education, informed choice, professional development, safety and efficacy of health services, and public health policy" (18).

The coronavirus disease (COVID-19) pandemic vividly demonstrated the power of open science, as publishers and journals decided to make COVID-19-related research freely accessible to all. Immediate free access to research publications and data clearly provided benefits to scientific discourse and public health policies. That is why the G7 Science and Technology Ministers' Comunique explicitly acknowledged that open science platforms should enable early development and more rapid, effective, and equitable access to medical countermeasures for the prevention and control of emerging and re-emerging infectious diseases. (11). OA benefits are not limited to the scientific and medical community alone; it "creates an opportunity for improving patient education, advocacy, and shared decision-making", discouraging patients from seeking information from less reliable sources (19).

Sharing research/scientific data, defined as data meeting quality standards for validating and replicating research findings, plays a crucial role in efficient resource utilization. By fostering scientific collaboration, and aiding decision-making in healthcare, this practice enhances transparency, allowing external researchers to reanalyze, synthesize, replicate and build upon existing evidence (20).

Clinical trial data sharing is particularly emphasized by the International Committee of Medical Journal Editors. Its new Recommendations require that manuscripts reporting the results of clinical trials must contain a data sharing statement, addressing various aspects such as the nature, timing, and criteria for sharing (21). Despite challenges, experiences during the COVID-19 pandemic have shown encouraging progress in medical data sharing (22).

Challenges facing open access publishing

Despite evident advantages of OA for biomedical research and clinical practice, recently published medical papers have highlighted several dilemmas. These challenges primarily include concerns related to article processing charges (APC), the potential erosion of the peer-review process's credibility, proliferation of publications and scientific journals, and the rise of predatory journals.

Article processing charges (APCs)

Article processing charges (APCs) are fees paid by authors of scholarly articles. They are used by open access journal publishers as a substitute for subscription fees that libraries and readers traditionally paid to gain access to articles. In this widespread business model, APCs shift the burden of journal production costs (editing, peer review, hosting, archiving, preservation), from readers to authors.

From todays' perspective, it seems that the second goal of OA movement – reduced total costs of publication to the research community – had not been achieved. Moreover, in an essay published in NEJM, Haug shows that the total costs of publishing are actually increasing (23). According to Fernández Pinto, the implementation of open science principles has in fact contributed to the commercialization of research (24).

Journal APCs vary, typically depending on factors such as the publisher's size, the proportion of papers sent for peer review and metrics such as impact factor, etc. (25). According to Morrison et al. the global average of APC per article increased over the past few years from $904 to $1.626. (26), while Crawford reported the average cost per article in DOAJ journals in 2021 was US $1.997 (27). However, APCs differ depending on the field of research. Vervoort et al. concluded that medical journals charge the highest APCs among academic disciplines, and that the fees are prohibitive for unfunded and lesser-funded researchers (28). For instance, Lancet provides an OA option for $6,830 and BMJ for $6,950.

Koong et al. studied publication costs in oncology journals and found that hybrid journals tended to have significantly higher OA publication fees compared to their full OA counterparts (19). Since hybrid journals allow both subscription-based publishing (not OA, no APCs to publish) and an OA option (freely accessible for readers, but APCs to publish), only authors with special interest in having their articles published in OA, and those willing and able to pay the APC choose the OA option. To date, majority of medical journals remain hybrid. For example, in cardiology and cardiac surgery, 60.9% of journals are hybrid (28).

Protests by editors of scientific journals against excessively high APCs imposed by publishers have strongly resonated within the scientific community. More than 40 editors recently resigned from two leading neuroscience journals arguing that the publishing fees are unethical (25). The editors of one of Wiley's journal have done the same (29).

Still, APCs remain a crucial problem for many young authors, institutions and even certain countries (4), creating financial barriers for researchers and potentially influencing the direction of published research.

Compromised credibility of the peer-review process

The peer-review process in medicine is of utmost importance. Scientific rigor and the meticulous evaluation of scientific results before their publication are critical components for integrating new knowledge to our understanding and treatment of diseases (30). Besides, publishing biomedical papers without rigorous peer review can have severe negative consequences on patients and clinical outcomes (31).

For established journals and their editors, the peer-review process serves as the primary tool for determining the acceptance or rejection of articles. A high-quality review not only aids editors but is also crucial for authors, helping them address weaknesses in their manuscripts (31). However, the advent of new publishing outlets such as preprints, mega-journals, cascade journals, and profit-oriented journals has raised concerns about the credibility of the assessment process. In response, experts like Frank J et al. argue for reinforcing peer review rather than bypassing it entirely. The authors assert that while increased reliance on self-archiving and preprint publication can be beneficial, robust peer review remains indispensable, particularly in health research (4). The need for swift dissemination of knowledge should not compromise the integrity of the peer-review process.

Moreover, the surge in the number of published primary studies has made the systematic review process more inefficient. Thousands of papers now undergo a relevance test, leading to the identification of only a small fraction of reasonable quality (4). Given that systematic reviews play a critical role in shaping new research priorities, especially in clinical medicine, the inadequacies in the peer-reviewing of primary studies may have far-reaching implications on health outcomes. Therefore, upholding the integrity of the peer-review process remains pivotal for the advancement of medical knowledge and the improvement of healthcare practices.

Predatory journals

The proliferation of publications and journals, facilitated by the ease of online dissemination, is causing an overwhelming information overload (see Fig 1). This phenomenon dilutes the quality and significance of scientific contributions, paving the way for the emergence of so-called predatory journals.

In 2019, a group of scholars (many of them from the field of clinical medicine) reached a consensus defining predatory journals and publishers as "entities that prioritize self-interest at the expense of scholarship" characterized by "false or misleading information, deviation from best editorial and publication practices, a lack of transparency, and/or the use of aggressive and indiscriminate solicitation practices" (32). Rupp et al. noted that „predatory journals promise everything a scientist would like to see: secure publication within a short period of time managed by a short peer review process and an almost 100% acceptance rate" (31). Moreover, they offer lower article processing fees then the renowned publishers. According to Frank J, et al. „the pressure to publish among the researchers is a quintessential driving force for sustained growth of such journals" (4). In order to advance or receive financial support, researchers and faculty members, especially in scientifically peripheral countries, are frequently required to publish a certain number of papers in internationally visible journals. Some of them turn to predatory journals for publishing papers previously rejected by the other journals. In addition, young and unexperienced authors are more receptive to predatory journals' tactics.

In their study of predatory journals in plastic surgery literature, Assad et al. found that almost half of potentially predatory journals mention rapid publication and shorter review time (three journals reported 3- to 4-week turnaround times). On the other hand, median time from submission to publication in subscription-based plastic surgery journals is 10 months (34).

Boulos et al. showed that predatory journal articles may have started to infiltrate knowledge synthesis in Cochrane reviews. Even though only 0.8% of the evaluated studies were published in potentially predatory journals, the authors pose the question „if even one citation in a systematic review to a predatory journal may be too many" (35).

The future of open access publishing

It is difficult to determine the direction in which the OAP will develop. In May 2023, the Council of the European Union highlighted the importance of not-for-profit OA publishing models, extending support to development of such ventures led by public research organizations. Will this path prevail in the EU countries? The Croatian model where almost all scientific journals are not-for-profit, available in OA, predominantly not charging for article processing, and receiving government subsidies fits into that framework (36).

Despite noble intentions, mandatory publishing in OA proposed by many research funding bodies, and the initiatives like Plan S (37) have contributed to progression of APC-financing publishing models. Today "we face a growing risk that the ability to pay APCs—rather than the merits of the research—will determine what and who gets published." (38).

Will the governments, funders and institutions stop supporting APCs and invest funds currently allocated to APCs in shared infrastructure, tools and services that can support multiple journals simultaneously? (39)

Will diamond open access, following models such as Hrčak and SciELO (40) and promoted by the EU-funded project DIAMAS (41) gain broader acceptance? Could one of the viable solutions involve non-profit scholarly OA publishing platforms and OA repositories?

Major for-profit publishers are unlikely to concede, and the strength and persistence of the scientific community's push for an open, equitable, and sustainable scholarly publishing system will play a crucial role. Could we conclude that open access publishing is becoming the norm in publishing, irrespective whether for-profit journal publishers like it or not?!

References

1. Budapest Open Access Initatiative; c2023 [accessed 11.11.2023.]. Available at: https://www.budapestopenaccessinitiative.org/read/
2. Suber P, et al. Bethesda Statement on Open Access Publishing; c2003 [accessed 11.11.2023]. Available at: https://dash.harvard.edu/bitstream/handle/1/4725199/Suber_bethesda.htm?sequence=3&isAllowed=y
3. Max Planck Gesellscaft. Berlin Declaration on Open Access to Knowledge in the Sciences and Humanities; c2023. [accessed 11.11.2023]. Available at: https//openaccess.mpg.de/Berlin-Declaration
4. Frank J, Foster R, Pagliari C. Open access publishing - noble intention, flawed reality. Soc Sci Med. 2023 Jan;317:115592. doi: 10.1016/j.socscimed.2022.115592.
5. Aronson JK. When I use a word . . . . Bioscience journals-an open and shut case? BMJ. 2022 Mar 1;376:o536. doi: 10.1136/bmj.o536
6. Rosman T, Bosnjak M, Silber H, Koßmann J, Heycke T. Open science and public trust in science: Results from two studies. Public Underst Sci. 2022 Nov;31(8):1046-1062. doi: 10.1177/09636625221100686
7. Richardson SL, Hedrick SG. Journal impact factors and the future of open access publishing. J Appl Clin Med Phys. 2023 Jul;24(7):e14083. doi: 10.1002/acm2.14083.
8. Council of the European Union. Draft Council conclusions on high-quality, transparent, open, trustworthy and equitable scholarly publishing. Bruxelles, 4 May 2023. [Accessed 10.11.2023]. Available at: https:// data.consilium.europa.eu/doc/document/ST-8827-2023-INIT/en/pdf
9. Office of Science and Technology Policy. Increasing access to the results of federally funded scientific research. February 22, 2013. [Accessed 10.11.2023]. Available at: https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/ostp_public_access_memo_2013.pdf
10. Office of Science and Technology Policy. Ensuring free, immediate, and equitable access to federally funded research. August 25, 2022. [Accessed 10.11.2023]. Available at: https://www.whitehouse.gov/wp-content/uploads/2022/08/08-2022-OSTP-Public-access-Memo.pdf.
11. G7 Science and Technology Ministers' Communique. Sendai. May 12-14, 2023. [Accessed 15.11.2023]. Available at: https://www8.cao.go.jp/cstp/kokusaiteki/g7_2023/230513_g7_communique.pdf
12. O Hrčku; c2021 [Accessed 15.11.2023]. Available at: https://hrcak.srce.hr/o-hrcku
13. Što je Dabar? [Accessed 13.11.2023]. Available at: https://dabar.srce.hr/dabar
14. PubMed® celebrates its 10th anniversary! NLM Techn Bull. 2006;352
15. PubMed Central. In: Wikipedia, last edited on 12 November 2023 [Accessed 14.11.2023]. Available at: https://en.wikipedia.org/wiki/PubMed_Central
16. National Library of Medicine. NIH Preprint Pilot - PMC. [Accessed 14.11.2023]. Available at: https:// www.ncbi.nlm.nih.gov/pmc/about/nihpreprints/
17. Healthcare Information for All. The HIFA Vision, Mission, Strategy. [Accessed 10.11.2023]. Available at: https:// www.hifa.org/about-hifa/hifa-vision-mission-strategy.
18. World Medical Association. WMA statement on healthcare information for all. 2019, October [Accessed 10.11.2023]. Available at: https:// www.wma.net/policies-post/wma-statement-on-healthcare-information-for-all/.
19. Koong A, Gardner UG, Burton J, Stewart C, Thompson P, Fuller CD, et al. Factors associated with open access publishing costs in oncology journals: cross-sectional observational study. JMIR Form Res. 2023 Mar 16;7:e44633. doi: 10.2196/44633.
20. Naudet F, Siebert M, Pellen C, Gaba J, Axfors C, Cristea I, et al. Medical journal requirements for clinical trial data sharing: Ripe for improvement. PLoS Med. 2021 Oct 25;18(10):e1003844. doi: 10.1371/journal.pmed.1003844
21. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Updated May 2023. Pg. 14. [accessed 20.11.2023]. Available at: http://www.icmje.org/icmje-recommendations.pdf
22. Dron L, Kalatharan V, Gupta A, Haggstrom J, Zariffa N, Morris AD, et al. Data capture and sharing in the COVID-19 pandemic: a cause for concern. Lancet Digit Health. 2022 Oct;4(10):e748-e756. doi: 10.1016/S2589-7500(22)00147-9.
23. Haug CJ. No free lunch - what price Plan S for scientific publishing? N Engl J Med. 2019 Mar 21;380(12):1181-1185. doi: 10.1056/NEJMms1900864
24. Fernández Pinto M. Open science for private Interests? How the logic of open science contributes to the commercialization of research. Front Res Metr Anal. 2020 Nov 10;5:588331. doi: 10.3389/frma.2020.588331.
25. Sanderson K. Editors quit top neuroscience journal to protest against open-access charges. Nature. 2023 Apr;616(7958):641. doi: 10.1038/d41586-023-01391-5.
26. Morrison H, Luan B, Zhao X, Kakou TL, Shanbhoug AN, Open access journals and article processing charges 2011–2021. c2021. [accessed 30.11.2023]. Avasilable at: https://ruor.uottawa.ca/handle/10393/42327
27. Crawford W. Gold open access 2016–2021: Articles in journals (GOA7). Cites & Insights Books; 2022. Available at: https://waltcrawford.name/goa7.pdf

28. Vervoort D, Luc JGY, Sá MPBO, Etchill EW. Open Access and Article Processing Charges in Cardiology and Cardiac Surgery Journals: a Cross-Sectional Analysis. Braz J Cardiovasc Surg. 2021 Aug 6;36(4):453-460. doi: 10.21470/1678-9741-2021-0289.
29. Retraction Watch. Wiley journal editors resign en masse, fired chief editor speaks. c2023 [accessed 25.11.2023]. Available at: https://retractionwatch.com/2023/08/07/wiley-journal-editors-resign-en-masse-fired-chief-editor-speaks/
30. Sawalha AH, Solomon DH, Allen KD, Katz P, Yelin E. Immediate open access: the good, the bad, and the impact on academic society publishing. Arthritis Rheumatol. 2023 Jul;75(7):1083-1084. doi: 10.1002/art.42522.
31. Al-Khatib A, Teixeira da Silva JA. Is Biomedical Research Protected from Predatory Reviewers? Sci Eng Ethics. 2019 Feb;25(1):293-321. doi: 10.1007/s11948-017-9964-5.
32. Rupp M, Walter N, Giannoudis PV, Alt V. Academic publishing and predatory journals - a tension between dissemination of scientific knowledge and the academic performance pressure. Injury. 2022 Nov;53(11):3567-3568. doi: 10.1016/j.injury.2022.10.002.
33. Grudniewicz A, Moher D, Cobey KD, Bryson GL, Cukier S, Allen K, et al. Predatory journals: no definition, no defence. Nature. 2019 Dec;576(7786):210-212. doi: 10.1038/d41586-019-03759-y.
34. Asaad M, Elmorsi R, Winocour S, Mericli AF, Reece E, Selber JC, et al. Impact of predatory journals in plastic surgery literature: researchers beware. Plast Reconstr Surg. 2022 Jun 1;149(6):1234e-1243e. doi: 10.1097/PRS.0000000000009054.
35. Boulos L, Rothfus M, Goudreau A, Manley A. A descriptive study found low prevalence of presumed predatory publications in a subset of Cochrane reviews. J Clin Epidemiol. 2022 Dec;152:316-325. doi: 10.1016/j.jclinepi.2022.09.004.M
36. Macan B, Škorić L, Petrak J. David among Goliaths: Open access publishing in scientific (semi-)periphery. Learned Publishing. 2020:33:410-17. doi: 10.1002/leap.1320
37. Plan S. Accelerating the transition to full and immediate Open Access to scientific publications. [Accessed 05.11.2023]. Available at: https:// www.coalition-s.org/wp-content/uploads/Plan_S.pdf
38. Timmer J. The feds' new open-access policy: Who's gonna pay for it? Ars Technica. 2022 [accessed 15.11.2023]. Available at: https://arstechnica.com/science/2022/10/the-feds-new-open-access-policy-whos-gonna-pay-for-it/
39. Alperin JP. Why I think ending article-processing charges will save open access. Nature. 2022 Oct;610(7931):233. doi: 10.1038/d41586-022-03201-w.
40. SciELO. About SciELO. [accessed 20.11.2023]. Available at: https://scielo.org/en/about-scielo
41. Diamas. Objectives. [accessed 15.11.2023] Available at: https://diamasproject.eu/objectives/

Tapping the potential of bone regeneration by delivery of concentrated extracellular vesicles to the fracture site: A new horizon in bone regeneration therapy research?

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Abstract:

Background A small pilot study was conducted in order to investigate in situ regenerative potential of extracellular vesicles (EVs) in a rat subcutaneous implant model.
Material and methods An implant device was implanted in the axillary regions of four animals and consisted of a rat ABC enriched with an EV isolate obtained from human patients 7-21 days post bone fracture, or healthy individuals.
Results Upon histological examination of the implanted devices, there were clear evidence of early signs of immature cartilage and bone formation in the implants of fracture-EV treated animals, 21 days post implantation.
Conclusion These preliminary results suggest a potential for near-term innovation in the development of an affordable, non-invasive and completely autologous therapeutic device that can potentially enhance the existing regenerative capacity of skeletal tissues. EV can be used to concentrate the body's inherent regenerative potential and utilise it as a personalised self-healing therapy.

Keywords: Extracellular vesicles, regeneration, subcutaneous assay, bone, fracture

Sažetak:

Istraživanje novih mogućnosti koštane regeneracije primjenom koncentrata izvanstaničnih vezikula na mjesto prijeloma: Novi pristupi u istraživanju terapije regeneracije kosti?
Uvod U navedenom istraživanju provedena je mala pilot studija kako bi se istražio in situ regenerativni potencijal izvanstaničnih vezikula (EV) u potkožnom štakorskom modelu.
Materijali i metode Nosač je implantiran u aksilarne regije životinja i sastojao se od autolognog krvnog ugruška (ABC) štakora obogaćenog izoliranim EV iz krvi pacijenata 7-21 dana nakon prijeloma kosti ili zdravih dobrovoljaca.

Rezultati Nakon histološkog pregleda implantata, potvrđeni su rani znakovi stvaranja nezrele hrskavice i koštanog tkiva u implantatima životinja koje su primile nosač i koncentrat EV nakon prijeloma, 21 dan nakon implantacije.
Zaključak Ovi preliminarni rezultati sugeriraju inovacijski potencijal u razvoju pristupačnog, neinvazivnog i potpuno autolognog nosača koji potencijalno može poboljšati postojeće terapije u regeneraciji kosti. EV nam omogućavaju da koncentriramo endogene molekule s regenerativnim potencijalom koje se mogu koristiti u personaliziranim terapijskim pristupima.

Ključne riječi: Izvanstanične vezikule, regeneracija, potkožni test, kost, prijelom

Introduction

Bone fractures often lead to loss of quality of life, long-term disability and increased mortality (1–3). They are a major economic burden on national healthcare systems, costing the European Union over €56 billion annually (4). Due to a globally ageing population with an increased incidence of osteoporosis, fracture-related burden is expected to increase significantly over the coming decades. Bone is an active organ that undergoes continuous lifelong remodelling and has a significant regenerative potential. Formation of new skeletal tissue involves three overlapping phases: inflammation, renewal and remodelling (5). Upon trauma, bone fragments tear the neighbouring blood vessels, triggering blood clotting, hematoma formation and inflammation. Within days, the fracture site progresses to a temporary fibrocartilaginous callus that is replaced over several weeks by a bony callus, that joins the broken ends. Finally, the newly formed bone is remodelled over a longer period (months to years) effectively erasing the breakage site (6,7). Standard therapy assisting fracture repair relies on mechanical support by plaster and/or mechanical devices (e.g. nails, plates and screws). Although effective, this passive immobilisation approach dates back to the beginnings of recorded human history (8,9) and in large bone defects and some pathological fractures, the underlying physiological bone repair is insufficient. Therefore there is a pressing medical need for new personalised therapies that enhance bone regeneration, shorten healing times and prevent bone non-unions (10). A common therapy in such cases is bone grafting, a procedure that includes highly invasive autologous bone transplantation and has a limited success rate (7). A more sophisticated approach encourages skeletal regeneration by deploying recombinant human bone morphogenetic proteins (BMP) 2 or 7 to the fracture site via a bovine collagen carrier. However, this method is plagued by low efficiency and severe side effects due to the immunogenic nature of bovine carriers (7). A second generation of similar devices utilises BMP6, a superior bone formation inducer, that is deployed using a non-immunogenic autologous blood coagulum (ABC). Since fracture repair starts with a blood clot, the ABC is an ideal vector, however, the production of clinical grade rhBMP6 is expensive, time consuming and complex (7,11). We propose a third generation of completely autologous, highly inductive endogenous materials that enhance the body's natural capacity for bone regeneration.

Extracellular vesicles (EVs) are lipid bilayer-delimited particles released by most cell types. They provide a readily available sample of the inner workings of the cell that are dependent on current (pato)physiological events or trauma. These vesicles shuttle a variety of proteins, lipids, nucleic acids (including mRNA and microRNA), and are an under-recognized form of intercellular communication (12,13). EVs are commonly divided by size into microvesicles (MVs) (200 nm-1 μm) and exosomes (50-200 nm), but a functionally more relevant classification is their location of origin (12,13). MVs are produced by direct outward budding of the plasma membrane, so their cargo is a fraction of the "mother" cells' cytoplasmic content (14). Conversely, exosomes are generated by the endosomal compartment in multivesicular bodies, and they therefore express typical endosomal markers and surface molecules that can target them to recipient cells (15,16). The fact that EVs can traffic a mixture of functional bioactive molecules and remotely influence recipient cells at the post-transcriptional level, has profoundly changed our understanding of gene regulation (14). Due to specific membrane markers, the vesicles are recognized and internalised by neighbouring or remote cells through receptor-ligand interactions, endocytosis and/or phagocytosis, or they can fuse with the target cell membrane and deliver their contents into the cytosol (17–19). Crucially, EVs isolated from different sources have different contents reflecting their current environmental conditions. Being derived from cells, these vesicles are biocompatible, stable and non-immunogenic and they present an ideal tool for different therapeutic strategies.

Participants and methods

Study outline

This prospective observational study was approved by the Ethics Committee of the Hospital Center "Sisters of Charity", University Hospital Center (SCUHC) Zagreb (EP-003-06/20-03/023) and the Ethics Committee of the School of Medicine, University of Zagreb (EP 331/2021) with informed consent obtained from the patients to use the samples for research purposes. Study outline is presented in Figure 1.

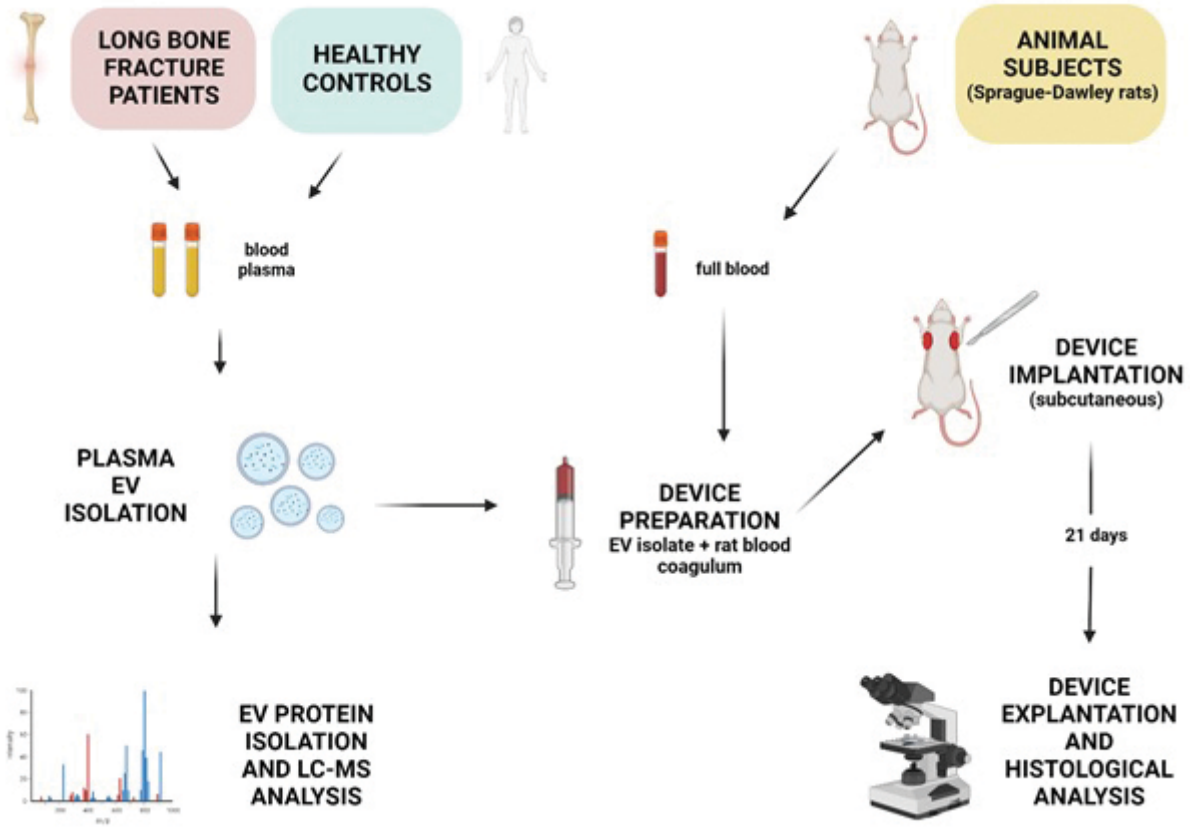

Figure 1. Study outline which consists of human plasma derived EV isolation, subcutaneous animal assay preparation and LC-MS analysis. Created with Biorender.com.

Human subjects

The study included two subject groups: 1) patients with a metaphyseal long bone fracture (N=15); and 2) healthy control group (volunteers; N=15) (Figure 1). Each participant in the study met the inclusion criteria, which included being within the age range from 18 to 70 years, possessing clinical and radiological confirmation of a fracture (for individuals in the fracture group). Exclusion criteria were malignancy, active infection, osteoporosis, or immunocompromised conditions. Blood samples were collected in the first group within the 7 to 21-day window following the occurrence of the fracture. This specific timeframe was chosen to capture the transition phase from inflammation to fibrocartilaginous healing, with the expectation that the patients would exhibit peak blood expression levels of growth and signalling factors during this period

Blood withdrawal

Withdrawal of 10 mL of venous blood from the patient of concern was obtained into the provided plain vacutainer which contains citrate as anticoagulant substance. Blood was then centrifuged at 1500 x g for 15 minutes in order to separate platelet-free plasma. The obtained plasma was separated and stored at -80°C until further analysis. Plasma samples were pooled into two above-mentioned groups; from which EVs were isolated by differential centrifugation (20). These pools were used for implant preparation and for proteomic analysis.

Animal subjects

This study included N=4, nine-month-old male Sprague-Dawley rats body weights between 350 to 400 grams from registered breeding facility School of Medicine, University of Zagreb, Department of Pharmacology, No: HR-POK-007 . As the main carrier, autologous blood (ABC) from each laboratory animal was used. Animals were divided into four groups: 1) positive control (BMP6 in ABC), 2) negative control (ABC only); 3) EV isolate from healthy individuals in ABC; 4) EV isolate from patients with long bone fractures in ABC, Table 2. Recombinant BMP6 (rhBMP6) obtained from R&D Systems was used for preparation of positive control devices.

Implant device preparation

Implant device (ABC) was prepared from 0.5 mL of full blood obtained from rat tail vein, which was mixed with an appropriate amount of EVs (isolated from 10 and 15 ml of human plasma) and left for 60 minutes to coagulate in a 1 mL syringe. After removing the serum, the coagulum (ABC) was ready for implantation.

Rat subcutaneous implant assay

EVs osteogenic activity in ABC was tested at different doses in the rat subcutaneous assay (Table 2). Animals were anaesthetised using injections of ketamine (60 mg/kg i.p.) and xylapan (20mg/kg i.p.). Anaesthesia was maintained with 2-3% of isoflurane. Animals received analgesic (carprofen 5-15 mg/kg s.c.) per day. A vertical incision (1 cm) was made under sterile conditions in the skin over the thoracic region, and the pockets were prepared by blunt dissection on both sides of the incision. A small pocket was created under the skin in the axial regions to implant the prepared device. After implantation the site was sealed with a single suture to the fascia and three sutures for the skin. The implant response of EVs was tested by histology analyses. The day of implantation was designated as day 0 of the experiment. Implants were removed on day 21 for analysis after the euthanasia procedure using 100 mg/kg of ketamine and 60 mg/kg of xylapan i.p. Laboratory animals were cervically dislocated to confirm the success of euthanasia method.

Histology

Histological examination was used to assess the extent of biological/regenerative activity in the implant. Tissue samples were collected and fixed in 10% formalin solution. Samples were cut at 5 µm slices and stained with hematoxylin-eosin and safranin staining methods. Stained slides were analysed, using an optical microscope (Zeiss Axiostar plus, Artisan technology group. magnification range 20x and 40x) by three independent researchers. Among them, one was an expert in animal histopathology.

Table 2. Animal subjects and implanted devices

Animal designation	Device components	Right axillary region	Left axillary region
1 - Positive control	Inductor	1 µg rhBMP6	2µg rhBMP6
	Carrier	0,5 mL of rat-1 blood	0,5 mL of rat-1 blood
2 – Negative control	Inductor	100 µl saline	150 µl saline
	Carrier	0,5 mL of rat-2 blood	0,5 mL of rat-2 blood
3 – EV isolate from healthy individuals	Inductor	100 µl of EV isolate derived from 10 mL of healthy individuals' plasma	150 µl of EV isolate derived from 15 mL of healthy individuals' plasma
	Carrier	0,5 mL of rat-3 blood	0,5 mL of rat-3 blood
4 – EV isolate from post-fracture patients	Inductor	100 µl of EV isolate derived from 10 mL of patients' plasma	150 µl of EV isolate derived from 15 mL of patients' plasma
	Carrier	0,5 mL of rat-4 blood	0,5 mL of rat-4 blood

Characterization of EV proteins

After EV isolation (20), vesicle membranes were lysed by sonication (5 min / 75% amplitude). The released proteins were precipitated by acetone (1 hour / -80°C), centrifuged (10 min / 16000 g) and resuspended in 8 M urea. Protein concentrations of the were determined by Lowry assay (BioRad RC DC Proteins Assay) and a plate reader (*SpectraMax i3x - Molecular Devices LLC.*).

Protein pools (40 µg) were further processed 10-kDa centrifugal filter units. After alkylation with 55 mM iodoacetamide in 8 M urea (20 min / RT / dark) and digestion by 0.8 µg of trypsine (ON / 37 °C; Worthington, TPCK treated), the obtained peptides were purified using stage tips (21). Peptides were then separated on a 15 cm C18 nano-column by HPLC (Ultimate 3000, Thermo Fischer Scientific) and injected to an LTQ Orbitrap Discovery (Thermo Fischer Scientific) mass spectrometer. Raw data was processed using MaxQuant software version 1.5.1.2. (Max Planck Institute of Biochemistry) using the default settings. Functional enrichment of the identified proteins across sample pools was performed by FunRich software 3.1.3 by using quantitative analysis and by using the FunRich protein database.

Enrichment of biological pathways was analysed by comparing the dataset of identified proteins in the bone fracture group against the healthy control group. Biological pathways relevant for bone metabolism were selected by manual curation guided by extensive literature search. Samples were analysed in technical triplicates.

Results

EV protein cargo analysis

Analysis of the protein cargo of isolated EVs yielded 28 identified proteins in the bone fracture group and 30 proteins from the healthy control group. The datasets of identified proteins were analysed for common proteins and outliers (Figure 2). We found that there were 17 commonly identified proteins in both groups, and a substantial number of proteins expressed only in the bone fracture and control groups (outliers), 11 and 13, respectively. The dataset of identified proteins was also analysed by comparing the bone fracture group against the control group for enrichment of relevant biological pathways (Figure 3). We found that the proteins identified in the fracture group were enriched in several pathways such as cell-cell communication, cell-ECM communication, Wingless-related integration site (Wnt) signalling network, Platelet-derived growth factor (PDGF) receptor, Vascular Endothelial Growth Factor (VEGF) and Granulocyte macrophage colony-stimulating factor (GMCSF) signalling network and Insulin growth factor 1 (IGF1) pathway.

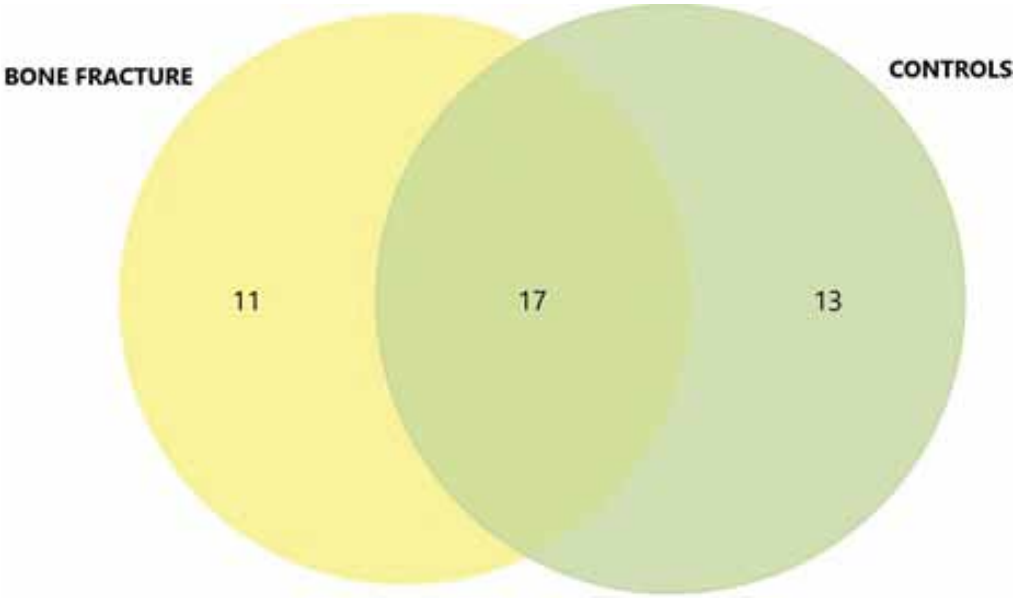

Figure 2. Venn diagram showing identified overlap of identified EV proteins and proteins identified only in one group.

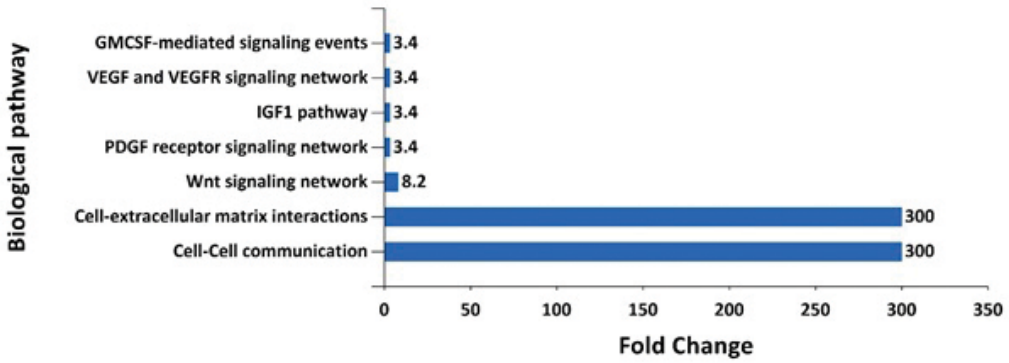

Figure 3. Bar chart showing fold enrichment in a selection of relevant biological pathways in the bone fracture group compared to the healthy control group.

Histological evaluation of autologous carrier/EV implants

Histological analyses of implants which contained EV isolate from long bone fracture patients, explanted from rats after 21 days and stained by HE revealed that a certain level of cell grouping was observed. While normal structure of surrounding connective tissue was not disturbed, regions of implantation were marked by presence of cells which formed rather distinguishable islets (Figure 4). Interestingly, in the case of larger islets, a gradient from outside towards the inner region of the islets in some morphological parameters was visible: cells in the outer zone of the islets were marked by a smaller amount of extracellular matrix (ECM). Cells in the middle of larger islets are surrounded by a large amount of ECM and some of them are clearly characterised by smaller nuclei (see Figure 4; A,B asterisk). Notably, these results were not observed in implants containing EV isolate from healthy volunteers, wherein remnants of the coagulum carrier were still evident (see Figure 4C, black arrows). Additional staining with safranin, which is selective for cartilage-typical proteoglycans, revealed that islets do contain molecules which safranin recognizes (Figure 4, D red colour). Implants with BMP6 as positive control demonstrate mineralized bone with a bone marrow and absence of inflammation and fibrosis at the external surface of the implant (data not shown).

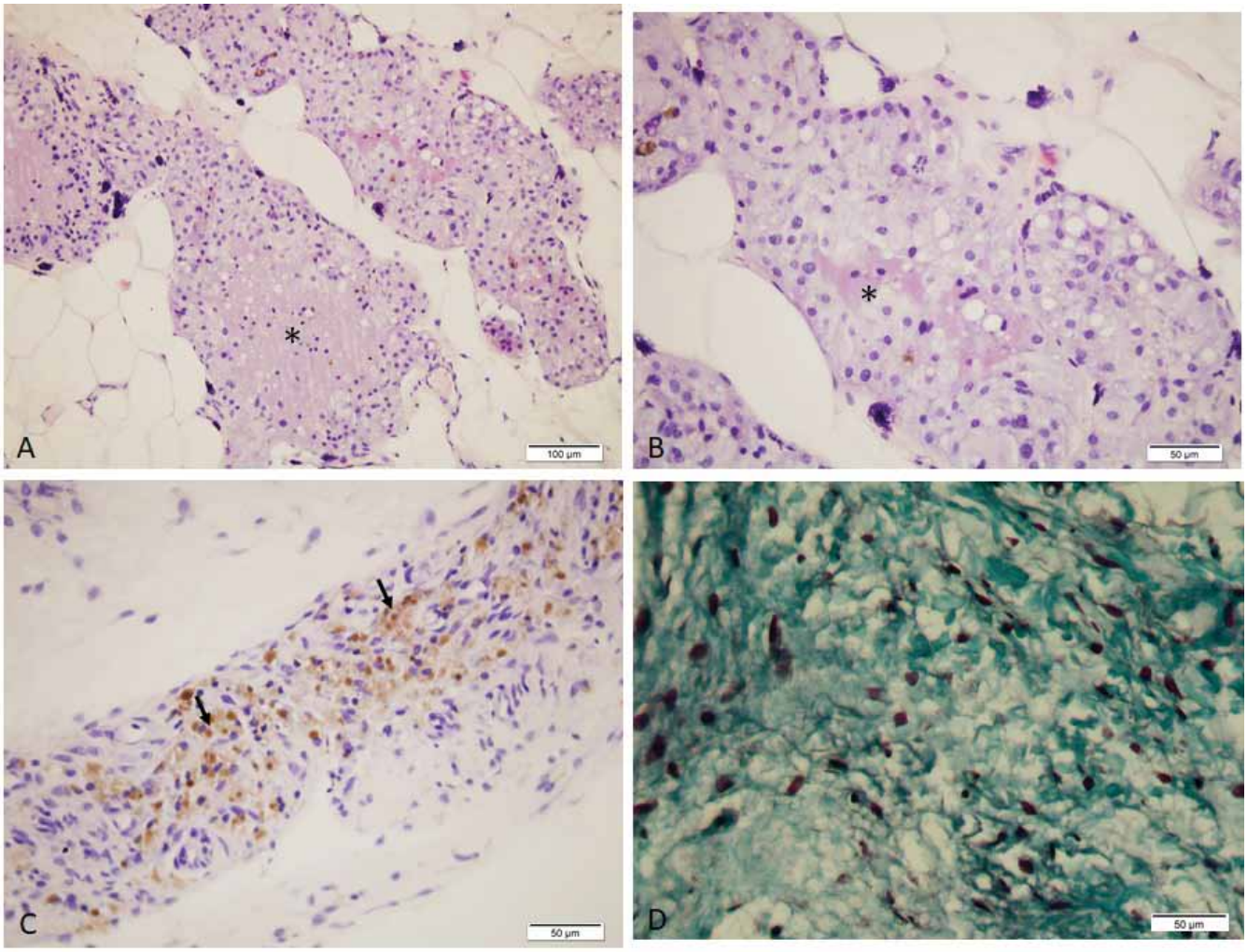

Figure 4. Histological analysis of implant after 21 days following implantation. A) H&E staining of implant enriched with ECVs of patients with fracture (magnification 20x); B) H&E staining of implant enriched with ECVs of patients with fracture (magnification 40x). Cells in the middle of larger islets are surrounded by large amount of ECM and some of them are clearly characterised by smaller nuclei (asterisk); C) H&E staining of implant enriched with ECVs of healthy volunteers (magnification 40x) where remnants of autologous blood coagulum are visible (black arrows); D) safranin red staining of implant enriched with ECVs of patients with fracture (magnification 40x)

Discussion

The need for personalised therapeutic regenerative approaches is significant. In this small pilot study, we aimed to demonstrate the endogenous regenerative potential of EVs for the purpose of improving and developing new therapeutic solutions, particularly in the field of bone and cartilage regeneration. Our goal was also to show a significant shift in the different molecular profiles between healthy individuals and individuals with bone fractures by analysing the proteomic profile of vesicles and their biological impact.

Our histology analysis results indicate the regenerative potential of EVs in the direction of tissue regeneration. To some extent this resembles a normal differentiation pattern of bone formation, especially during intramembranous ossification (forming of flat bones): while cells at the edge of the islet are metabolically very active (osteoblasts), cells which remain trapped inside the islet are surrounded by larger amount of ECM, alongside metabolic downregulation which is as well characterised by smaller diameter of nuclei (osteocytes). Another process of differentiation in the connective tissue which might be, in some elements present here is differentiation of hyaline cartilage, which is also marked by more dense packed cells at the edge (chondroblasts) and cells trapped within a huge ECM forming territory (chondrocytes). Since surrounding tissue stained by safranin did not exhibit any significant positivity, this is an additional proof that the observed islets are composed of cells which undergo a certain level of differentiation and secretion of ECM highly resembling the one normally found in either bone or cartilage. It is necessary to increase the number of samples and include additional histological staining methods to fully ascertain the direction and dosage critical for initiating differentiation. A dose-dependent effect of ECV was not observed, therefore, the range of implanted ECV dose should be expanded.

Our proteomic analysis of EV cargo further strengthens our histology findings. Namely, our gene enrichment analysis revealed a clear distinction in proteomic profiles between EV isolates of long bone fracture group when compared to healthy volunteers. We found several pathways which are known to play vital roles in bone formation and remodelling, including cell-cell and cell-ECM communication, Wnt signalling network, PDGF receptor, VEGF and GM-CSF signalling networks, as well as activity in the IGF1 pathway (22–28). Taking both the histological and proteomic disparities between the two groups into account, it is likely that specific EV-derived molecular factors associated with fracture repair play a pivotal role in triggering bone regenerative potential. These findings further highlight the potential EV-based therapies might play in the field of bone regeneration therapies.

There are three major limitations of the present study. The used Sprague-Dawley rats were adult animals (9 months old) with a decreased regenerative capacity in comparison to the commonly used two month-old animals that are at peak age for bone regeneration (29). This was a deliberate choice, i.e. a built in fail-safe in order to more strictly test the bone-induction potency of EVs. Secondly, the present study describes the regenerative potential of human EVs delivered in a rat ABC. Although the mechanism of bone regeneration was not scrutinised, plausibly, it is mediated through regulatory microRNA and signalling pathways included in bone metabolism. Although microRNA, as well as some of the bone morphogens (eg. BMP family) are evolutionarily conserved, it is expected that human bone tissue would respond better to stimulation by human EVs (30,31). However, due to their heterogeneity and small size, the isolation and analysis of EVs is not standardised and a variety of isolation and detection methods are available (19). The role of EVs in health and disease is emerging, and their biomarker and therapeutic potential appear promising across almost all biomedical fields (32–34).

Conclusions

The hypothesis derived from this preliminary pilot study provides novel insights, indicating that EVs may potentially exhibit regenerative efficacy, particularly through refinement of dosage titration. Consequently, our forthcoming actions will focus on augmenting the quantity of EVs and investigating a diverse array of biological combinations. These initiatives form an integral part of our ongoing commitment to advancing the development of personalised self-healing therapy.

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Conflicts of interest

The authors declare no conflicts of interest

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of the Hospital Center "Sisters of Charity", University Hospital Center (SCUHC) Zagreb (EP-003-06/20-03/023) and the Ethics Committee of the School of Medicine, University of Zagreb (EP 331/2021).

References:

1. Bergh C, Wennergren D, Möller M, Brisby H. Fracture incidence in adults in relation to age and gender: A study of 27,169 fractures in the Swedish Fracture Register in a well-defined catchment area. PLoS One [Internet]. 2020 Dec 21;15(12):e0244291. Available from: https://doi.org/10.1371/journal.pone.0244291
2. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton 3rd LJ. Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res [Internet]. 2014 Mar;29(3):581–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23959594
3. Adachi JD, Adami S, Gehlbach S, Anderson Jr FA, Boonen S, Chapurlat RD, et al. Impact of prevalent fractures on quality of life: baseline results from the global longitudinal study of osteoporosis in women. Mayo Clin Proc [Internet]. 2010/07/15. 2010 Sep;85(9):806–13. Available from: https://pubmed.ncbi.nlm.nih.gov/20634496
4. Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos [Internet]. 2021;16(1):82. Available from: https://doi.org/10.1007/s11657-020-00871-9
5. Wang X, Wang Y, Gou W, Lu Q, Peng J, Lu S. Role of mesenchymal stem cells in bone regeneration and fracture repair: a review. Int Orthop. 2013 Dec;37(12):2491–8.
6. Majidinia M, Sadeghpour A, Yousefi B. The roles of signaling pathways in bone repair and regeneration. J Cell Physiol. 2018 Apr;233(4):2937–48.
7. Song K, Krause C, Shi S, Patterson M, Suto R, Grgurevic L, et al. Identification of a key residue mediating bone morphogenetic protein (BMP)-6 resistance to noggin inhibition allows for engineered BMPs with superior agonist activity. J Biol Chem. 2010 Apr;285(16):12169–80.
8. Hak DJ, Fitzpatrick D, Bishop JA, Marsh JL, Tilp S, Schnettler R, et al. Delayed union and nonunions: epidemiology, clinical issues, and financial aspects. Injury. 2014 Jun;45 Suppl 2:S3-7.
9. Harness NG, Meals RA. The history of fracture fixation of the hand and wrist. Clin Orthop Relat Res. 2006 Apr;445:19–29.
10. Giannoudis P V, Einhorn TA, Marsh D. Fracture healing: the diamond concept. Injury. 2007 Sep;38 Suppl 4:S3-6.
11. Grgurevic L, Oppermann H, Vukicevic S. Whole blood-derived coagulum device for treating bone defects [Internet]. Australia; AU2007275579, 2012. Available from: https://patents.google.com/patent/AU2007275579B2/en?oq=Patent+AU+2007275579%2C+issue+date+Aug+16%2C+2012
12. Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, et al. Detection of microRNA expression in human peripheral blood microvesicles. PLoS One. 2008;3(11):e3694.
13. Panfoli I, Santucci L, Bruschi M, Petretto A, Calzia D, Ramenghi LA, et al. Microvesicles as promising biological tools for diagnosis and therapy. Expert Rev Proteomics. 2018 Oct;15(10):801–8.
14. Mittelbrunn M, Sánchez-Madrid F. Intercellular communication: diverse structures for exchange of genetic information. Nat Rev Mol Cell Biol [Internet]. 2012 Apr 18;13(5):328–35. Available from: https://pubmed.ncbi.nlm.nih.gov/22510790
15. Mathivanan S, Lim JWE, Tauro BJ, Ji H, Moritz RL, Simpson RJ. Proteomics Analysis of A33 Immunoaffinity-purified Exosomes Released from the Human Colon Tumor Cell Line LIM1215 Reveals a Tissue-specific Protein Signature*,. Mol Cell Proteomics [Internet]. 2010;9(2):197–208. Available from: https://www.sciencedirect.com/science/article/pii/S1535947620337932
16. Cosenza S, Ruiz M, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis. Sci Rep [Internet]. 2017;7(1):16214. Available from: https://doi.org/10.1038/s41598-017-15376-8
17. Tkach M, Théry C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. Cell [Internet]. 2016;164(6):1226–32. Available from: https://www.sciencedirect.com/science/article/pii/S0092867416300575
18. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding C V, Melief CJ, et al. B lymphocytes secrete antigen-presenting vesicles. J Exp Med [Internet]. 1996 Mar 1;183(3):1161–72. Available from: https://doi.org/10.1084/jem.183.3.1161
19. Morelli AE, Larregina AT, Shufesky WJ, Sullivan MLG, Stolz DB, Papworth GD, et al. Endocytosis, intracellular sorting, and processing of exosomes by dendritic cells. Blood [Internet]. 2004 Nov 15;104(10):3257–66. Available from: https://doi.org/10.1182/blood-2004-03-0824
20. Carnino JM, Lee H, Jin Y. Isolation and characterization of extracellular vesicles from Broncho-alveolar lavage fluid: a review and comparison of different methods. Respir Res. 2019;20(1):240.
21. Rappsilber J, Mann M, Ishihama Y. Protocol for micro-purification, enrichment, pre-fractionation and storage of peptides for proteomics using StageTips. Nat Protoc. 2007;2(8):1896–906.
22. Locatelli V, Bianchi VE. Effect of GH/IGF-1 on Bone Metabolism and Osteoporsosis. Int J Endocrinol. 2014;2014:235060.
23. Kim JH, Liu X, Wang J, Chen X, Zhang H, Kim SH, et al. Wnt signaling in bone formation and its therapeutic potential for bone diseases. Ther Adv Musculoskelet Dis. 2013 Feb;5(1):13–31.

24. Lee MS, Kim HS, Yeon J-T, Choi S-W, Chun CH, Kwak HB, et al. GM-CSF regulates fusion of mononuclear osteoclasts into bone-resorbing osteoclasts by activating the Ras/ERK pathway. J Immunol. 2009 Sep;183(5):3390–9.
25. Brun J, Andreasen CM, Ejersted C, Andersen TL, Caverzasio J, Thouverey C. PDGF Receptor Signaling in Osteoblast Lineage Cells Controls Bone Resorption Through Upregulation of Csf1 Expression. J bone Miner Res Off J Am Soc Bone Miner Res. 2020 Dec;35(12):2458–69.
26. Lin X, Patil S, Gao Y-G, Qian A. The Bone Extracellular Matrix in Bone Formation and Regeneration. Front Pharmacol. 2020;11:757.
27. Alcorta-Sevillano N, Macías I, Infante A, Rodríguez CI. Deciphering the Relevance of Bone ECM Signaling. Cells. 2020 Dec;9(12).
28. Stains JP, Civitelli R. Cell-to-cell interactions in bone. Biochem Biophys Res Commun. 2005 Mar;328(3):721–7.
29. Yun MH. Changes in Regenerative Capacity through Lifespan. Int J Mol Sci. 2015 Oct;16(10):25392–432.
30. Xiong P, Schneider RF, Hulsey CD, Meyer A, Franchini P. Conservation and novelty in the microRNA genomic landscape of hyperdiverse cichlid fishes. Sci Rep [Internet]. 2019;9(1):13848. Available from: https://doi.org/10.1038/s41598-019-50124-0
31. Najas S, Pijuan I, Esteve-Codina A, Usieto S, Martinez JD, Zwijsen A, et al. Evolutionary conserved canonical BMP activity controls cortical neurogenesis. bioRxiv [Internet]. 2019 Jan 1;558486. Available from: http://biorxiv.org/content/early/2019/02/22/558486.abstract
32. Chen S, Tang Y, Liu Y, Zhang P, Lv L, Zhang X, et al. Exosomes derived from miR-375-overexpressing human adipose mesenchymal stem cells promote bone regeneration. Cell Prolif. 2019 Sep;52(5):e12669.
33. Draebing T, Heigwer J, Juergensen L, Katus HA, Hassel D. Extracellular Vesicle-delivered Bone Morphogenetic Proteins: A novel paracrine mechanism during embryonic development. bioRxiv [Internet]. 2018 Jan 1;321356. Available from: http://biorxiv.org/content/early/2018/05/13/321356.abstract
34. Feng Q, Zheng S, Zheng J. The emerging role of microRNAs in bone remodeling and its therapeutic implications for osteoporosis. Biosci Rep. 2018 Jun;38(3).

Arterial stiffness in prehypertensive patients with white coat hypertension

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Abstract:

Introduction: White-coat hypertension (WCH) is associated with higher cardiovascular risk and increased all-cause mortality in the general population. The aim of this study was to determine whether there are differences in primary laboratory findings and pulse wave velocity (PWV) between prehypertensive patients with and without WCH.

Materials and Methods: This study included healthy 62 patients (37 women, 25 men) with prehypertension without medication based on ambulatory blood pressure monitoring [ABPM]) from one family practice in Health center Zagreb-West. Patients were divided into two groups depending on having WCH (>20 mmHg difference from in office SBP from average ABPM SBP values). Basic laboratory, anthropometric, 24h ambulatory blood pressure, and pulse wave velocity (PWV) measurements were done in all patients. Mann-Whitney U test, Kruskal-Wallis's test and descriptive statistics were used in data processing in Statistica v.12.0.

Results: WCH was found in 11 patients (17,7 %). Prehypertensive patients with WCH had significantly higher fasting glucose (median 5.7 [5.0–5.8] vs 5.3 [5.4–6.1] mmol/L;p < 0.001) and higher PWV (median 8.1 [7.1-8.8] vs. 9.0 [8.3–10.0] m/s; p=0.008). Patients with WCH had higher PWV in all three examined age groups (40–49 years p=0,074; 50-59 years p=0,003; 60-70 years p < 0,001). No differences were found in the concentration of potassium,
LDL cholesterol, triglycerides, and body mass index (median 25.6kg/m2).

Conclusion: This pilot study indicates the possible existence of accelerated atherosclerosis in prehypertensive individuals with WCH. It is necessary to conduct research on a larger sample to confirm these findings.

Keywords: Cardiometabolic risk factors, Vascular stiffness, White coat hypertension

Sažetak:

Krutost arterija u prehipertenzivnih bolesnika s hipertenzijom bijele kute

Uvod: Hipertenzija bijele kute (*engl. WCH*) povezana je s većim kardiovaskularnim rizikom i povećanom smrtnošću od svih uzroka u općoj populaciji. Cilj ovog istraživanja bio je utvrditi postoje li razlike u primarnim laboratorijskim nalazima i brzini pulsnog vala (*engl. PWV*) između prehipertenzivnih bolesnika sa i bez WCH.

Materijali i metode: Istraživanjem su obuhvaćena 62 zdrava bolesnika (37 žena, 25 muškaraca) s prehipertenzijom bez lijekova na temelju ambulantnog mjerenja krvnog tlaka (*engl. ABPM*) iz jedne obiteljske ordinacije Doma zdravlja Zagreb-Zapad. Bolesnici su podijeljeni u dvije skupine ovisno o tome imaju li WCH (>20 mmHg razlika između SBP u ordinaciji i prosječnih vrijednosti ABPM SBP). U svih bolesnika učinjena su osnovna laboratorijska, antropometrijska, 24-satna ambulantna mjerenja krvnog tlaka i brzine pulsnog vala. U obradi podataka u Statistici v.12.0 korišteni su Mann-Whitney U test, Kruskal-Wallisov test i deskriptivna statistika.

Rezultati: WCH je nađen u 11 bolesnika (17,7 %). Prehipertenzivni bolesnici s WCH imali su značajno višu glukozu natašte (medijan 5,7 [5,0–5,8] naspram 5,3 [5,4–6,1] mmol/L; p < 0,001) i viši

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PWV (medijan 8,1 [7,1-8,8] naspram 9,0 [8,3] –10,0] m/s; p=0,008). Bolesnici s WCH imali su viši PWV u sve tri ispitivane dobne skupine (40-49 godina p=0,074; 50-59 godina p=0,003; 60-70 godina p < 0,001). Nisu pronađene razlike u koncentraciji kalija,
LDL kolesterol, trigliceridi i indeks tjelesne mase (medijan 25,6 kg/m2).
Zaključak: Ova pilot studija ukazuje na moguće postojanje ubrzane ateroskleroze u prehipertenzivnih osoba s WCH. Za potvrdu ovih nalaza potrebno je provesti istraživanje na većem uzorku.

Ključne riječi: kardiometabolički čimbenici rizika, vaskularna krutost, hipertenzija bijele kute

Introduction

White coat hypertension (WCH) is defined as a condition in which the patient's arterial pressure is elevated only when measured in the physician's office; home and 24-hour ambulatory arterial pressure measurements give results that are inside the reference range for normotension (1). The prevalence of WCH is estimated to be around 30% among patients treated in hypertension clinics (2). However, the prevalence is notably lower when the physician or nursing staff are not involved in the process of arterial pressure measurement in the physician's office (3). One of the most important studies that illuminated the nature and risks of WCH was the PAMELA (Pressione Arteriose Monitorate E Loro Associazioni) Study (4). The PAMELA study was conducted on a random sample of 1651 subjects that represented the 25-64-year-old population of Monza, Italy. The subjects had their arterial pressures measured in the physician's office, at home by a semi automatic device and by a 24-hour ambulatory blood pressure monitoring (ABPM) device. The measurements obtained were used to determine the "normal" range of arterial pressure values in the general population, as well as classify and phenotype the elevated arterial pressure values into groups based on patterns and patient outcomes. The results of the study demonstrated that not only does WCH (referred to as "isolated office hypertension" in some of the articles cited) exist, it also carries an increased risk of hypertension-mediated organ remodelling. An analysis of the data from the PAMELA study by Sega et al shows that subjects with WCH had a significantly higher prevalence of left ventricular hypertrophy when compared to true normotensive subjects (5). Furthermore, an analysis of the data on plasma glucose concentrations of the PAMELA study participants over time, conducted by Mancia et al, demonstrated that participants with WCH or masked hypertension had an approximately threefold greater risk of new-onset diabetes mellitus, compared to participants with true normotension. This increase in relative risk was the same as the one seen in patients with sustained hypertension (elevated arterial pressure values measured both at home and in the physician's office) (6). Additionally, Mancia et al measured the arterial pressure values of the PAMELA study participants 10 years following the first measurement in the study and found that participants who had white coat hypertension at the index measurement had a significantly greater risk (odds ratio 2.5) of progressing to sustained hypertension during the 10-year period between measurements when compared to participants with true normotension (7). A 29-year follow-up of the PAMELA study population examining fatal cardiovascular (CV) event rates and all-cause mortality found that participants with WCH, but without evidence of end-organ damage had a two-fold greater adjusted risk of fatal CV events compared to normotensive participants without end-organ damage. Participants with white coat hypertension without organ damage also had a significantly higher adjusted risk (odds ratio 1.7) of developing organ damage during the follow-up period when compared to true normotensive participants, while participants with WCH and verified end-organ damage had a significantly higher adjusted risk of both CV (odds ratio 4.1) and all-cause mortality (odds ratio 2.1) when compared to true normotensive participants with verified end-organ damage (8). These results might stem from the fact that PAMELA participants with white coat hypertension also have a more unfavourable metabolic profile than normotensive participants, with higher blood concentrations of total cholesterol, triglycerides and glucose and lower blood concentrations of high-density lipoprotein cholesterol, resulting in higher rates of diabetes mellitus and metabolic syndrome (9). Taking all the aforementioned facts into account, precise phenotyping of elevated arterial pressure is of utmost importance, and offering 24-hour ABPM to patients with elevated values of arterial pressure on office measurements is both a thing of common sense, as well as endorsed by the currently available evidence and the latest European Society of Hypertension (ESH) guidelines, which state that: "Out of office blood pressure measurement by ABPM and/or home blood pressure management should be done when white coat hypertension is suspected, particularly in people with grade 1 hypertension" (1).

Given the available facts from the literature, the authors of this article were interested in whether further phenotyping of patients with white coat hypertension according to pulse wave velocity (PWV) values (an indirect measure of arterial stiffness), using oscillometric measurements of PWV immediately following the removal of the 24-hour ABPM device, would be useful in identi-

fying those patients with WCH that are at higher risk of adverse CV outcomes than others.
The aim of this study, therefore, is to determine whether there are significant differences in PWV between patients with WCH and those with true normotension.

Methods

This cross-sectional study was conducted in four family medicine practices (FMP) in the Health Center Zagreb - West from October 2021 to April 2023 (19 months). A total of 62 subjects (37 women and 25 men) with prehypertension were included in the study, divided into two groups depending on the presence of white coat syndrome. Prehypertension is defined as a systolic arterial pressure between 120 and 139 mmHg and/or a diastolic arterial pressure between 80 and 89 mmHg measured in two or more sitting measurements at two or more physician visits (according to the eighth Joint National Committee (JNC 8) criteria). White coat syndrome (WCH) is defined by systolic blood pressure measured in the office higher than 20 mmHg in relation to the average daily arterial pressure measured by ambulatory blood pressure monitoring (ABPM). Additionally, the respondents were divided into three groups depending on their age group (40-49, 50-59, 60-69). Only those subjects who did not have any acute illness at the time of the examination and who did not have any chronic or mental illness recorded in the medical documentation were included in the research.
The device used for ABPM was the BTL Cardiopoint®. All measurements were made by one researcher. The ABPM was performed with an adequate cuff placed on the lower half of the subject's upper arm determined by the circumference of the middle part of the distal half of the upper arm. All subjects were divided into two groups (dipper ≥ 10 %, non-dipper < 10 %) according to the percentage change in the average value of night AT compared to the average daily AT values. In case of threshold values (eg more than 5 measured values of systolic AT above 170 mmHg, etc.), duration of ABPM shorter than 20 hours or less than 70% of correct measurements, ABPM was repeated two weeks after the first measurement. ABPM was performed in FMP during working hours according to a special schedule. During the morning shift, the ABPM was set every working day at 12:30 p.m. and read the next day at the beginning of the shift at 1:30 p.m. Then it was set to the next respondent according to the schedule that the device returned for reading the next day at 12:30 p.m. Each respondent was asked for information about the usual time of going to sleep and waking up. The device is set so that it measures BP every 15 minutes during the day (subject's wakefulness), and every 30 minutes during the night (subject's sleep). Subjects were warned not to bathe or shower or work with water, and to improve measurement precision, they were asked to keep a diary of their activities while wearing the device.

Pulse wave velocity

PWV was measured with an oscillometric device Agedio® B900 (Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft GmbH (IEM), Stolberg, Germany) in a sitting position at a room temperature of 20-22 °C with the application of a wristband in the same previously described manner as in the execution of ABPM. The measurement itself lasts an average of three minutes and consists of two parts with a break of 30 seconds between them. The first measurement is a calibration (measurement of arterial pressure), while in the second measurement, the cuff is inflated to a pressure 35 mmHg higher than the measured pressure, and using the sensor in the cuff, pulse waves are detected and analysed for eight seconds, determining the central arterial pressure, the augmentation index (AIx) and evaluating the aortic PWV (PWVao). Measurements are programmed using a special application connected via Bluetooth to the specified device.

Biochemical parameters

Biochemical parameters in the serum of the subjects were determined by sampling two tubes of 8-10 mL of venous blood. The values of hematocrit, concentration of creatinine, sodium ions, potassium ions and glucose in the serum, triglycerides, HDL, LDL and total cholesterol and urate were determined. The devices used to analyse the analysed parameters were Sysmex XN 1000 and B-C AU500. The glomerular filtration rate (GFR) was estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

Other

SCORE and SCORE 2 CV risks were determined for all subjects according to the ESC tables for regions with a high-risk person profile.
All anamnestic data and findings of the subjects were collected from the Medicus.Net system. The research was approved by the ethics committee of the institution (number 251-12-02-21-19). All respondents signed an informed consent to participate in the research.

Statistical analysis

The normality of the data distribution was checked with the Kolmogorov-Smirnov test, and appropriate statistical tests were applied according to the obtained results. Numerical variables are presented as arithmetic mean and standard deviation (± SD), or median [interquartile range]. Nominal and ordinal (categorical) variables are presented by frequency distribution by group and share (%) for each analyzed group. Kruskal-Wallis test was used in order to determine the differences between the three age groups of respondents. The correlation between variables was checked by Spearman's rank correlation test. Statistical analysis of the data was performed in Statistica, StatSoft Inc., version 12.0.

Results

A total of 11 subjects (18%) in this sample met the conditions for WCH. By comparing the analysed parameters between the group with and without WCH, a significant difference was found only in fasting glucose concentration and AIx. Subjects with WCH tended to have higher values of PWV, LDL and lower GFR (Table 1). In the group without WCH, there were 6 (11.7%) smokers, while in the group with WCH, not a single respondent was a smoker.

Table 1. Characteristics of patients with and without white coat hypertension (WCH).

	Without WCH (N = 51, 82%) Median [IQR]	**Have WCH (N = 11, 18%)** Median [IQR]	**P**
Age (years)	55 [47 – 58]	55 [45 – 65]	0.733
ABPM SBP (mmHg)	122 [120 – 127]	119 [117 – 126]	0.171
ABPM DBP (mmHg)	75 [71 – 78]	73 [71 – 85]	0.846
Nocturnal indices (%)	10.8 [7.3 – 15.7]	10.6 [8.2 – 13.3]	0.803
HR (/min)	72 [67 – 77]	71 [63 – 81]	1.000
GFR (mL/min/ 1,73m2)	91.0 [85.0 – 95.6]	83.6 [72.1 – 91.7]	0.093
LDLc (mmol/L)	3.6 [3.0 – 4.3]	3.8 [3.7 – 4.5]	0.133
HDLc (mmol/L)	1.4 [1.3 – 1.6]	1.4 [1.2 – 1.7]	0.561
Triglycerides (mmol/L)	1.1 [0.8 – 1.7]	1.1 [0.9 – 1.6]	0.926
Uric acid (umol/L)	294 [247 – 339]	250 [240 – 385]	0.946
PWV (m/s)	8.1 [5.9 – 10.5]	10.7 [7.3 – 15.4]	0.101
AIx (%)	22 [15 – 32]	36 [26 – 42]	0.007
BMI (kg/m2)	25 [22 – 27]	26 [24 – 30]	0.178
Fasting glucose (mmol/L)	5.3 [5.0 – 5.8]	5.6 [5.4 – 6.1]	0.046

ABPM = ambulatory blood pressure monitoring; SBP = systolic blood pressure; DBP = diastolic blood pressure; GFR = glomerular filtration rate; PWV = pulse wave velocity; BMI = body mass index; HR = heart rate; AIx = augmentation index.

By age group, WCH had 4 (36%) respondents aged 40-49, 4 (36%) aged 50-59 and 3 (27%) aged 60-69. By comparing the observed parameters according to age groups, existence of WCH and groups of respondents, a significant difference between the values of the measured PWV was determined. Accordingly, PWV values increased with age and were significantly higher in the group with WCH in all three age groups (Figure 1). The measured value of PWV correlated significantly with the difference between the systolic pressure measured in the office and the average systolic pressure measured by KMAT ($r = 0.443$; $p < 0.001$).

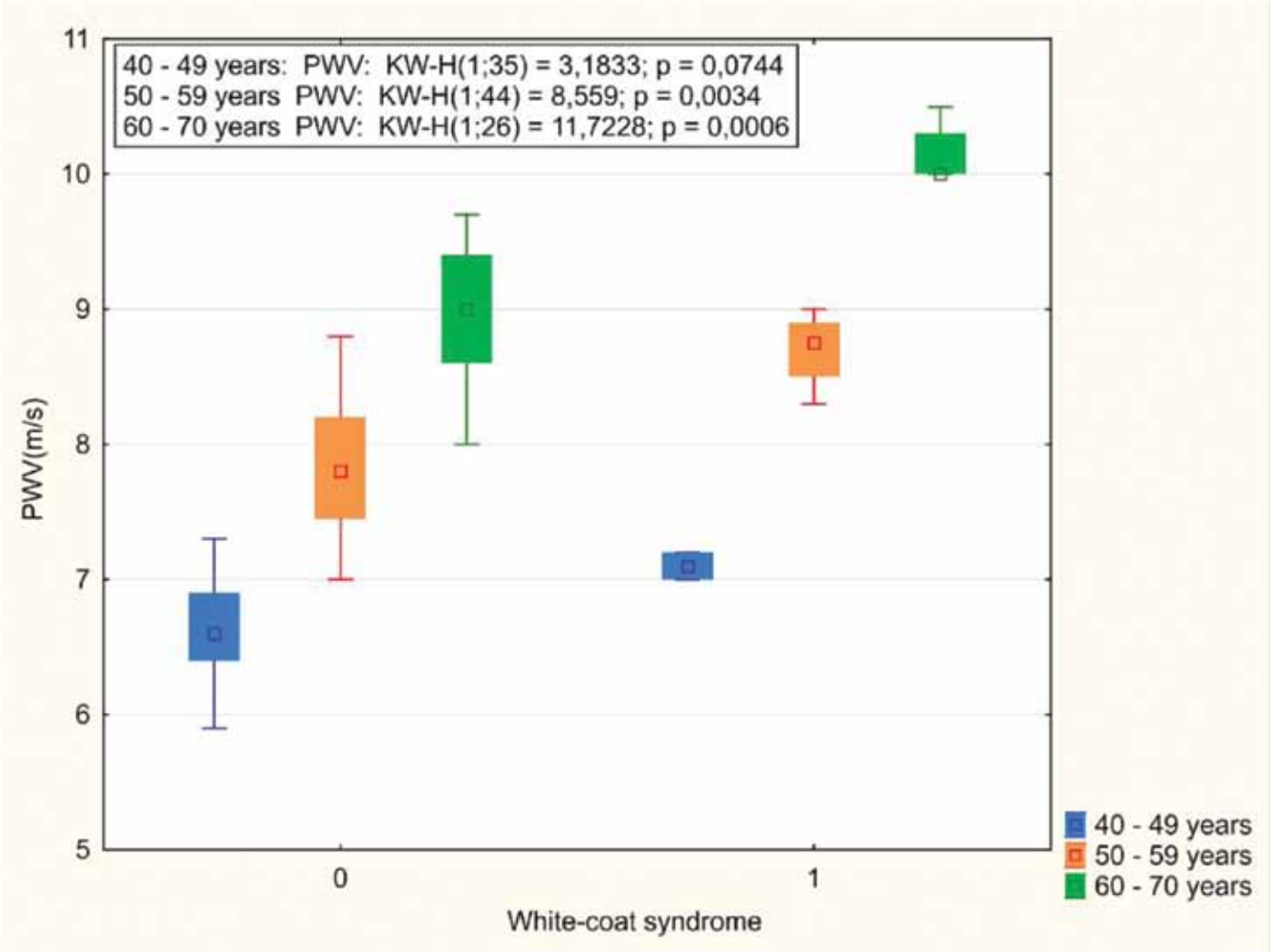

Figure 1. Pulse wave velocity (PWV) values in prehypertensive individuals with and without white coat hypertension (WCH) divided to age groups. PWV values depend on age.

Calculating CV risk according to SCORE (median 1.6 vs. 1.4 in subjects with WCH; p = 0.562) and SCORE 2 (median 3.8 vs. 2.6 in subjects with WCH; p = 0.846) tables revealed a lower median value of CV risk in the group with WCH. However, dividing by age groups, no significant difference was found between subjects with and without WCH according to the results of CV risk tables (Figure 2). Overall, according to SCORE risk, 56 respondents (90.32%) were in the low and moderate risk group, and according to SCORE 2, 39 respondents (62.90%) had such a risk. High risk was recorded in 6 (9.68%) and 18 (29.03%) subjects according to SCORE and SCORE 2 risk, respectively. According to the SCORE 2 tables, 5 respondents had a very high risk, while according to SCORE, no one had such a risk. The measured value of PWV was shown to be significantly correlated with the results of both CV risk tables (r = 0.673; p < 0.001 for SCORE; r = 0.801; p < 0.001 for SCORE 2), while no significant correlation was found for AIx with the result of the CV risk tables.

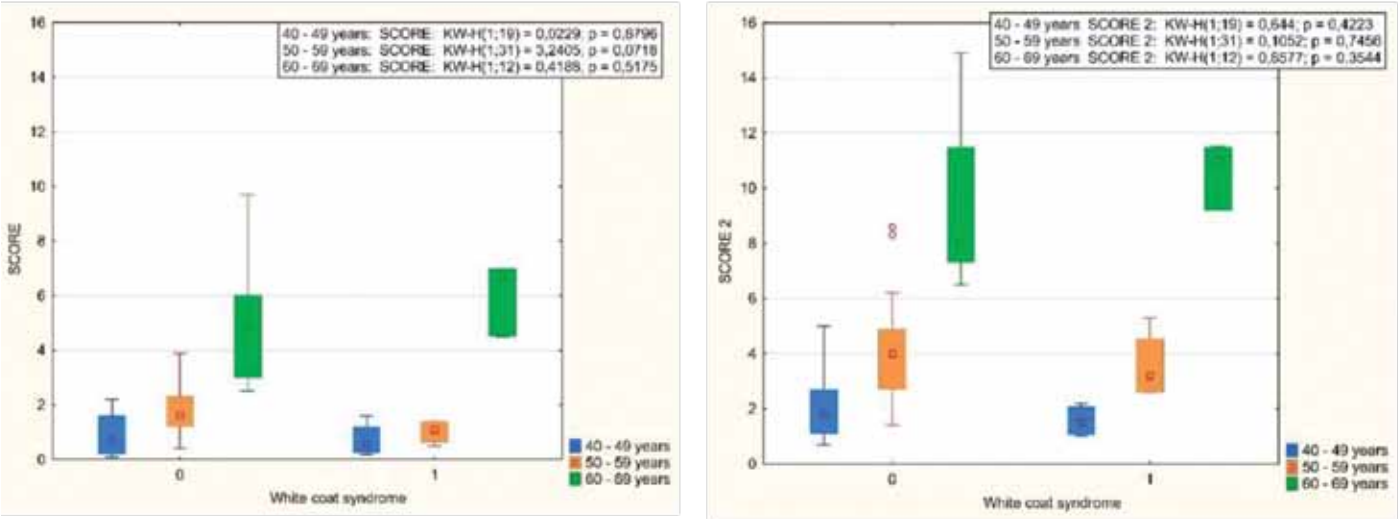

Figure 2. SCORE (left) and SCORE 2 (right) risks values in prehypertensive individuals with and without white coat hypertension depending on age group.

Discussion

Besides ours, several other studies examining pulse wave velocities and arterial stiffness in patients with white coat hypertension have been conducted. A study by Rong Cao et al measured brachial-ankle pulse-wave velocity (ba-PWV) in 444 patients deemed to have white coat hypertension based on data from a single 24-hour ambulatory blood pressure monitoring (ABPM) and at least 2 arterial pressure measurements in the physician's office at separate times (10). They further split the patients according to a quantitative increase in systolic blood pressure (SBP) on office measurements when compared to 24-hour ABPM - patients with an increase lower than 9.5mmHg were deemed "low white coat effect" and those with an increase of 9.5mmHg or greater were deemed "high white coat effect". Their results demonstrated that the absolute value of b-aPVW linearly correlated with the increase in SBP attributable to white coat effect and the correlation persisted and remained statistically significant ($p = 0.004$) when the model was adjusted for age, sex, diabetes mellitus, hyperlipidemia, smoking status, family history of hypertension, BMI, serum creatinine and uric acid.

A study on 120 patients with inflammatory bowel disease (IBD) by Premužić et al found that a significantly higher proportion of IBD patients with white coat hypertension had PWV values above the 8 m/s cutoff when compared to true normotensive IBD patients (84.8 vs 30.6, $p < 0.001$). Furthermore, IBD patients with white coat hypertension had significantly higher values of central SBP and central puls pressure when compared to true normotensive IBD patients, while having similar (non-significantly different) age, gender distribution, smoking status, duration of IBD, biochemical data, proportion of patients receiving biological or immunosuppressive treatment (11). Research by Stolarz et al compared PWV in a random sample of participants with either normotension, masked hypertension or white coat hypertension and found significantly higher values of PWV in patients with white coat hypertension when compared to those with true normotension (9.39+/-1.23 m/s vs 8.56+/-1.45 m/s; $p < 0.05$). However, the difference lost statistical significance when corrected for age, gender, BMI and smoking status (12). Saunders et al conducted a sub-group analysis of the Arterial Stiffness In lacunar Stroke and Transient ischemic attack (ASIST) study which included 32 patients with true normotension and 30 patients with white coat hypertension 14 days following an adverse cerebrovascular event (either a transient ischemic attack or a lacunar stroke) and found that patients with white coat hypertension had significantly higher carotid-femoral PWV (cfPWV) values (11.9 ± 3.0 m/s vs. 9.6 ± 2.3 m/s, $p = 0.002$) (13). Lithovius et al conducted ABPM and PWV measurements in 140 patients with type 1 diabetes mellitus and found that patients with white coat hypertension had significantly higher PWV values when compared to true normotensive patients (6.7 m/s vs 5.8 m/s, $p < 0.001$)(14). Paiva et al compared PWV values in 692 individuals divided into groups by hypertension phenotype according to data obtained by ABPM. They found that patients with controlled white coat hypertension had significantly higher office PWV values when compared to true normotensive patients (7.53 +/- 0.09 m/s vs 6.89 +/- 0.05 m/s, $p < 0.05$), while patients with uncontrolled white coat hypertension had significantly higher office (8.28 +/- 0.11 m/s vs 7.43 +/- 0.08 m/s, $p < 0.05$) and 24-hour (7.54 +/- 0.09 m/s vs 7.21 +/- 0.07 m/s, $p < 0.05$) PVW values when compared to patients with controlled hypertension (15).

Besides the individual studies cited, two meta-analyses related to the topic of arterial stiffness in white coat hypertension were published. A meta-analysis by Cai et al included 20 studies examining 1538 patients with white coat hypertension and 3582 patients with true normotension and concluded that, in the adult population, patients with white coat hypertension had significantly higher cfPWV values when compared to true normotensives [95% confidence interval (CI): 0.46-0.87, $p < 0.001$] (16). Another meta-analysis, conducted by Antza et al, included 7 studies and 2352 patients, and found that patients with white coat hypertension had significantly higher cfPWV values when compared to true normotensives (difference = 0.85 m/s, 95% CI: 0.48-1.22; $p < 0.01$). Furthermore, patients with white coat hypertension had similar (non-significantly different) values of PWV when compared to patients with sustained hypertension (difference = −0.75 m/s, 95% CI: −1.52-0.02) (17).

The results of this study are in line with the currently available literature, demonstrating significantly higher PWV values in patients with white coat hypertension compared to true normotensives. However, this association was only found in patients older than 50 years of age. This finding could be explained by the fact that arterial stiffness by itself increases with age (18), making the effects of other important factors, such as white-coat hypertension, more pronounced in patients whose arteries are stiffer at baseline (due to age-related changes in arterial tissue composition) and more prone to increases in "functional" arterial stiffness, defined by an increase in arterial tone, mediated by increased blood pressure (19).

Another important finding of our study is the fact that patients with white coat hypertension had a significantly higher fasting plasma glucose concentration when compared to true normotensive patients, which is in line with established facts from larger studies, such as the PAMELA study (9).

While our study did not establish an increase in CV risk in patients with white coat hypertension compared to true normotensive patients, the diagnostic accuracy of the instruments that we used (SCORE and SCORE2 tools) might be lower than desirable in general. A retrospective study by Karakayali et al calculated the SCORE and SCORE2 risk scores of 788 patients diagnosed with arterial hypertension and gathered data on adverse CV events from a 6-year follow-up period. They found that the diagnostic accuracy [expressed as area under the curve (AUC)] of SCORE and SCORE2 for major adverse CV and cerebrovascular events (MACCE) during a 6-year follow-up period was 0.689 and 0.724 respectively, indicating borderline acceptable diagnostic accuracy (20).

Therefore, the lack of significant differences in SCORE and SCORE2 scores in our patient cohort should not be interpreted as the lack of difference in CV risk overall between white coat hypertensive and true normotensive patients.

There are several important limitations to our study. The first one is the relatively small sample size. The second is the fact that this was a single-center study, making generalisability of our findings to the general population difficult. Furthermore, while a biochemistry panel was conducted on all participants, thyroid stimulating hormone (TSH) concentrations were not measured. According to epidemiological studies, 5-15% of the general population is affected by subclinical hypothyroidism. Patients with subclinical hypothyroidism are known to have increased PWV values, making TSH measurement an important step in removing potential confounding from studies involving PWV measurement.

Other factors that might influence PWV values, such as physical activity, alcoholic beverage consumption and nutrition were not evaluated in this study.

Finally, we have no validated method of determining both the exact duration of arterial hypertension and adherence to antihypertensive/antilipemic therapy in individual patients, both of which are factors that significantly affect PWV values.

Conclusion

In this single-centre cross-sectional study, patients with white coat hypertension older than 50 were found to have significantly higher values of PWV and significantly higher concentrations of fasting plasma glucose when compared to true normotensive patients. These findings add to the existing knowledge on white coat hypertension, indicating that phenotyping of elevated blood pressure using ambulatory blood pressure monitoring is of utmost importance for predicting adverse outcomes. However, more prospective multi-center studies should be conducted in order to corroborate these findings.

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Conflict Of Interest:

None declared.

REFERENCES

1. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071.
2. Stergiou GS, Palatini P, Parati G, O'Brien E, Januszewicz A, Lurbe E et al. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. J Hypertens. 2021;39(7):1293-1302.
3. Grassi G, Quarti-Trevano F, Seravalle G, Dell'Oro R, Vanoli J, Perseghin G et al. Sympathetic Neural Mechanisms Underlying Attended and Unattended Blood Pressure Measurement. Hypertension. 2021;78(4):1126-1133.
4. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G et al. Ambulatory blood pressure normality: results from the PAMELA study. J Hypertens. 1995;13(12 Pt 1):1377-90.
5. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R et al. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation. 2001;104(12):1385-92.
6. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Grassi G et al. Increased long-term risk of new-onset diabetes mellitus in white-coat and masked hypertension. J Hypertens. 2009;27(8):1672-8.
7. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Polo Friz H et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension. 2009;54(2):226-32.
8. Mancia G, Facchetti R, Vanoli J, Dell'Oro R, Seravalle G, Grassi G. White-Coat Hypertension Without Organ Damage: Impact on Long-Term Mortality, New Hypertension, and New Organ Damage. Hypertension. 2022;79(5):1057-1066.
9. Mancia G, Bombelli M, Cuspidi C, Facchetti R, Grassi G. Cardiovascular Risk Associated With White-Coat Hypertension: Pro Side of the Argument. Hypertension. 2017;70(4):668-675.
10. Cao R, Yue J, Gao T, Sun G, Yang X. Relations between white coat effect of blood pressure and arterial stiffness. J Clin Hypertens (Greenwich). 2022;24(11):1427-1435.
11. Premužić V, Prijić R, Jelaković M, Krznarić Ž, Čuković-Čavka S, Jelaković B. White coat hypertension is another clinical characteristic of patients with inflammatory bowel disease: A cross-sectional study. Medicine (Baltimore). 2022;101(44):e29722.
12. Stolarz K, Wojciechowska W, Olszanecka A, Lubaszewski W, Cwynar M, Grozdicki T et al. Pulse wave velocity in subjects with masked hypertension and white coat hypertension. Artery Research. 2006;1:46.
13. Saunders A, Nuredini GN, Kirkham FA, Drazich E, Bunting E, Rankin P. White-coat hypertension/effect is associated with higher arterial stiffness and stroke events. J Hypertens. 2022;40(4):758-764.
14. Lithovius R, Gordin D, Forsblom C, Saraheimo M, Harjutsalo V, Groop PH. Ambulatory blood pressure and arterial stiffness in individuals with type 1 diabetes. Diabetologia. 2018;61(9):1935-1945.
15. Paiva AMG, Gomes MICM, Campana ÉMG, Feitosa ADM, Sposito AC, Mota-Gomes MA et al. Impact of hypertension phenotypes on the office and 24-h pulse wave velocity and augmentation index in individuals with or without antihypertensive medication use. Hypertens Res. 2019;42(12):1989-1995.
16. Cai P, Peng Y, Wang Y, Wang X. Effect of white-coat hypertension on arterial stiffness: A meta-analysis. Medicine (Baltimore). 2018;97(42):e12888.
17. Antza C, Vazakidis P, Doundoulakis I, Bouras E, Haidich AB, Stabouli S et al. Masked and white coat hypertension, the double trouble of large arteries: A systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2020;22(5):802-811.
18. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR et al. American Heart Association Council on Hypertension. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015;66(3):698-722.
19. Pierdomenico SD, Coccina F, Madonna R. Pulse wave velocity in white coat and masked hypertension. J Clin Hypertens (Greenwich). 2020;22(5):812-813.
20. Karakayalı M, Püşüroğlu H, Altunova M, Yılmaz E, Güllü A. Predictive value of the SCORE, SCORE2, and pooled cohort risk equation systems in patients with hypertension. Turk Kardiyol Dern Ars. 2023;51(6):407-414.

Known and newly discovered atrial fibrillation in correlation with outcome after stroke

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Abstract:

Background: Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. Atrial fibrillation in stroke patients can be classified as: 1. previously known atrial fibrillation that was detected before the stroke occurred and 2. newly diagnosed atrial fibrillation, detected after the stroke occurred (AF de novo). The aim of this study is to analyse the severity and outcome of stroke in patients with newly diagnosed AF and those with known AF.

Materials and Methods: A retrospective analysis was made of 98 patients with acute stroke with AF hospitalised at the University Clinic for Neurology in Skopje, North Macedonia - at the Department of Urgent Neurology in the period from 2019 to 2022. Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke. In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale).

Results: The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (AF de novo) patients with a predominance of mild stroke, mild disability, but without proven statistical significance ($p>0.05$).

Conclusion: We found that stroke severity and scores quantified by NIHSS, GCS, and mRS in patients with newly diagnosed AF did not differ from those in patients with known AF.

Keywords: atrial fibrillation, stroke, NIHSS, GCS, mRS

Sažetak:

Korelacija ishoda nakon moždanog udara i novootkrivene ili ranije poznate fibrilacije atrija

Uvod: Fibrilacija atrija (FA) jedan je od najvažnijih čimbenika rizika za ishemijski moždani udar. Fibrilacija atrija u bolesnika s moždanim udarom se može klasificirati kao: 1. Ranije poznata FA koja je dijagnosticirana prije moždanog udara i 2. Novootkrivena FA. Cilj ove studije je analizirati težinu i ishode moždanog udara u bolesnika s novootkrivenom i od ranije poznatom FA.

Materijali i metode: Provedena je retrospektivna analiza 98 bolesnika s akutnim moždanim udarom i FA hospitaliziranih u Sveučilišnoj klinici za neurologiju u Skopju, Sjeverna Makedonija, na Odjelu hitne neurologije u periodu od 2019. Do 2022. Godine. Uključni kriteriji su bili FA, svih dobnih

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skupina, dijagnosticiranih s moždanim udarom. U analizi uključeni su i drugi pokazatelji poput neurološkog deficita kvantificiranog NIHSS skalom (engl. National Institutes of Health Stroke Scale), stanje svijesti procijenjeno GCS zbrojem (engl. Glasgow Coma Scale/Score) i stupanj neurološkog deficita kvantificarnog pomoću mRS (engl. Modified Rankin Scale).
Rezultati: Ovo istraživanje pokazalo je da su bolesnici skupine 1A (poznata FA) češće imali srednje težak do težak moždani udar (prema NIHSS zbroju), srednje težak neurološki deficit (prema mRS zbroju) i nizak GCS zbroj naspram bolesnika iz skupine 1B (novonastala FA) kod kojih je češće bio blaži moždani udar i manji neurološki deficit, ali bez statističkog značaja (p>0.05).
Zaključak: Prema našim rezultatima, težina moždanog udara i zbrojevi NIHSS, GCS i mRS se nisu razlikovali u bolesnika s novonastalom FA naspram onih s od ranije poznatom FA.

Ključne riječi: fibrilacija atrija, moždani udar, NIHSS, GCS, mRS

Introduction

Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. It is known that patients with AF have a 5 times higher risk of having a stroke than those without AF. With the availability of modern cardiac monitoring technologies, detection of AF after stroke or transient ischemic attack (TIA) has improved significantly [1]. Atrial fibrillation in stroke patients can be classified as: 1. previously known atrial fibrillation that was detected before the stroke occurred and 2. newly diagnosed AF, detected after the stroke occurred (AF de novo) [1].
Among acute ischemic stroke patients with AF, 7.8% to 36.2% were first diagnosed with AF after a registered stroke [2]. Ischemic stroke that occurs in patients with AF is likely to be severe or fatal. Half of patients with AF are asymptomatic, therefore detection of AF and subsequent anticoagulant therapy is crucial for stroke prevention [2]. Patients with newly diagnosed AF and those with known AF have different characteristics. However, differences in stroke severity and outcome have not been sufficiently evaluated [2][3].

Aim

The aim of this study is to analyse the severity and outcome of stroke in patients with newly diagnosed AF and those with known AF.

Materials and Methods

A retrospective analysis was made of 98 patients with acute stroke with AF hospitalised at the University Clinic for Neurology in Skopje, North Macedonia - at the Department of Urgent Neurology in the period from 2019 to 2022.
Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke (ischemic, hemorrhagic). Depending on whether it is known AF or newly diagnosed AF, we divided the patients into two groups: 1A known AF and 1B newly diagnosed AF (AF de novo).
According to the localization of the stroke registered on computed tomography, we divided the patients into two groups: 2A patients with a stroke in the anterior circulation, 2B patients with a stroke in the posterior circulation.
In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale). Depending on the NIHSS score, we divided stroke patients into 3 categories: mild stroke (1-5 points), moderate stroke (5-14 points), severe stroke (15-42 points). Depending on the GCS result, we divided the patients according to the level of consciousness into 3 groups: best response (15-9 points), coma (8-4 points), completely unresponsive (< 3 points). Depending on the mRS score, we divided the patients according to the degree of disability into: patients with mild disability (1-2 points), patients with moderate disability (3-4 points), patients with severe disability (5 points).

Statistical analysis

The data were analysed using IBM SPSS Statistics (chi square test) and the (chi-square) test was used, which is expressed in numbers and percentages. The results are presented tabular and graphically. Statistical significance was set at $p < 0.05$.

Results

In our study, 98 patients aged 49-89 years were analysed, of which 53.1% (52) were women and 46.9% (46) were men. 72.5% (71) of the patients had an ischemic stroke, 7.1% (7) had a hemorrhagic stroke, and 20.4% (20) had an ischemic stroke with hemorrhagic transformation. (figure 1).

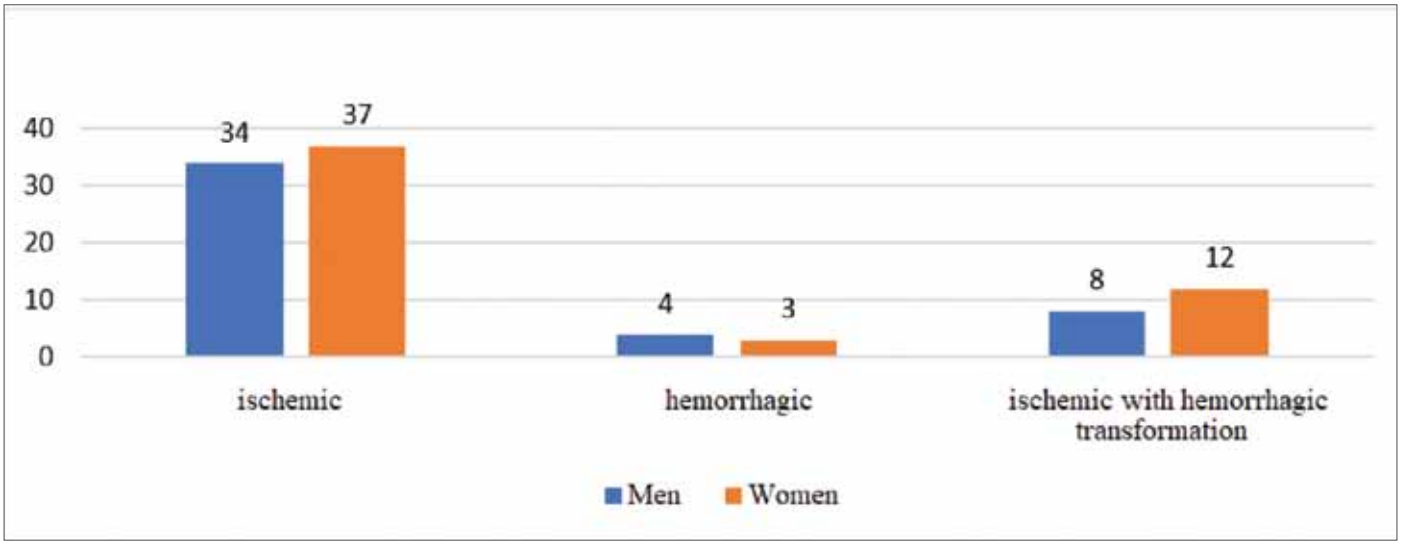

Figure 1. Distribution of the total number of patients according to gender and type of stroke

According to the localization of the stroke, 78.6% (77) of the patients had a stroke localized in the anterior circulation, and 19.4% (19) had a stroke localized in the posterior circulation. (table 1)

Table 1. Localization of the stroke and the number of patients

Localization of stroke / Gender	1 –Anterior circulation No.	%	2 –Posterior circulation No.	%	3 - Thrombolysed No.	%	In total No.	In total %
1 -Male	36	36,7%	8	8,2%	2	2,0%	46	**46,9%**
2 -Female	41	41,8%	11	11,2%		0,0%	52	**53,1%**
Total sum	**77**	**78,6%**	**19**	**19,4%**	**2**	**2,0%**	**98**	**100,0%**

Out of a total of 98 patients, 63.3% (62) had known atrial fibrillation (group 1A), of which 26.5% (26) were men, and 36.7% (36) were women. In 36.7% (36) of the patients, atrial fibrillation was newly diagnosed during hospitalisation (group 1B), of which 20.4% (20) were men, and 16.3% (16) were women. (Figure 2).

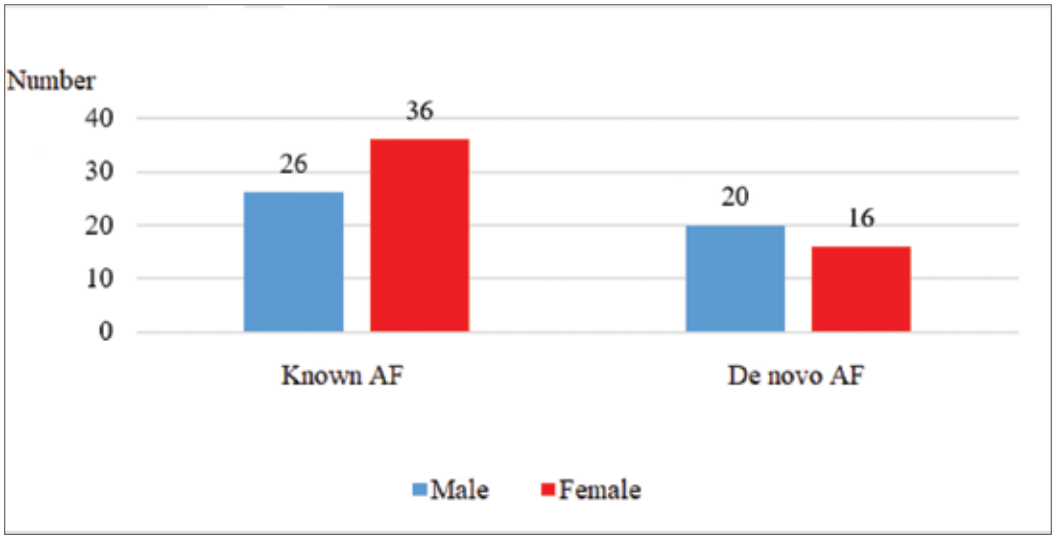

Figure 2. Patients with known versus newly diagnosed AF

X^2=1,696< X^2 (1 and 0,005)= 3,841 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and gender.
According to the score obtained from NIHSS; 25% of subjects from group 1A (known AF) had a mild stroke, 65% had a moderate stroke, 64.8% had a severe stroke. 75% of the individuals from group 1B (AF de novo) had a mild stroke, 35% a moderate stroke and 35.2% a severe stroke. (table 2, figure 3).

Table 2. NIHSS score (at discharge) of patients with known versus newly diagnosed AF.

			Mild stroke	Moderate stroke	Severe stroke	Total
	Known AF	Count	1	**26**	**35**	62
		% within NIHSS	25,0%	**65,0%**	**64,8%**	63,3%
	De novo AF	Count	**3**	14	19	36
		% within NIHSS	**75,0%**	35,0%	35,2%	36,7%
Total		Count	4	40	54	98
		% within NIHSS	100,0%	100,0%	100,0%	100,0%

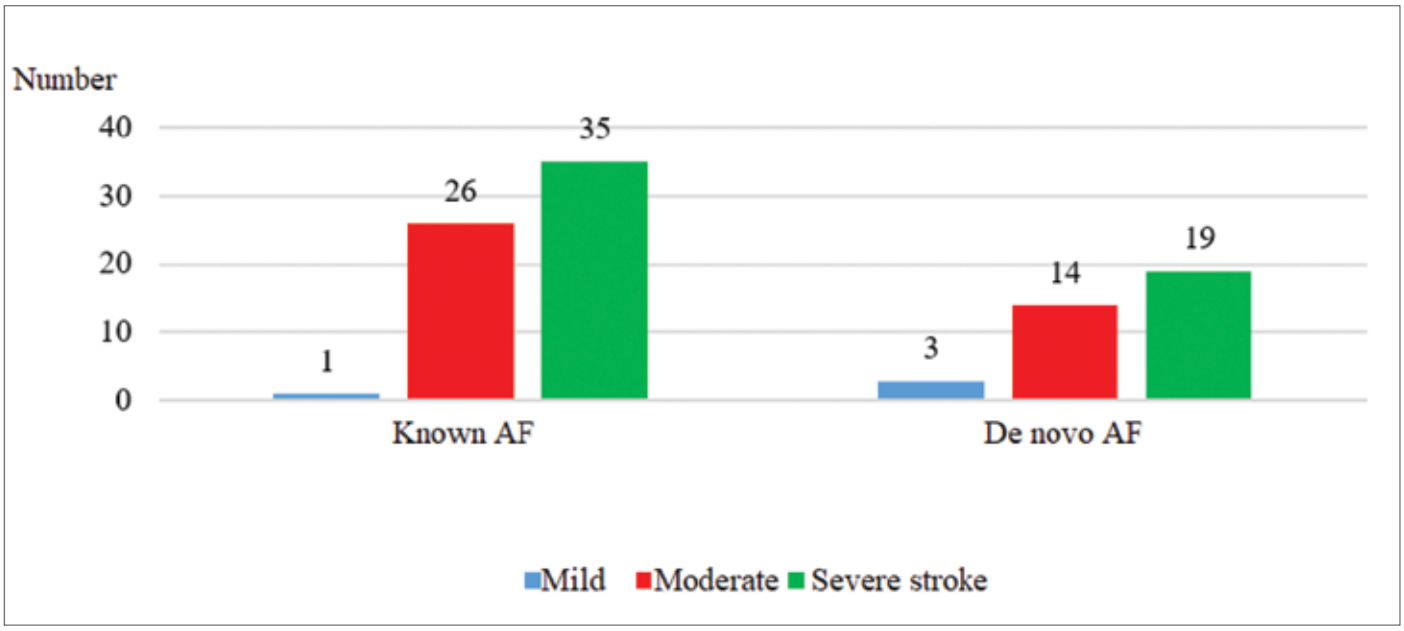

Figure 3. NIHSS score (at discharge) of patients with known versus newly diagnosed AF

X^2=2,628< X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and NIHSS.
According to the result obtained by GCS, 62% of subjects from group 1A (known AF) had the best response, 70.8% were in coma, 33.3% were completely unresponsive. 38.0% of the patients from group 1B (AF de novo) had the best response, 29.2% were in a coma, 66.7% were completely unresponsive. (Table 3, Figure 4).

Table 3. GCS result (at discharge) of patients with known versus newly diagnosed AF

			Best response	Coma	Completely unresponsive	Total
AF	Known AF	Count	**44**	**17**	1	62
		% within GCS	**62,0%**	**70,8%**	33,3%	63,3%
	De novo AF	Count	27	7	**2**	36
		% within GCS	38,0%	29,2%	**66,7%**	36,7%
Total		Count	71	24	3	98
		% within GCS	100,0%	100,0%	100,0%	100,0%

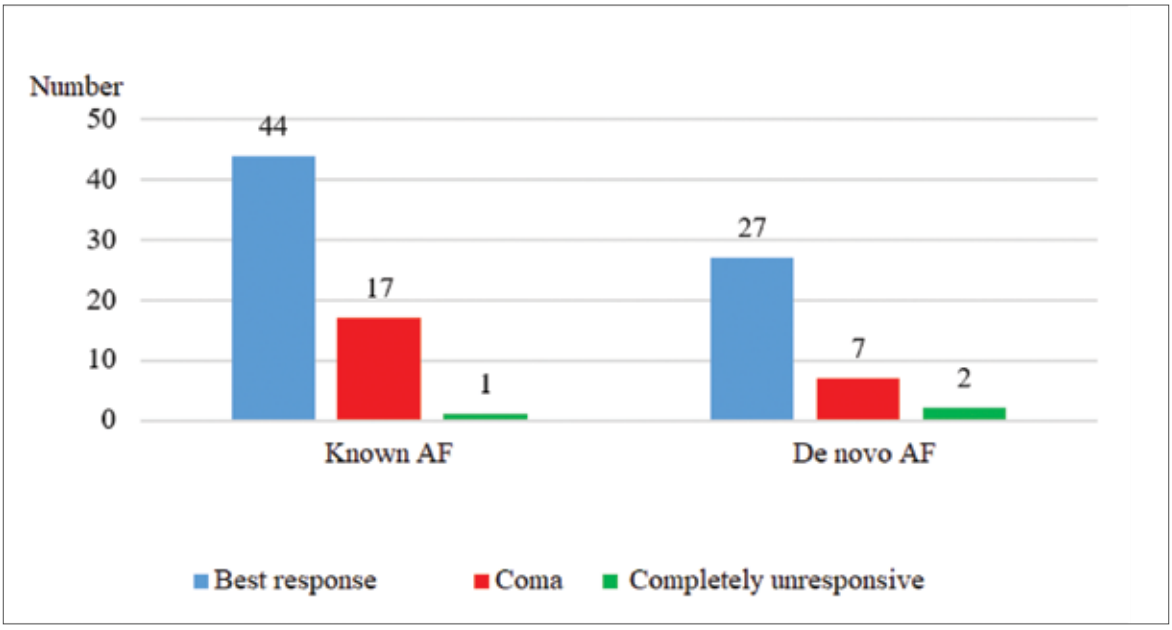

Figure 4. GCS result (at discharge) of patients with known versus newly diagnosed AF

X^2=1,799< X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and GCS.
According to the result obtained from the mRS, 50.0% of the respondents from group 1A (known AF) had light disability, 66.7% moderate disability, 62.9% severe disability. 50.0% of the respondents from group 1B (AF de novo) had mild disability, 33.3% moderate disability, 37.1% severe disability. (Table 4, Figure 5).

Table 4. mRS result (at discharge) of patients with known versus newly diagnosed AF

			Light disability	Moderate disability	Severe disability	Total
	Known AF	Count	2	**16**	**44**	62
		% within mRS	50,0%	**66,7%**	**62,9%**	63,3%
	De novo AF	Count	2	8	26	36
		% within mRS	50,0%	33,3%	37,1%	36,7%
Total		Count	4	24	70	98
		% within mRS	100,0%	100,0%	100,0%	100,0%

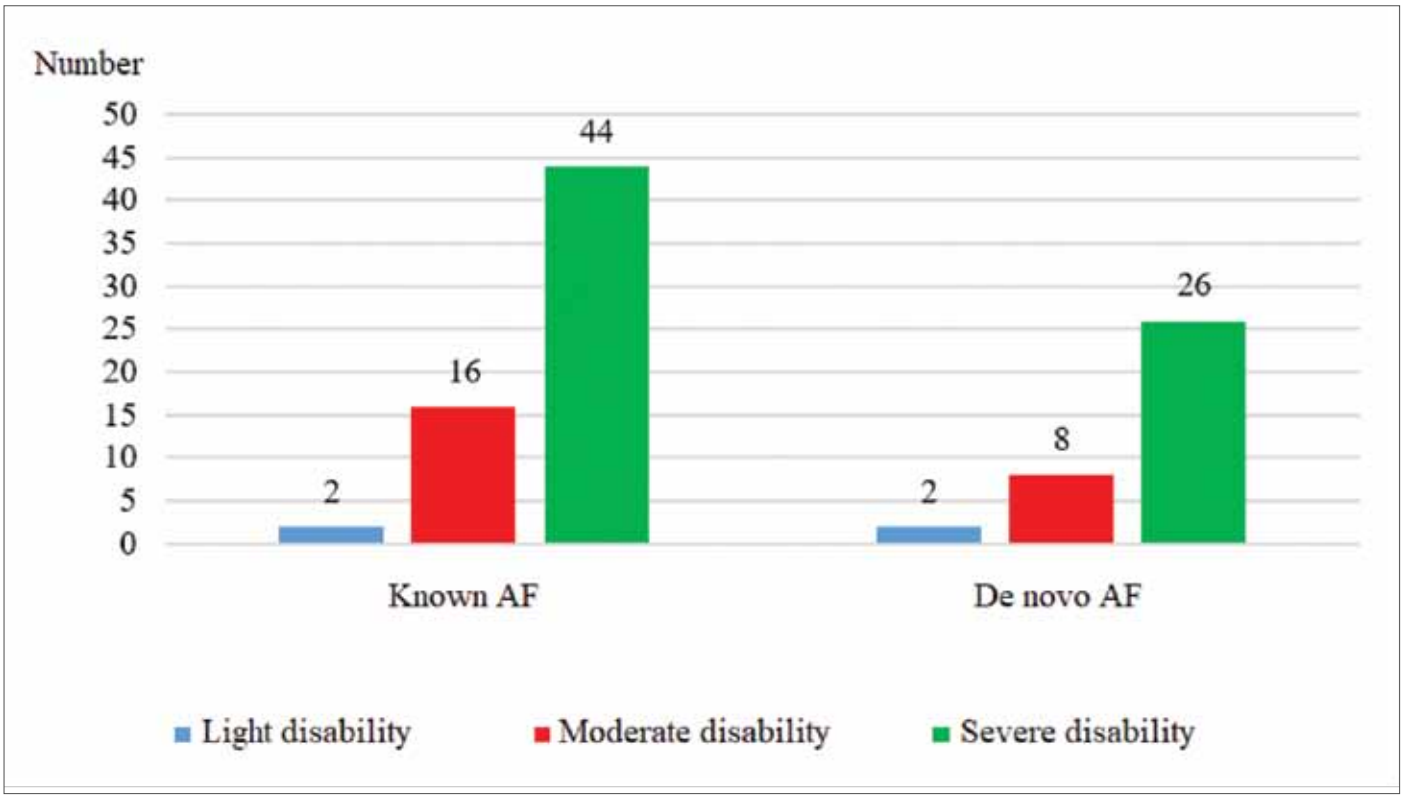

Figure 5. mRS result (at discharge) of patients with known versus newly diagnosed atrial fibrillation

X^2=0,427 < X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and mRS.

Discussion

In our study, in the period from 2019 to 2022, 98 patients with AF were hospitalised and treated at the Department of Urgent Neurology, due to a registered acute stroke. This study includes patients with AF. Other risk factors for acute stroke, such as diabetes mellitus, hypertension, hyperlipidemia, were not analysed in the study. Also, the results obtained with NIHSS, GCS and mRS were obtained when the patients were discharged from the hospital. The results showed that 36.7% (36) of the subjects were diagnosed with atrial fibrillation for the first time. The largest number of patients had ischemic stroke (72.5%), but the rate of patients with ischemic stroke with hemorrhagic transformation (20.4%) is also significant. In our group of patients dominates a stroke in anterior circulation (78.6%).

The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (AF de novo) patients with a predominance of mild stroke, mild disability, but without proven statistical significance (p>0.05).
In a study published in 2021, it was concluded that: Stroke severity and in-hospital outcomes in patients with newly diagnosed AF did not differ from those in patients with known AF after adjustment for clinically relevant factors [2].
The difference between our study and the study by Watanabe K et al, is that in their study NIHSS scores were obtained at hospital admission, but also in their study patient comorbidities were taken into account. In their study, mRS scores were measured at hospital discharge, which supports our study.
That study also emphasises the administration of anticoagulant therapy to patients with known atrial fibrillation and the importance of detection of latent AF and subsequent anticoagulation

in preventing severe stroke should be further emphasised[2].
A meta-analysis of 21 studies comparing known atrial fibrillation and newly diagnosed AF also takes stroke reversibility into account. A study by Fridman S et al claims that patients with AF detected after stroke (AFDAS) may have a lower prevalence of cardiovascular comorbidities and lower risk of stroke recurrence than AF known before stroke (KAF). They found significant differences in the prevalence of vascular comorbidities, structural heart disease, and stroke recurrence rates between AFDAS and KAF, suggesting that they constitute different clinical entities within the AF spectrum [5].
A study from Wang et al. also takes stroke reversibility into account, but it is suggested that the rate of stroke recurrence did not differ significantly. On the other hand, as Fridma et al. study, it claims that AF de novo patients had a lower prevalence of coronary artery disease, heart failure, and sustained AF, but higher rates of large vessel occlusion compared to known AF patients. NIHSS scores were lower in patients on pre-stroke anticoagulation [8]. In our study NIHSS score between patients with known AF and AF de novo did not significantly differ, compared to Wange et al. study.
In a study that compares known AF, AF diagnosed after stroke and sinus rhythm is said that patients with newly diagnosed AF had a higher proportion of brain infarcts and a higher frequency of insular involvement [7]. The results of Toledo et al study are in agreement with our research, as we concluded that a bigger number of strokes are in the anterior circulation. The difference is that, in this study, the results were compared between patients with AF and patients with sinus rhythm.
In one study, the distribution of ischemic lesions was described in a large series of patients with AF suffering their first ischemic stroke. It was concluded that the timing of AF diagnosis or the CHA2DS2-VASc score did not affect the lesion localization. Although some differences in lesion localization were observed according to oral anticoagulant use, the distinctions in absolute terms were small and do not seem meaningful. Strokes classified as embolic or thrombotic were more often located within the anterior cerebrovascular territory in comparison to strokes of other or undetermined aetiology. Anterior territory strokes were slightly more often located within the left hemisphere, but the observed difference was so small that its clinical significance is questionable [4].
This study on localization of strokes in patients with AF is in agreement with ours. But, Jaakkola J et al's study also determines the effects of CHA2DS2-VASc score, oral anticoagulant (OAC) use, and timing of AF diagnosis on lesion localization.
It is concluded that AF de novo had similar risk of 1-year ischemic stroke recurrence and mortality when compared with known AF and higher risk when compared with sinus rhythm. The potential risk of AF de novo should be given more emphasis, and appropriate treatment is needed to achieve reduction in the incidence of stroke recurrence and mortality[1].
In a cohort study from Borowsky et al it is stated that nearly one in 5 AF-related strokes occurred without a pre-stroke AF diagnosis [6]. AF was readily diagnosed using standard rhythm monitoring. This emphasises the importance of timely diagnosis of AF.
There are many studies examining the effects of anticoagulant and antiplatelet therapy when comparing known atrial fibrillation and atrial fibrillation diagnosed after stroke. National Institutes of Health Stroke Scale scores varied according to preceding antithrombotic therapy ($P<0.001$). It was higher in patients who did not receive antithrombotics than in those who received antiplatelets or anticoagulants. Favourable outcome at discharge (modified Rankin Scale score, 0–2) was more prevalent in patients who received antiplatelets or anticoagulants ($P<0.001$). Use of antiplatelets and anticoagulants was associated with a mild initial neurological deficit (National Institutes of Health Stroke Scale score ≤5) in patients with acute ischemic attack with AF [9].
We should acknowledge the various limitations of this study. First, this was a retrospective observational analysis. Unlike randomised studies, the selection of patients and undocumented confounding factors could affect the validity of our findings. However, it was impossible to randomise patients with stroke and AF. Secondly, there were no studies that examine the GCS score on patients with known AF and AF de novo.

Conclusion

We found that stroke severity and scores quantified by NIHSS, GCS, and mRS in patients with newly diagnosed AF did not differ from those in patients with known AF. Given the severity of stroke in patients with AF, it should be further emphasised that detection of latent AF and subsequent anticoagulation is crucial to prevent severe stroke.

References

1. Xiao-Meng Yang, Zhen-Zhen Rao, Hong-Qiu Gu, Xing-Quan Zhao, Chun-Juan Wang, Li-Ping Liu, Chelsea Liu, Yi-Long Wang, Zi-Xiao Li, Rui-Ping Xiao, Yong-Jun Wang. Atrial Fibrillation Known Before or Detected After Stroke Share Similar Risk of Ischemic Stroke Recurrence and Death. 2019;50:1124–1129
2. Watanabe K, Okazaki S, Kitano T, Sugiyama S, Ohara M, Kanki H, Sasaki T, Sakaguchi M, Mochizuki H, Todo K. Stroke Severity and Outcomes in Patients With Newly Diagnosed Atrial Fibrillation. Front Neurol. 2021 Jun 29;12:666491. doi: 10.3389/fneur.2021.666491. PMID: 34267720; PMCID: PMC8275857.
3. Hsieh CY, Lee CH, Wu DP, Sung SF. Characteristics and outcomes of ischemic stroke in patients with known atrial fibrillation or atrial fibrillation diagnosed after stroke. Int J Cardiol. 2018 Jun 15;261:68-72. doi: 10.1016/j.ijcard.2017.11.047. PMID: 29657060.
4. Jaakkola J, Hartikainen P, Kiviniemi TO, Nuotio I, Palomäki A, Hartikainen JEK, Ylitalo A, Mustonen P, Airaksinen KEJ. Distribution of ischemic strokes in patients with atrial fibrillation: The FibStroke Study. Neurol Clin Pract. 2019 Aug;9(4):330-336. doi: 10.1212/CPJ.0000000000000683. PMID: 31583188; PMCID: PMC6745749.
5. Sebastian Fridman, Amado Jimenez-Ruiz, Juan Camilo Vargas-Gonzalez, Luciano A. Sposato; Differences between Atrial Fibrillation Detected before and after Stroke and TIA: A Systematic Review and Meta-Analysis. Cerebrovasc Dis 16 March 2022; 51 (2): 152–157.
6. Borowsky LH, Regan S, Chang Y, Ayres A, Greenberg SM, Singer DE. First Diagnosis of Atrial Fibrillation at the Time of Stroke. Cerebrovasc Dis. 2017;43(3-4):192-199. doi: 10.1159/000457809. Epub 2017 Feb 17. PMID: 28208140.
7. González Toledo ME, Klein FR, Riccio PM, Cassará FP, Muñoz Giacomelli F, Racosta JM, Roberts ES, Sposato LA. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. J Stroke Cerebrovasc Dis. 2013 Nov;22(8):e486-91. doi: 10.1016/j.jstrokecerebrovasdis.2013.05.015. Epub 2013 Jun 22. PMID: 23800494.
8. Ruihao Wang, Kosmas Macha, David Haupenthal, Luise Gaßmann, Gabriela Siedler, Svenja Stoll, Kilian Fröhlich, Julia Koehn, Stefan Schwab, Bernd Kallmünzer. Acute care and secondary prevention of stroke with newly detected versus known atrial fibrillation. Volume29, Issue7.2022:1963-1971
9. Han Jung, Young Dae Kim, Jinkwon Kim, Sang Won Han, Mi Sun Oh, Ji Sung Lee and Kyung-Yul Lee. Initial Stroke Severity in Patients With Atrial Fibrillation According to Antithrombotic Therapy Before Ischemic Stroke. 2020;51:2733–2741

CGRP-induced headache and hemodynamic response for prediction of therapy based on CGRP antagonism

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Abstract:

Migraine is increasingly recognized as a disorder of the calcitonin gene-related peptide (CGRP) pathway. However, other factors are involved in migraine pathophysiology such as vasoactive intestinal peptide (VIP) and PACAP-38. Indeed, the CGRP-test can discriminate migraine from non-migraine and other non-CGRP induced migraine using CGRP-induced headache (CGRP-IH) and cerebral hemodynamic changes. Recent studies support the evidence of CGRP susceptible migraine prone to CGRP antagonism. Therefore, the CGRP-test may have an important role in therapeutic decisions regarding anti-CGRP monoclonal antibodies and gepants. This may improve the clinical effects of CGRP antagonism in migraine patients and increase therapeutic adherence. From the perspective of pain medicine may improve placebo response which can enhance favourable therapeutic outcomes.

Keywords: migraine, calcitonin gene-related peptide (CGRP), transcranial Doppler (TCD), migraine susceptible to CGRP

Sažetak:

CGRP-om inducirana glavobolja i hemodinamski odgovor kao predskazatelj terapije zasovane na CGRP antagonizmu

Migrene su sve više prepoznate kao poremećaj puta kalcitonin-gen-povezanog peptida (CGRP). Međutim, drugi čimbenici su uključeni u patofiziologiju migrena, poput vazoaktivnog crijevnog peptida (VIP) i PACAP-38. CGRP test može razlikovati migrenu od nemigrenozne glavobolje i drugih migrena koje nisu inducirane CGRP-om pomoću CGRP-om inducirane glavobolje (CGRP-IH) i cerebralnih hemodinamskih promjena. Nedavne studije podržavaju dokaze CGRP osjetljivih migrena podložnih antognizmu CGRP-a. Stoga, CGRP test može imati važnu ulogu u terapijskim odlukama vezanih za anti-CGRP monoklonska protutijela i gepante. Ovaj test bi mogao poboljšati kliničke učinke CGRP antagonizma u bolesnika s migrenom i povećati adherenciju na terapiju. Iz perspektive analgezije, mogao bi biti poboljšan placebo odgovor koji može pospiješiti povoljne terapijske ishode.

Ključne riječi: migrena, kalcitonin-gen povezani peptid (CGRP), transkranijalni dopler, migrena podložna CGRP-u

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Introduction

Understanding migraine through calcitonin gene-related peptide represents (CGRP) (1) a great step in our knowledge of functional disorders in pain medicine. Although, the research goes back to the eighties of the last century, clinical applicability has reached in recent years. The role of CGRP in human physiology is not clearly explained. It is supposed that is important in the dangerous physiologic states such as ischemia of the central nervous system. In the peripheral nervous system, it contributes to neurogenic inflammation to decrease damage and initiate healing of the tissue. Nevertheless, CGRP consists of a defense response to actual or potential damage. From the perspective of migraine, we can consider the CGRP as the part of potential damage response because our brain predicts future unsafe situations and can form the response to virtual brain lesions leading to migraine attacks.

Exogenous CGRP

CGRP is an endogenous signaling molecule formed in the neurons in the body's periphery as well as in the central nervous system. It could be detected in the peripheral blood in pico levels. It is elevated after migraine attack and chronic migraine (2, 3). Therefore, we can consider that intracranial structures are an important source of CGRP. It is believed that the trigeminovascular system is an important generator of CGRP. According to current knowledge, the nociceptive activity in migraine originates from a complex consisting of trigeminal ganglia, its peripheral projections, and arteries innervated with them. It is still a mystery what is a primer for increased activity of the trigeminovascular system. Using the human model of migraine (4), CGRP was applied in the form of intravenous infusion. They established the clinical and hemodynamic responses to exogenous CGRP. Indeed, not all migraineurs show responses to exogenous CGRP. It is known that CGRP is not the only agent that can trigger migraine attacks. In a human model, another molecule such as pituitary adenylate cyclase-activating peptide-38 (PACAP-38) and vasoactive intestinal polypeptide (VIP) can evoke the migraine attack (5). This indicates migraine as a heterogeneous and multifactorial brain disorder with different pathways for increasing trigeminovascular activity. Thus, the response to exogenous CGRP could be useful for determining the therapeutic effect of CGRP antagonism, such as treatment with anti-CGRP monoclonal antibodies.

CGRP-test

CGRP-test appears to discriminate migraine from non-migraine (6). The test includes the clinical response of CGRP-induced headache (CGRP-IH) and hemodynamic responses related to cerebral vascular and systemic cardiovascular responses detected by polymodal monitoring. CGRP-IH is a phenomenon, subject to neurocognitive features of individuals and could be independent of biological reactions to CGRP. On the other hand, hemodynamic responses associated with CGRP should be more biological, specific to the CGRP mechanism. However, the discriminative power of hemodynamic variables such as arterial velocity in a middle cerebral artery (vm MCA) and posterior cerebral arteries (vm PCA) appears to be low (6). Indeed, during the CGRP test, End-tidal carbon dioxide (Et-CO_2), besides vm in MCA in PCA showed a significant response to CGRP. Thus, the combination of hemodynamic response to CGRP could be useful for testing the susceptibility of migraine to CGRP antagonism.

Methodology for CGRP testing

The methods used to determine suitability to CGRP-antagonism were described in detail in a publication of our research group (6), Therefore, only the essentials are listed here. For cerebral circulation variables, TCD sonography with 2 MHz probes applies to measure the vm MCA through the left and vm PCA through the right temporal acoustic window. During the experiment, the mean blood pressure (MAP) and heart rate (HR) are continuously measured using noninvasive plethysmography. An infrared capnograph measures the Et-CO_2. All variables are recorded simultaneously, enabling to comparison of the signals and conducting correlations between them. This is a multichannel recording technology developed in our laboratory (7). The experiment lasts 40 min, consisting of a 10-minute baseline period, a 20-minute period during which an intravenous infusion of exogenous CGRP is administered, and 10 minutes after the end of the application of CGRP. The average values of all parameters (vm MCA and vm PCA, MAP, HR, and Et-CO_2) were calculated during 5-minute intervals.

Important findings of CGRP-test

CGRP-test produces CGRP-induced headache (CGRP-IH) in migraineurs and non-migraineurs. However, the migranours have a significantly higher proportion of CGRP-IH. This means that CGRP-IH is not specific to migraines, the CGRP does not induce CGRP-IH in every patient with a migraine. CGRP-IH is supposed to be a homeostatic feeling based on the neurocognitive process of each individual. From this perspective, CGRP-IH is dependent on multiple sensory inputs and internal states related to previous experiences. In addition, beliefs and expectations concerning nocebo or placebo may be influencial.

Biological response to CGRP-test including cerebral and systemic hemodynamic alternations during CGRP infusion. The main finding of the study was a significant decrease of vm MCA and vm PCA during the exogenous CGRP infusion (6). This is explained by proximal arterial vasodilatation and drop of vm because of constant cerebral blood flow during CGRP infusion. The constancy of cerebral blood flow is provided by an additional drop of Et-CO_2 (8). According to the segmental concept of cerebral vasculature

regulation (9), the distal segment including cerebral arterioles and microcirculation compensates for vasodilatation on a proximal part. Thus, exogenous CGRP induces cerebral vasodilatation of the proximal segment which is evident from experimental studies, (10). From the physiology of cerebral circulation, It is known that partial carbon dioxide in arterial blood has a potent vasoconstrictor effect on cerebral circulation, acting predominantly on the distal segment. That's why we can consider a change of Et-CO_2 after CGRP infusion as a compensatory response.

On the other side, an enhanced response of vm MCA is observed in migraine with a positive relationship between vm MCA responses and migraine (11). According to the previous explanation, hemodynamic changes in cerebral circulation after CGRP infusion are attributed to an enhanced vasodilatation of proximal large arteries in migraine (12). Thus, the vm MCA can be used for discrimination of migranous susceptible to CGRP from others, migranours and non-migranours.

Regarding systemic variables such as mean arterial pressure (MAP) and heart rate (HR). intravenous infusion of exogenous CGRP significantly decreases MAP. The maximal decrease of MAP at the end of the infusion. Changes in HR are significant and in the opposite direction to the changes in MAP (13). However, the study concluded that CGRP does not have direct significant effects on MAP in migraine (11). This is by the finding that blocking CGRP does not affect systemic blood pressure in healthy volunteers (14). In addition, associations were found between MAP and vm MCA, as well as between MAP and vm PCA, which indicates uncoupling between cerebral flow and systemic arterial pressure and therefore normal regulation of cerebral blood flow during CGRP stimulation. Accordingly, MAP and HR can not discriminate between migranours who have specific responses to CGRP and others.

For the reasons described in previous paragraphs both, vm MCA and Et-CO2 can be used as discriminatory factors. In addition, if we use them together, we can get a stronger discriminator and predict the migraineurs susceptible to CGRP antagonism. For this reason, we introduced the product of vm MCA and Et-CO2 to augment CGRP effects on cerebral circulation and use it for discriminative factors. Analysis of ROC curves for the product vm MCA and Et-CO2 showed a significant area under the curve of the product migraineurs and non-migraineurs (15). Therefore, hemodynamic parameters of CGRP effects on cerebral circulation might be used to accurately discriminate migraine susceptible to CGRP from non-susceptible CGRP migraineurs and non-migraineurs. Therefore, hemodynamic changes during CGRP provocation might predict the efficiency of CGRP antagonism. CGRP-IH seems to be affected by non-nociceptive, subjective factors. However, some authors proposed CGRP-IH as a test for predicting response to anti-CGRP mAb (16), but it has not been tested yet. Nevertheless, the product of vm MCA and Et-CO2 appears promising discriminator with better sensitivity and specificity compared to CGRP-IH.

Other possible discriminants for migraine

The current concept considers trigeminovascular reflex (TVR) with CGRP release should be the fundamental generator of migraine headache and source of central sensitization of brain structures. According to this concept, CGRP in plasma should be increased even in the interictal period as was found in chronic migraine (2). On the other hand, increased levels of vasoactive intestinal peptide (VIP) in addition to CGRP were found elevated in plasma interictally (17) It is attributed to activation of not only sensory and parasympathetic arms of the TVS. The infusion of VIP provoked migraine (18), but the effect on cerebral and systemic hemodynamic factors is not known. In addition, intravenous infusions of the neuropeptide PACAP-38 induced delayed migraine-like headaches (19). Nevertheless, the hemodynamic effect of PACAP-38 is not known. Thus, the CGRP mechanism is neither sufficient nor necessary to evoke migraine. Blocking CGRP pathways seems not to be successful in every migraine. This supports the concept of non-CGRP and CGRP susceptible migraine phenotype as suggested previously (20). Accordingly, PACAP-38 and VIP could be useful discriminators for other than CGRP migraine types.

Conclusions

In conclusion, our studies showed that hemodynamic changes during CGRP provocation might predict the efficiency of CGRP antagonism. CGRP-IH seems to be affected by non-nociceptive factors. However, some authors proposed CGRP-IH as a test for predicting response to anti-CGRP mAb (20), but it has not been tested yet. Nevertheless, the product vm MCA and Et-CO_2 appears as promising, objective discriminator with better sensitivity and specificity compared to CGRP-IH for migraine susceptible to CGRP.

Literature

1. Edvinsson L. The CGRP Pathway in Migraine as a Viable Target for Therapies. Headache. 2018; 58(Suppl 1): 33-47.
2. Cernuda-Morollón E, Larrosa D, Ramón C, Vega J, Martínez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology. 2013; 81(14): 1191-6.
3. Vural S, Albayrak L. Can calcitonin gene-related peptide (CGRP) and pentraxin-3 (PTX-3) be useful in diagnosing acute migraine attack? J Recept Signal Transduct Res. 2022; 42(6): 562-6.
4. Ashina M, Hansen JM, Olesen J. Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience. Cephalalgia. 2013; 33(8): 540-53.
5. Pérez-Pereda S, Toriello-Suárez M, Ocejo-Vinyals G, Guiral-Foz S, Castillo-Obeso J, Montes-Gómez S, Martínez-Nieto RM, Iglesias F, González-Quintanilla V, Oterino A. Serum CGRP, VIP, and PACAP usefulness in migraine: a case-control study in chronic migraine patients in real clinical practice. Mol Biol Rep. 2020; 47(9): 7125-38.
6. Visočnik D, Žvan B, Zaletel M, Zupan M. αCGRP-Induced Changes in Cerebral and Systemic Circulation; A TCD Study. Front Neurol. 2020;11: 578103.
7. Zvan B, Zaletel M, Pogacnik T, Kiauta T. Testing of cerebral endothelium function with L-arginine after stroke. Int Angiol. 2002; 21(3): 256-9.
8. Zupan M, Zaletel M, Visočnik D, Žvan B. The Influence of Calcitonin Gene-Related Peptide on Cerebral Hemodynamics in Nonmigraine Subjects with Calcitonin Gene-Related Peptide-Induced Headaches. Biomed Res Int. 2021; 2021: 5540254.
9. Hoiland RL, Fisher JA, Ainslie PN. Regulation of the Cerebral Circulation by Arterial Carbon Dioxide. Compr Physiol. 2019; 9(3): 1101-54.
10. Erdling A, Sheykhzade M, Edvinsson L. Differential inhibitory response to telcagepant on αCGRP induced vasorelaxation and intracellular Ca2+ levels in the perfused and non-perfused isolated rat middle cerebral artery. J Headache Pain. 2017; 18(1): 61.
11. Visočnik D, Zaletel M, Žvan B, Zupan M. Enhanced Hemodynamic and Clinical Response to αCGRP in Migraine Patients-A TCD Study. Front Neurol. 2021;12: 638903.
12. Zupan M, Zaletel M, Visočnik D, Žvan B. Calcitonin gene-related peptide-induced hemodynamic changes in migraine with and without aura. Acta Neurol Scand. 2021 ; 144(6): 616-22.
13. Visočnik D, Zaletel M, Žvan B, Zupan M. The Vasodilatory Response to CGRP of the Anterior and Posterior Cerebral Circulation in Migraine. Front Neurol. 2022 19; 13: 854134.
14. Petersen KA, Birk S, Lassen LH, Kruuse C, Jonassen O, Lesko L, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. Cephalalgia. 2005; 25(2):139–47.
15. M. Zaletel, G. Požlep, B. Žvan. Can We Descriminate Migraine Susceptibile to CGRP Antagonism? 16th European Headache Congress. 2022; abstract book:P265.
16. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M. Migraine induction with calcitonin gene-related peptide in patients from erenumab trials. J Headache Pain. 2018; 19(1): 105.
17. Cernuda-Morollón E, Martínez-Camblor P, Ramón C, Larrosa D, Serrano-Pertierra E, Pascual J. CGRP and VIP levels as predictors of efficacy of Onabotulinumtoxin type A in chronic migraine. Headache. 2014; 54(6): 987-95.
18. Pellesi L, Al-Karagholi MA, De Icco R, Chaudhry BA, Lopez CL, Snellman J, Hannibal J, Amin FM, Ashina M. Plasma Levels of CGRP During a 2-h Infusion of VIP in Healthy Volunteers and Patients With Migraine: An Exploratory Study. Front Neurol. 2022; 13: 871176.
19. Waschek JA, Baca SM, Akerman S. PACAP and migraine headache: immunomodulation of neural circuits in autonomic ganglia and brain parenchyma. J Headache Pain. 2018; 19(1): 23.
20. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M. Migraine induction with calcitonin gene-related peptide in patients from erenumab trials. J Headache Pain. 2018 Nov 8;19(1):105.

Anticoagulant therapy in secondary stroke prevention in patients with atrial fibrillation

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Abstract:

Background: Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. It is not completely known whether ischemic stroke patients with AF that use oral anticoagulant therapy are at increased risk for further recurrent strokes or how ongoing secondary prevention should be managed. The aim of this study is to determine the role of anticoagulant therapy in secondary stroke prevention in patients with AF.

Materials and Methods: A retrospective analysis was made of 98 patients with acute stroke and AF hospitalized at the University Clinic for Neurology in Skopje, N. Macedonia at the Department of Urgent Neurology in the period from 2019 to 2022. Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke. In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale).

Results: The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (newly diagnosed AF) patients with a predominance of mild stroke, mild disability, but without proven statistical significance ($p>0.05$). It was also found that even though the patients were treated with anticoagulant therapy, they still had developed a stroke.

Conclusion In this study, it was concluded that patients, despite receiving anticoagulant therapy, still had developed a stroke. It might be related with incompliance, reduced pharmacological efficacy of the anticoagulant in individual patients, or other factors such as alternative stroke mechanisms (eg, small vessel occlusion). Regular monitoring and good patient education are important for successful treatment.

Keywords: atrial fibrillation, stroke, anticoagulant therapy, secondary prevention

Sažetak:

Antikoagulantna terapija u sekundarnoj prevenciji moždanog udara u bolesnika s fibrilacijom atrija

Uvod: Fibrilacija atrija (FA) jedan je od najvažnijih čimbenika rizika za ishemijski moždani udar. Nije u potpunosti poznato jesu li bolesnici koji su preboljeli moždani udar i imaju FA radi koje uzimaju oralnu antikoagulantnu terapiju pod većim rizikom ponovnih moždanih udara ili kako bi se trebalo

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postupati s postojećom sekundarnom prevencijom. Cilj ovog istraživanja je odrediti ulogu antikoagulantne terapije u sekundarnoj prevenciji moždanog udara u bolesnika s FA.
Materijali i metode: Provedena je retrospektivna analiza 98 bolesnika s moždanim udarom i FA hospitaliziranih na Sveučilišnoj klinici za neurologiju u Skopju, Sj. Makedonija, na Odjelu za hitnu neurologiju u periodu od 2019. do 2022. Godine. U analizu su uključeni i drugi pokazatelji poput neurološkog deficita kvantificiranog NIHSS skalom (engl. National Institutes of Health Stroke Scale), stanje svijesti procijenjeno GCS zbrojem (engl. Glasgow Coma Scale/Score) i stupanj neurološkog deficita kvantificarnog pomoću mRS (engl. Modified Rankin Scale).
Rezultati: Rezultati su pokazali da je su bolesnici u grupi 1A (poznata FA) imali češći srednje težak do težak moždani udar (kvantificiran NIHSS zbrojem), srednje težak neurološki deficit (kvantificiran mRS zbrojem), niži GCS zbroj, naspram bolesnika u skupiini 1B (novootkrivena FA) koji su češće imali blaži moždani udar, blaži neurološki deficit, ali bez statističkog značaja (p>0.05). Iako su bolesnici bili na antikoagulantnoj terapiji, svejedno su razvili moždani udar.
Zaključak: Prema našim rezultatima, unatoč antikoagulantnoj terapiji bolesnici su razvili moždani udar. Ovo može biti povezano s nekomplijentnosti, smanjenom farmakološkom učinkovitosti antikoagulantnih lijekova u pojedinih bolesnika ili drugih čimbenicima poput alternativnih mehanizama za razvoj moždanog udara (npr. okluzija malih krvnih žila). Redovito praćenje i dobra edukacija bolesnika su važni za uspješno liječenje.

Ključne riječi: fibrilacija atrija, moždani udar, antikoagulantna terapija, sekundarna prevencija

Introduction

Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. It is known that patients with AF have a 5 times higher risk of having a stroke than those without AF. With the availability of modern cardiac monitoring technologies, detection of AF after stroke or transient ischemic attack (TIA) has improved significantly [1].
Although the burden of AF-related stroke is high, AF is a potentially treatable risk factor. Numerous studies have revealed that vitamin K antagonists, such as warfarin, or non-vitamin K antagonist oral anticoagulants (NOACs), such as rivaroxaban, dabigatran, and edoxaban, reduce the risk of ischemic stroke. Based on these data, current guidelines recommend warfarin or NOACs over aspirin for stroke prevention in the high-risk patients with AF [2].
It is not known whether patients with ischemic stroke and AF, despite oral anticoagulant therapy, are at increased risk for further recurrent strokes or how ongoing secondary prevention should be managed [3].
AF causes one-fifth of ischemic strokes, with a high risk of early recurrence. Although long-term anticoagulation is highly effective for stroke prevention in AF, initiation after stroke is usually delayed by concerns over intracranial hemorrhage risk. NOACs offer a significantly lower risk of intracranial hemorrhage than other anticoagulants, potentially allowing earlier anticoagulation and prevention of recurrence, but the safety and efficacy of this approach has not been established [4].
Despite strong evidence of efficacy, OAC use is limited by nonprescription (≈50% patients do not receive OAC, despite an appropriate indication), nonadherence (30% 1-year discontinuation for warfarin), and subtherapeutic dosing (≈25%–38% of warfarin-treated patients) [5].

Aim

The aim of this study is to determine the role of anticoagulant therapy in secondary stroke prevention in patients with AF.

Materials and Methods

A retrospective analysis was made of 98 acute stroke patients with AF hospitalized at the University Clinic of Neurology in Skopje, N. Macedonia, at the Department of Urgent Neurology in the period from 2019 to 2022.
Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke (ischemic, hemorrhagic). Depending on whether it is known AF or newly diagnosed AF, we divided the patients into two groups: 1A known atrial fibrillation and 1B newly diagnosed atrial fibrillation (AF de novo).
According to the localization of the stroke registered on computed tomography (CT) of the brain, we divided the patients into two groups: 2A patients with a stroke in the anterior circulation, 2B patients with a stroke in the posterior circulation.
In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of

Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale). Depending on the NIHSS score, we divided stroke patients into 3 categories: mild stroke (1-5 points), moderate stroke (5-14 points), severe stroke (15-42 points). Depending on the GCS result, we divided the patients according to the level of consciousness into 3 groups: best response (15-9 points), coma (8-4 points), completely unresponsive (< 3 points). Depending on the mRS score, we divided the patients according to the degree of disability into: patients with mild disability (1-2 points), patients with moderate disability (3-4 points), patients with severe disability (5 points).

Statistical analysis

The data were analyzed using IBM SPSS Statistics (chi square test) and the (chi-square) test was used, which is expressed in numbers and percentages. The results are presented tabular and graphically. Statistical significance was set at $p < 0.05$.

Results

In our study, 98 patients aged 49-89 years were analyzed, of which 53.1% (52) were women and 46.9% (46) were men. 72.5% (71) of the patients had an ischemic stroke, 7.1% (7) had a hemorrhagic stroke, and 20.4% (20) had an ischemic stroke with hemorrhagic transformation. (figure 1).

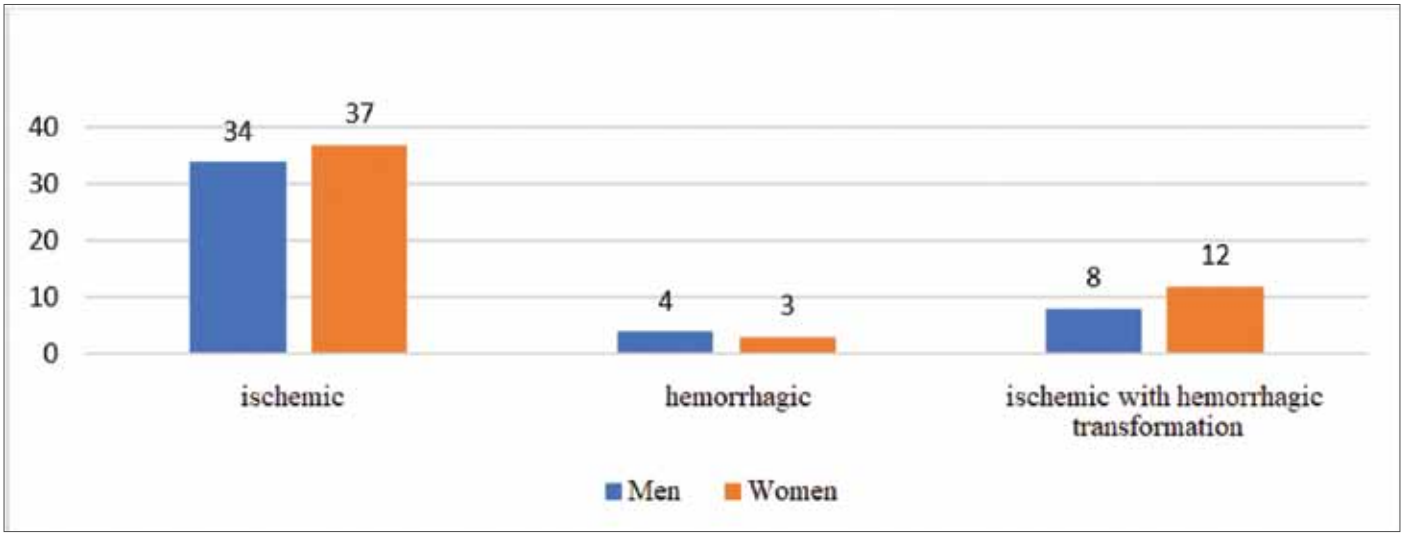

Figure 1. Distribution of the total number of patients according to gender and type of stroke

According to the localization of the stroke, 78.6% (77) of the patients had a stroke localized in the anterior circulation, and 19.4% (19) had a stroke localized in the posterior circulation. (table 1)

Table 1. Localization of the stroke and the number of patients

Localization of stroke / Gender	1 –Anterior circulation No.	%	2 –Posterior circulation No.	%	3 - Thrombolysed No.	%	In total No.	In total %
1 -Male	36	36,7%	8	8,2%	2	2,0%	46	**46,9%**
2 -Female	41	41,8%	11	11,2%		0,0%	52	**53,1%**
Total sum	**77**	**78,6%**	**19**	**19,4%**	**2**	**2,0%**	**98**	**100,0%**

Out of a total of 98 patients, 63.3% (62) had known AF (group 1A), of which 26.5% (26) were men, and 36.7% (36) were women. In 36.7% (36) of the patients, AF was newly diagnosed during hospitalization (group 1B), of which 20.4% (20) were men, and 16.3% (16) were women (Figure 2).

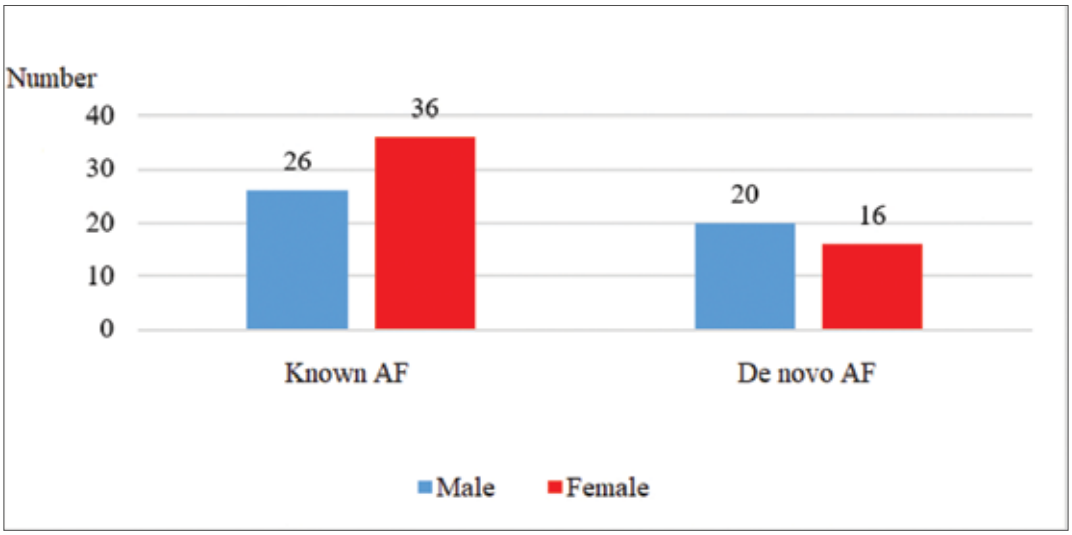

Figure 2. Patients with known versus newly diagnosed AF

X^2=1,696< X^2 (1 and 0,005)= 3,841 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and gender.
According to the score obtained from NIHSS; 25% of subjects from group 1A (known AF) had a mild stroke, 65% had a moderate stroke, 64.8% had a severe stroke. 75% of the individuals from group 1B (AF de novo) had a mild stroke, 35% a moderate stroke and 35.2% a severe stroke. (table 2, figure 3).

Table 2. NIHSS score (at discharge) of patients with known versus newly diagnosed AF.

	Known AF	Count	1	**26**	**35**	62
		% within NIHSS	25,0%	**65,0%**	**64,8%**	63,3%
	De novo AF	Count	**3**	14	19	36
		% within NIHSS	**75,0%**	35,0%	35,2%	36,7%
Total		Count	4	40	54	98
		% within NIHSS	100,0%	100,0%	100,0%	100,0%

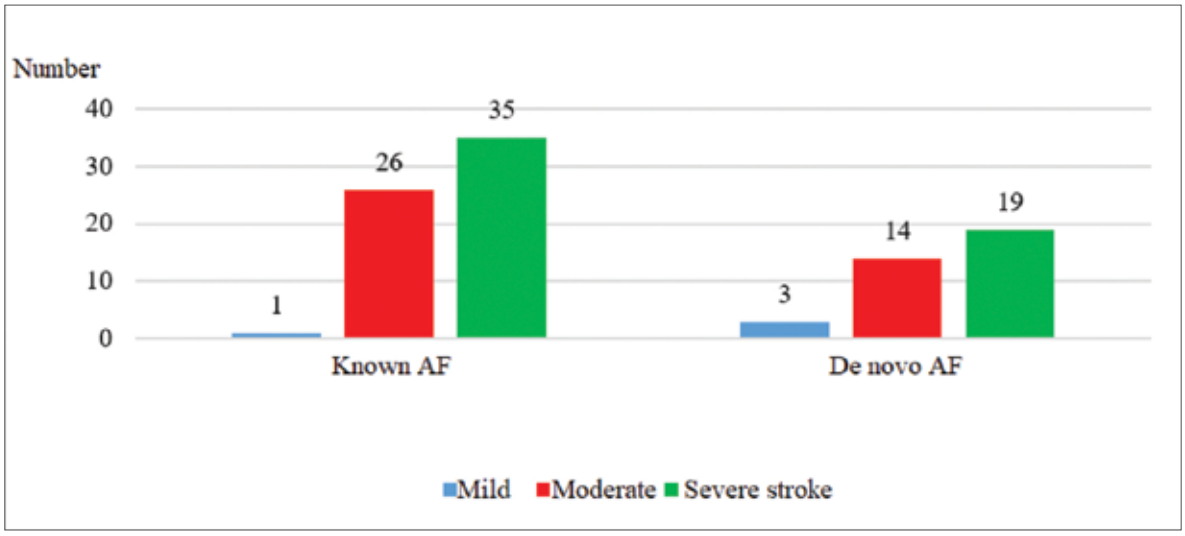

Figure 3. NIHSS score (at discharge) of patients with known versus newly diagnosed AF

X^2=2,628< X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and NIHSS.
According to the result obtained by GCS, 62% of subjects from group 1A (known AF) had the best response, 70.8% were in coma, 33.3% were completely unresponsive. 38.0% of the patients from group 1B (AF de novo) had the best response, 29.2% were in a coma, 66.7% were completely unresponsive. (Table 3, Figure 4).

Table 3. GCS result (at discharge) of patients with known versus newly diagnosed AF

			Best response	Coma	Completely unresponsive	Total
AF	Known AF	Count	**44**	**17**	1	62
		% within GCS	**62,0%**	**70,8%**	33,3%	63,3%
	De novo AF	Count	27	7	**2**	36
		% within GCS	38,0%	29,2%	**66,7%**	36,7%
Total		Count	71	24	3	98
		% within GCS	100,0%	100,0%	100,0%	100,0%

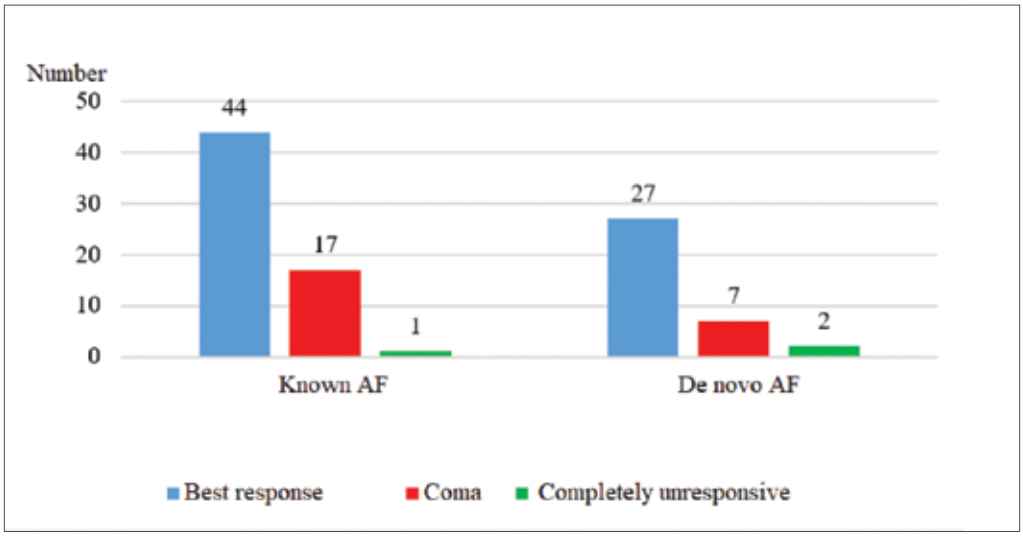

Figure 4. GCS result (at discharge) of patients with known versus newly diagnosed AF

X^2=1,799< X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and GCS.
According to the result obtained from the mRS, 50.0% of the respondents from group 1A (known AF) had light disability, 66.7% moderate disability, 62.9% severe disability. 50.0% of the respondents from group 1B (AF de novo) had mild disability, 33.3% moderate disability, 37.1% severe disability. (Table 4, Figure 5).

Table 4. mRS result (at discharge) of patients with known versus newly diagnosed AF

			Light disability	Moderate disability	Severe disability	Total
	Known AF	Count	2	**16**	**44**	62
		% within mRS	50,0%	**66,7%**	**62,9%**	63,3%
	De novo AF	Count	2	8	26	36
		% within mRS	50,0%	33,3%	37,1%	36,7%
Total		Count	4	24	70	98
		% within mRS	100,0%	100,0%	100,0%	100,0%

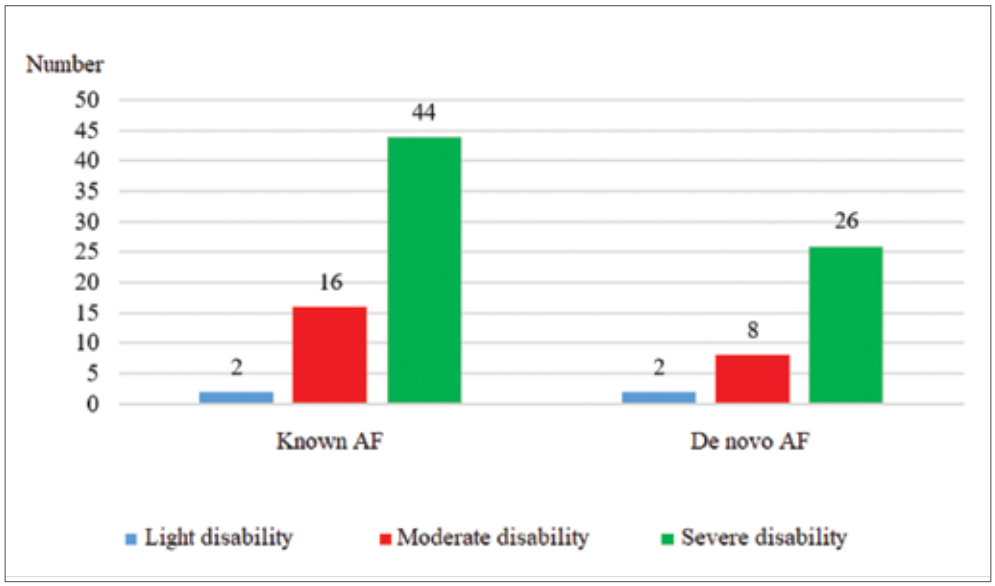

Figure 5. mRS result (at discharge) of patients with known versus newly diagnosed AF

X^2=0,427 < X^2 (2 and 0,05)= 5,991 and p>0,05
H0 (null hypothesis) is accepted. There is no association between AF and mRS.

According to therapy before admission, 45.5% of group 1A (Known AF) and 54.5% of group 1B (AF de novo) received antiaggregation therapy. Anticoagulant therapy received 97.5 % of patients with known AF and 2.5% of patients with AF de novo. Patients who did not receive therapy were 36.1% in group 1A and 63.9% in group 1B.

Table 5. Therapy before hospital admission

			Antiaggregation therapy	Anticoagulant therapy	No therapy
	Known AF	Count	10	39	13
		% within therapy before admission	45,5%	**97,5%**	36,1%
	De novo AF	Count	12	1	23
		% within therapy before admission	**54,5%**	2,5%	63,9%
Total		Count	22	40	36
		% within therapy before admission	100,0%	100,0%	100,0%

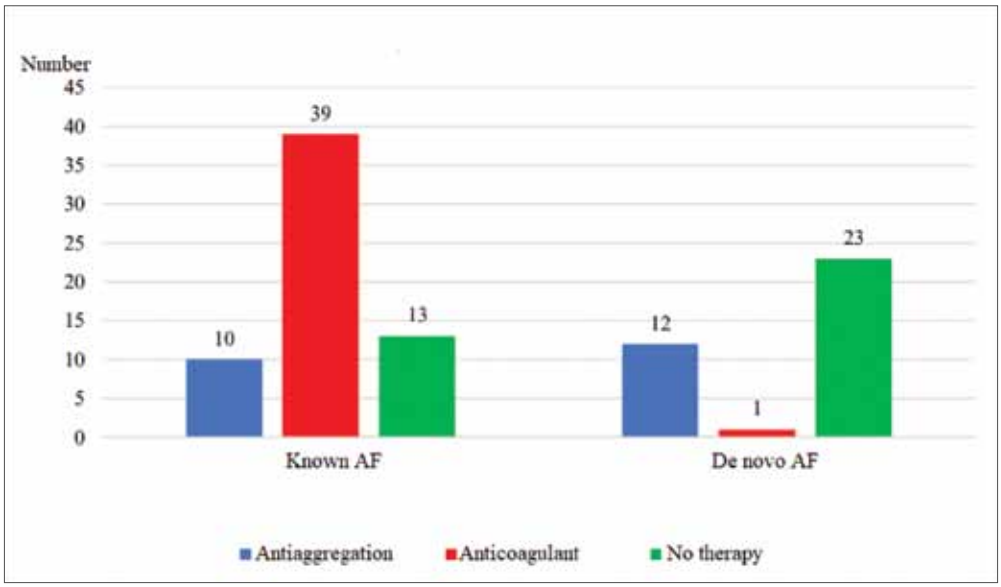

Figure 6. Therapy before hospital admission

X^2=34,597< X^2 (2 and 0,005)= 5,991 and p<0,05
H0 (null hypothesis) is rejected and H1 (working or alternative hypothesis) is accepted.
There is association between AF and pre-admission therapy.

Discussion

In our study, in the period from 2019 to 2022, 98 patients with AF were hospitalized and treated at the Department of Urgent Neurology, due to a registered acute stroke. This study includes patients with AF. Other risk factors for acute stroke, such as diabetes mellitus, hypertension, hyperlipidemia, were not analyzed in the study. Also, the results obtained with NIHSS, GCS and mRS were obtained when the patients were discharged from the hospital. The results showed that 36.7% (36) of the subjects were diagnosed with AF for the first time. The largest number of patients had ischemic stroke (72.5%), but the rate of patients with ischemic stroke with hemorrhagic transformation (20.4%) is also significant. In our group of patients dominates a stroke in anterior circulation (78.6%).
The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (AF de novo) patients with a predominance of mild stroke, mild disability, but without proven statistical significance (p>0.05).
Also it was concluded that patients, despite receiving anticoagulant therapy, still had a stroke. It might be related with noncompliance, reduced pharmacological efficacy of the anticoagulant in individual patients, or other factors such as alternative stroke mechanisms (eg, small vessel occlusion).
One of the first studies to ask the question, "Why do strokes occur in patients with atrial fibrillation who receive anticoagulant therapy?" is the study by David J Seiffge et al.
The study suggested that one possible reason is the failure to follow the prescribed anticoagulation therapy before the initial event. A significant majority (73%) of patients using VKA medication before the initial event had INR levels below the therapeutic range, which suggests poor adherence to the treatment regimen. Among those patients who continued using VKA after the event, 61% experienced further recurrent ischemic strokes with subtherapeutic INR values, indicating that poor adherence might have played a role, despite their prior experience of a significant outcome event, i.e., ischemic stroke. However, it's important to note that patients who initiate NOACs for secondary prevention typically demonstrate high adherence rates, making this less likely to be a complete explanation. Additionally, patients who had not previously used oral anticoagulants (OAC) before experiencing a stroke were found to have lower adherence rates compared to those with prior anticoagulant use, which contradicts the direction of bias suggested by our findings. Furthermore, a recent analysis in a study conducted in Japan revealed that in patients taking VKA, having an INR of ≥2.0 at the onset of a stroke was linked to a higher risk of recurrent ischemic stroke [3].
The study also says that genetic variability could be a cause of susceptibility to recurrent stroke in patients with AF. "Two genes (CYP2C9 and VKORC1) may play a role in individual patient response to and efficacy of VKA, but no such variability of response is known for NOACs. However, most patients who changed anticoagulation after the event were switched from VKA

to a NOAC (76%), so a genetic variability in 1 of the aforementioned genes is not likely to explain the high continued ischemic stroke risk we observed"[3].
A study from Oldgren et al. concluded that early initiation was noninferior to delayed start of NOAC after acute ischemic stroke in patients with AF [6]. Numerically lower rates of ischemic stroke and death and the absence of symptomatic intracerebral hemorrhages implied that the early start of NOAC was safe and should be considered for acute secondary stroke prevention in patients eligible for NOAC treatment.
The study is known as TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation - registry-based, randomized, noninferiority, open-label, blinded end-point study at 34 stroke units using the Swedish Stroke Register for enrollment and follow-up). Within 72 hours from stroke onset, patients were randomized to early (≤4 days) or delayed (5-10 days) NOAC initiation, with choice of NOAC at the investigators' discretion. The primary outcome was the composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality at 90 days. The prespecified noninferiority margin was 3%. Secondary outcomes included the individual components of the primary outcome [6].
Other study (Optimal timing of anticoagulation after acute ischemic stroke with atrial fibrillation (OPTIMAS)) investigated whether early treatment with a direct oral anticoagulant, within four days of stroke onset, is as effective or better than delayed initiation, 7 to 14 days from onset, in atrial fibrillation patients with acute ischemic stroke. The primary outcome is a composite of recurrent stroke (ischemic stroke or symptomatic intracranial hemorrhage) and systemic arterial embolism within 90 days. Secondary outcomes include major bleeding, functional status, anticoagulant adherence, quality of life, health and social care resource use, and length of hospital stay [4].
Data from Paciaroni et al. showed that the best time for initiating anticoagulation treatment for secondary stroke prevention is 4 to 14 days from stroke onset. Moreover, patients treated with oral anticoagulants alone had better outcomes compared with patients treated with low molecular weight heparins alone or before oral anticoagulants [7].
A study from Klijn et al. suggests that assessing the size and severity of the index infarct or stroke is crucial before deciding on measures to reduce the risk of hemorrhagic transformation of the infarct or other intracranial bleeding[8]. While studies have linked hemorrhagic transformation and infarct size to poorer outcomes [7], there is a lack of randomized data to confirm that early anticoagulation poses greater risks, potentially leading to more harm in patients with larger infarcts. Nevertheless, in the absence of definitive data, many expert clinicians currently recommend taking into account stroke severity and infarct size when determining the optimal timing for anticoagulation [8].
For patients with mild strokes and small infarcts (<1.5 cm), some experts suggest that anticoagulation treatment may be suitable around the third or fourth day following the initial stroke.
In cases of moderate infarcts, it is recommended to initiate anticoagulation treatment around the seventh day from the initial stroke.
In situations involving large infarcts, it may be advisable to delay anticoagulation treatment for up to 14 days after the initial stroke [8].
According to the European Heart Rhythm Association guidelines, for patients with TIA and AF, VKAs or NOACs can be started as early as the first day. For those already on VKAs or NOACs, treatment can continue due to a low risk of intracranial hemorrhage (ICH). For patients with mild strokes (NIHSS<8), NOACs can be initiated within three days or after ruling out ICH through imaging (computed tomography or magnetic resonance imaging). For moderate strokes (NIHSS 8–16), anticoagulation can commence at 5–7 days, and for severe strokes (NIHSS > 16), it may be delayed until 12–14 days.
Recently published ELAN study was an open-label trial at 103 sites in 15 countries to analyze the effect of early vs later initiation of NOACs in persons with AF who have had an acute ischemic stroke [9]. They included 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke). Of them, 1006 were assigned to early anticoagulation (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) and 1007 on later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke). The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days. By 30 days, a primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group. Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days. Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days. Authors concluded that the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days ranged from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs.
Two large randomized intervention studies (IST and CAST) have shown that administering aspirin within 48 hours of a stroke only marginally reduces case fatality and the recurrence of strokes [10,11]. A meta-analysis revealed a slight reduction in the combined outcome of death or non-fatal recurrent stroke (nine per 1000 patients treated). This benefit was observed even in patients with AF. Therefore, it's reasonable to administer aspirin

(100–300 mg/day) within 48 hours after an acute ischemic stroke or TIA for short-term treatment, while awaiting the introduction of anticoagulation [10,11].
Randomized Controlled Trials (RCTs) have failed to provide evidence supporting the use of anticoagulants in patients with acute ischemic stroke within the first 48 hours of stroke onset. Therefore, in patients already taking VKAs, it may be considered to temporarily discontinue anticoagulant therapy, conduct a follow-up brain CT scan within 24–72 hours, and decide when to restart treatment based on the size of the lesion. Consequently, until more evidence becomes available, aspirin should be administered to all patients during this acute time frame [8].
They consider it reasonable to start anticoagulant therapy at day 3 or 4 from the index stroke in patients with mild stroke and small infarcts (<1.5 cm) and at day 7 for moderate infarcts. [8] For large infarcts, anticoagulation treatment might be best delayed for 14 days after the index stroke. [3]
The risk of early recurrent ischemic stroke occurring within the first 2 weeks, is higher in patients with AF than in patients with stroke resulting from other causes. In patients with AF and acute ischemic stroke, unfractionated heparin (UFH), LMWH, or heparinoids are commonly used in routine clinical practice outside clinical trials while awaiting the commencement or effect of OAC. However, RCTs indicate that in patients with acute cardioembolic stroke, early anticoagulation with UFH or LMWH is associated with increased intracranial bleeding, a non-significant reduction in recurrence of ischemic stroke, and no substantial reduction in death and disability. Furthermore, observational studies reported that patients who had received VKA alone had a significantly lower risk of bleeding events, compared with patients treated with LMWH followed by OAC [8].
According to Ahmad and Lip's study, bleeding is the most feared complication of antithrombotic therapy, and this can limit the prescription of oral anticoagulants. The HAS-BLED score is a simple tool to aid clinicians in undertaking a bleeding risk assessment and prompts them to consider the correctable risk factors for bleeding, such as labile international normalized ratios (INRs), uncontrolled hypertension and concomitant drugs. It can periodically be reassessed and has been validated in various large real-world cohorts, performing favourably compared with other bleeding risk scores. The HAS-BLED score has been incorporated into international guidelines [12].
According to one study, adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy in participants from the trials included in this meta-analysis were less than the absolute reductions in stroke. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation [13].
Although warfarin has been a highly effective treatment to reduce stroke in AF, its limitations are well known by physicians and patients. New oral anticoagulants have been shown to be convenient and to have important advantages in improving clinical outcomes, including fewer strokes, less intracranial hemorrhage, and lower mortality. These benefits are consistent whether or not patients have been on warfarin previously. Moreover, the cost appears to be acceptable, particularly in light of the major advantage with regard to convenience. Thus, the newer agents should generally be used as first-line treatment for stroke prevention in AF.
Some have suggested that although the new agents provide important benefits for patients not previously on warfarin, there is little advantage to switching if patients are tolerating warfarin with good INR control. Although on the surface this conclusion seems rational, it is not supported by the data. The benefits of the new anticoagulants were similar regardless of prior use of warfarin [14]. With dabigatran, there was no statistically significant evidence of less benefit of stroke prevention in centers with better INR control. Importantly, the benefit of dabigatran over warfarin in reducing intracranial hemorrhage appeared to be nearly identical across INR control ranges. The pattern of a consistent benefit regardless of INR control appears to be the case for rivaroxaban and apixaban as well [15].
Among new-onset AF patients, non-vitamin K antagonist oral anticoagulant use has increased and antiplatelet monotherapy has decreased. However, anticoagulation is used frequently in low-risk patients and inconsistently in those at high risk of stroke. Significant geographic variability in anticoagulation persists and represents an opportunity for improvement [16].
We should acknowledge the various limitations of this study. First, this was a retrospective observational analysis. Unlike randomized studies, the selection of patients and undocumented confounding factors could affect the validity of our findings. However, it was impossible to randomize patients with stroke and AF. Secondly, there were not studies that examine the GCS score on patients with known AF and AF de novo.

Conclusion

Oral anticoagulation substantially reduces the risk for ischemic stroke in patient with AF. Nevertheless, patients with AF may still have an ischemic stroke despite taking oral anticoagulants. This is often regarded as a treatment failure, whose mechanisms include incompliance, reduced pharmacological efficacy of the anticoagulant in individual patients or other factors such as alternative stroke mechanisms (eg, small vessel occlusion). Anticoagulant therapy can be a challenging drug to manage, but if used appropriately it can be effective for the prevention of stroke associated with AF. Regular monitoring and good patient education are important for successful treatment.

References

1. Xiao-Meng Yang, Zhen-Zhen Rao, Hong-Qiu Gu, Xing-Quan Zhao, Chun-Juan Wang, Li-Ping Liu, Chelsea Liu, Yi-Long Wang, Zi-Xiao Li, Rui-Ping Xiao, Yong-Jun Wang. Atrial Fibrillation Known Before or Detected After Stroke Share Similar Risk of Ischemic Stroke Recurrence and Death. 2019;50:1124–1129
2. O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, Guyatt G, Gould L, D'Uva C, Kapral M, Silver F; Investigators of the Registry of the Canadian Stroke Network. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol. 2006 Sep;5(9):749-54. doi: 10.1016/S1474-4422(06)70536-1. PMID: 16914403.
3. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, Macha Md K, Tsivgoulis G, Ambler G, Arihiro S, Bonati LH, Bonetti B, Kallmünzer B, Muir KW, Bovi P, Gensicke H, Inoue M, Schwab S, Yaghi S, Brown MM, Lyrer P, Takagi M, Acciarrese M, Jager HR, Polymeris AA, Toyoda K, Venti M, Traenka C, Yamagami H, Alberti A, Yoshimura S, Caso V, Engelter ST, Werring DJ; RAF, RAF-DOAC, CROMIS-2, SAMURAI, NOACISP, Erlangen, and Verona registry collaborators. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation. Ann Neurol. 2020 Feb 12;87(5):677–87. doi: 10.1002/ana.25700. Epub ahead of print. PMID: 32052481; PMCID: PMC7383617.
4. Best JG, Arram L, Ahmed N, Balogun M, Bennett K, Bordea E, Campos MG, Caverly E, Chau M, Cohen H, Dehbi HM, Doré CJ, Engelter ST, Fenner R, Freemantle N, Hunter R, James M, Lip GY, Murray ML, Norrving B, Sprigg N, Veltkamp R, Zaczyk I, Werring DJ; OPTIMAS investigators. Optimal timing of anticoagulation after acute ischemic stroke with atrial fibrillation (OPTIMAS): Protocol for a randomized controlled trial. Int J Stroke. 2022 Jun;17(5):583-589. doi: 10.1177/17474930211057722. Epub 2022 Jan 12. PMID: 35018878.
5. Andrade J, Khairy P, Dobrev D, Nattel S. The Clinical Profile and Pathophysiology of Atrial Fibrillation. 25 Apr 2014, 114:1453–1468.
6. Åsberg S, Hijazi Z, Norrving B, Terént A, Öhagen P, Oldgren J. Timing of oral anticoagulant therapy in acute ischemic stroke with atrial fibrillation: study protocol for a registry-based randomised controlled trial. Trials. 2017 Dec 2;18(1):581. doi: 10.1186/s13063-017-2313-9. PMID: 29197413; PMCID: PMC5712199.
7. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, Csiba L, Szabó L, Sohn SI, Tassinari T, Abdul-Rahim AH, Michel P, Cordier M, Vanacker P, Remillard S, Alberti A, Venti M, Scoditti U, Denti L, Orlandi G, Chiti A, Gialdini G, Bovi P, Carletti M, Rigatelli A, Putaala J, Tatlisumak T, Masotti L, Lorenzini G, Tassi R, Guideri F, Martini G, Tsivgoulis G, Vadikolias K, Liantinioti C, Corea F, Del Sette M, Ageno W, De Lodovici ML, Bono G, Baldi A, D'Anna S, Sacco S, Carolei A, Tiseo C, Acciarresi M, D'Amore C, Imberti D, Zabzuni D, Doronin B, Volodina V, Consoli D, Galati F, Pieroni A, Toni D, Monaco S, Baronello MM, Barlinn K, Pallesen LP, Kepplinger J, Bodechtel U, Gerber J, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Mosconi MG, Bubba V, Silvestri I, Lees KR. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. Stroke. 2015 Aug;46(8):2175-82. doi: 10.1161/STROKEAHA.115.008891. Epub 2015 Jun 30. PMID: 26130094.
8. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Kõrv J, Lal A, Putaala J, Werring DJ. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. Eur Stroke J. 2019 Sep;4(3):198-223. doi: 10.1177/2396987319841187. Epub 2019 Apr 9. PMID: 31984228; PMCID: PMC6960695.
9. Fischer U, Koga M, Strbian D, Branca M, Abend S, Trelle S, Paciaroni M, Thomalla G, Michel P, Nedeltchev K, Bonati LH. Early versus later anticoagulation for stroke with atrial fibrillation. New England Journal of Medicine. 2023 May 24.
10. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997 May 31;349(9065):1569-81. PMID: 9174558.
11. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997 Jun 7;349(9066):1641-9. PMID: 9186381.
12. Ahmad Y, Lip GY. Anticoagulation in Atrial Fibrillation. Arrhythm Electrophysiol Rev. 2012 Sep;1(1):12-16. doi: 10.15420/aer.2012.1.12. PMID: 26835023; PMCID: PMC4711491.
13. Katritsis DG, Gersh BJ, Camm AJ. Anticoagulation in Atrial Fibrillation - Current Concepts. Arrhythm Electrophysiol Rev. 2015 Aug;4(2):100-7. doi: 10.15420/aer.2015.04.02.100. PMID: 26835109; PMCID: PMC4711523.
14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering

Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. doi: 10.1056/NEJMoa0905561. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877. PMID: 19717844.

15. Granger B. C, Armaganijan V. L. Newer Oral Anticoagulants Should Be Used as First-Line Agents to Prevent Thromboembolism in Patients With Atrial Fibrillation and Risk Factors for Stroke or Thromboembolism. 3 Jan 2012; 125:159–164
16. Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ, Ezekowitz MD, Fonarow GC, Gersh BJ, Goldhaber S, Haas S, Hacke W, Kowey PR, Ansell J, Mahaffey KW, Naccarelli G, Reiffel JA, Turpie A, Verheugt F, Piccini JP, Kakkar A, Peterson ED, Fox KAA; GARFIELD-AF; ORBIT-AF Investigators. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. Am Heart J. 2017 Dec;194:132-140. doi: 10.1016/j.ahj.2017.08.011. Epub 2017 Aug 24. PMID: 29223431.

Extracorporeal shock wave lithotripsy – a non-invasive treatment modality for urolithiasis in University Hospital Centre Zagreb

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Abstract:

Urolithiasis is one of the most common pathologies in urology, with high prevalence and recurrence rates. Urinary tract stones differ in their symptomatology, number, size, location, structure, as well as in some other characteristics and thus in the way of their treatment. Computed tomography (CT) is considered the best method of diagnosing stones and choosing the optimal treatment method for patients with urinary tract stones. Extracorporeal shock-wave lithotripsy (ESWL) is an effective treatment modality in patients with stones less than 20 mm in size. Because of the characteristics of stones, in some cases, more than one procedure is needed to achieve complete disintegration. From January 2019 to November 2023, 3,844 EWSL treatments for urinary tract stones were performed at the Clinical Hospital Center Zagreb Urology Clinic. The average stone size was 0.9 cm, and the average age of the patients was 53 years. One ESWL treatment was needed in 22%, two in 21%, and three in 18% of our patients. The procedure could not be performed due to the radiolucency of stones on X-ray images in 10% of patients, while it was interrupted in 3% due to pain, and in 3% of patients due to hypertension.

In patients with unsuccessful extracorporeal treatments or an initially high burden of stones, some of the minimally-invasive, endoscopic methods are advised for further or initial treatment, such as ureteroscopy (URS), flexible ureterorenoscopy (FURS), percutaneous nephrolithotomy (PCNL), and endoscopic combined intrarenal surgery (ECIRS).

ESWL is considered an effective, non-invasive treatment modality in selected patients, with good stone-free rates and low complication rates, which can be performed as an outpatient procedure.

Keywords: Extracorporeal shock-wave lithotripsy; ESWL; urolithiasis

Sažetak:

Ekstrakorporalna litotripsija udarnim valom – neinvazivni način liječenja urolitijaze u KBC-u Zagreb

Urolitijaza je jedna od najčešćih patologija u urologiji, s visokom prevalencijom i stopom recidiva. Kamenci mokraćnog sustava razlikuju se po svojoj simptomatologiji, broju, veličini, smještaju, strukturi, ali i po nekim drugim karakteristikama pa tako i po načinu liječenja. Kompjuterizirana tomografija (CT) smatra se najboljom metodom dijagnostike kamenaca i odabira optimalne metode liječenja bolesnika s kamencima mokraćnog sustava. Ekstrakorporalna litotripsija udarnim valom (ESWL) je efikasan način liječenja bolesnika s kamencima manjim od 20 mm. U nekim je slučajevima, zbog

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svojstava kamenaca potrebno više od jednog postupka, kako bi se postigla potpuna dezintegracija. Od siječnja 2019. do studenog 2023. u Klinici za urologiju KBC-a Zagreb obavljena su 3844 EWSL tretmana kamenaca mokraćnog sustava. Prosječna veličina kamenca je bila 0,9 cm, a prosječna dob pacijenata 53 godine. Jedan ESWL tretman bio je potreban u 22%, dva u 21%, a tri u 18% naših pacijenata. Zahvat se nije mogao izvesti zbog radiolucencije kamenaca na rendgenskim snimkama u 10% pacijenata, dok je u 3% prekinut zbog boli, a u 3% bolesnika zbog hipertenzije.
U bolesnika s neuspješnim izvantjelesnim tretmanima ili inicijalno velikim kamencima mokraćnog sustava savjetuju se neke od minimalno invazivnih, endoskopskih metoda naknadnog, odnosno inicijalnog liječenja, kao što su ureteroskopija (URS), fleksibilna ureterorenoskopija (FURS), perkutana nefrolitotomija (PCNL) ili endoskopska kombinirana intrarenalna kirurgija (ECIRS).
ESWL se smatra učinkovitim, neinvazivnim modalitetom liječenja u odabranih pacijenata, s dobrim rezultatima i malom stopom komplikacija koji se može izvesti kao ambulantni postupak.

Ključne riječi: vantjelesno mrvljenje kamenaca; ESWL; urolitijaza

Introduction

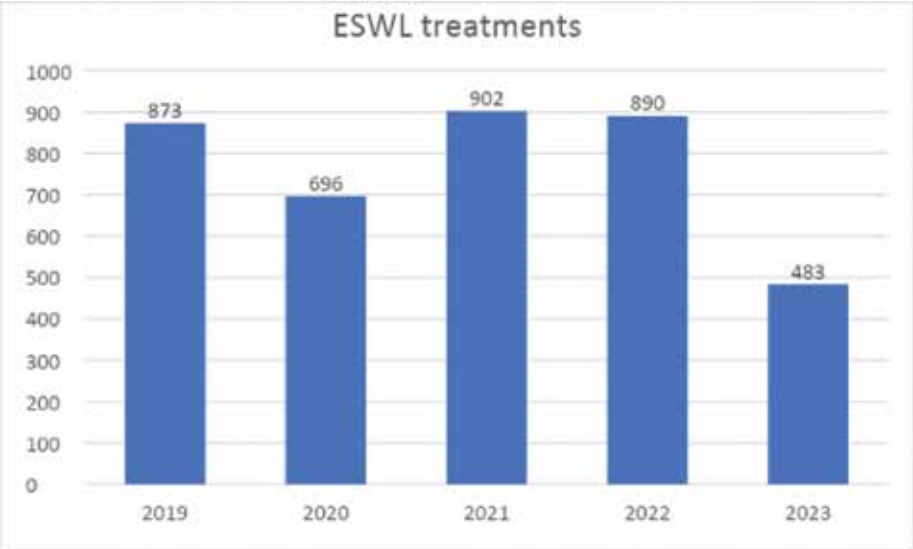
Urolithiasis is one of the most common pathologies in urology, with high prevalence and recurrence rates. Although it is rarely a life-threatening disease, it is the cause of a large number of visits to the general practitioner, but also to the urologist, and to the emergency urology service in the hospital.
Kidney stones are a complex disease, and they can be divided into several subgroups. For example, depending on the cause, they can be divided into infectious, non-infectious and genetic. The composition of the stone is often mixed, consisting of various substances and mineral components, most often calcium, carbonate, phosphate, ammonia, sodium, and magnesium.
Many patients with urolithiasis can be asymptomatic, but the most common clinical symptom is renal colic (1). It is often associated with nausea and vomiting, dysuria, and the presence of blood in the urine. After medical history and physical examination, ultrasound (US) should be used as the initial imaging modality of choice, primarily to check for hydronephrosis. It has a sensitivity of 45% for renal and ureteral stones, and specificity of 94% for ureteral, and 88% for renal stones (2). The plain X-ray of the kidney, ureter, and bladder has a sensitivity and specificity of 44-77%, but it is helpful in the differentiation of radiolucent stones and during follow-up (3). CT is the "gold standard" for urinary stones diagnosis, and it is mandatory for planning the right approach to urolithiasis treatment. It can determine stone density, shape, location, and size, as well as the surrounding anatomy and skin-to-stone distance (4). Immediate imaging is indicated in patients with fever and/or solitary kidney with hydronephrosis. A low-dose CT can be used to reduce radiation risk. A CT urography should be used if an anomaly or variation of urinary tract anatomy is suspected. The active treatment of kidney stones is indicated in patients with stones larger than 15 mm, or with growing stones on follow-up, and in those with symptomatic stones less than 15 mm in size. Obstruction or infections caused by stones are an indication for a more urgent intervention. Also, the patient's social situation, profession and preferences need to be considered when choosing between observation and active treatment.

Materials and methods

The data from the protocol book of patients treated with extracorporeal shock wave lithotripsy (ESWL) in the Department of Urology was analyzed for a time period from January 2019 until November 2023. The data regarding number of procedures, stone size and position, patient age and relevant clinical information was collected. Data were analyzed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA).

Results

There were a total of 3,844 procedures, over a period of almost 5 years. Figure 1 shows the distribution of procedures in each year. The average patient age was 52 years, and the average stone size was 0.9 cm. The stone location distribution is shown in figure 2. Figure 3 shows the proportion of repeated procedures, that is, the number of procedures required for stone destruction. One procedure was sufficient in 22% of patients, two in 21%, and three in 18% of patients. Others required more than three procedures. In 16% of patients, the procedure was canceled or interrupted because of radiotransparency on X-ray (10%), hypertension (3%) and pain (3%).



ESWL – extracorporeal shock-wave lithotripsy

Figure 1. Number of ESWL treatments during the years

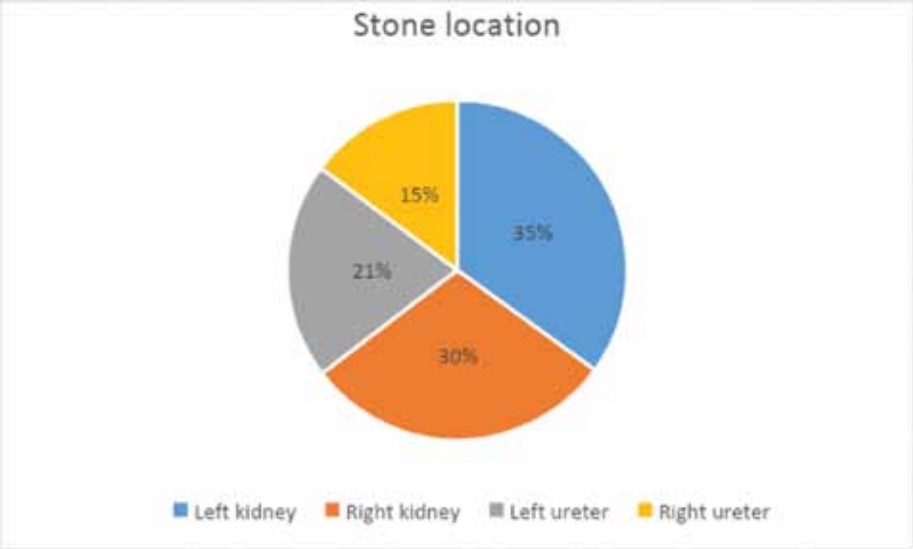


Figure 2. Distribution of stone locations

Figure 3. Number of ESWL procedures

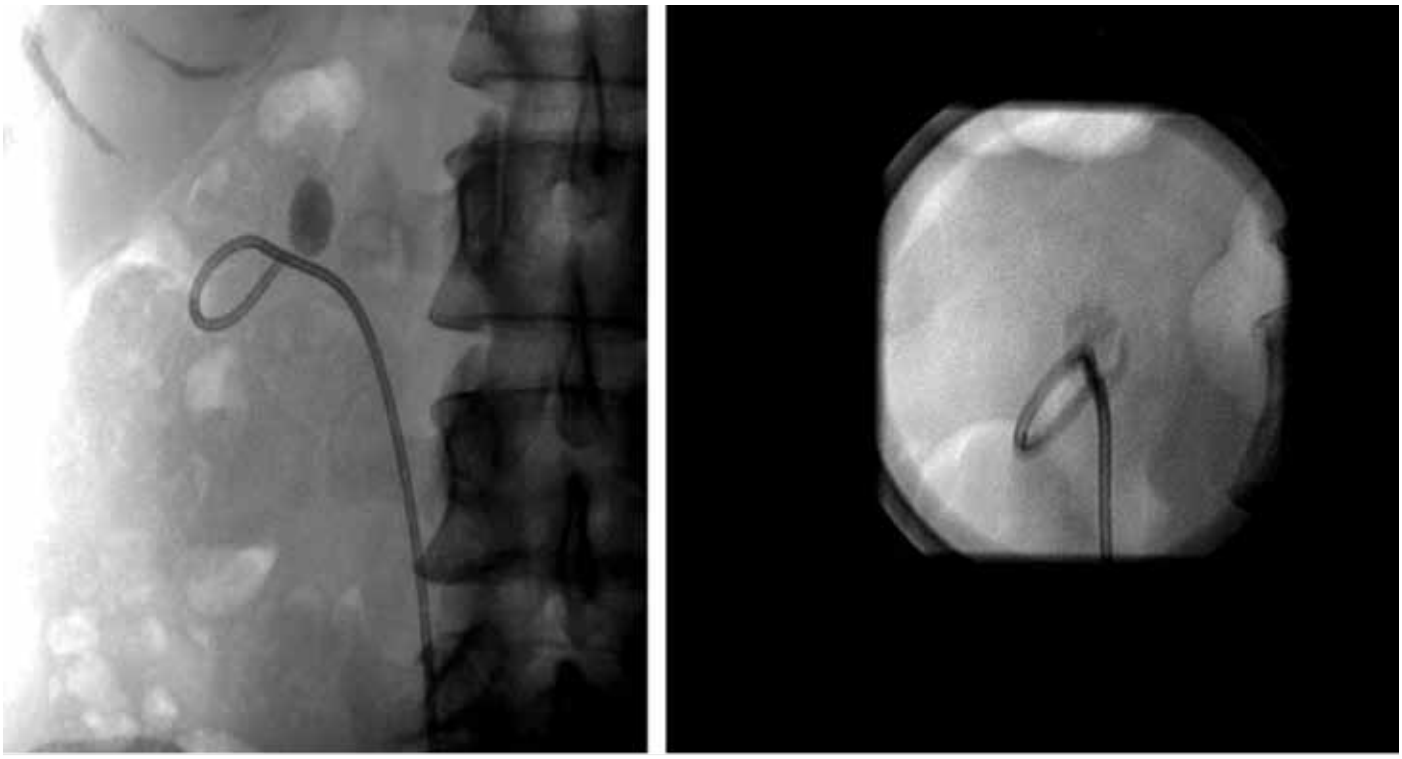


Figure 3. X ray imaging of 16 mm kidney stone before ESWL (on the left) and after ESWL, with visible fragmentation (on the right).

Discussion

Extracorporeal shock wave lithotripsy is a non-invasive method for the treatment of urolithiasis. The lithotripter device delivers shock waves to the targeted stone in the kidney or ureter. The beginning of ESWL dates to the middle of the last century and is linked to Claude Dornier. Dornier was a German scientist who did research for the aircraft industry and discovered shock waves, which resulted in the first device for extracorporeal shock wave lithotripsy (5). In the 1970s and early 1980s, clinical research began, that is, the introduction of the ESWL method into clinical practice (6). A few years later, ESWL became widely used as the standard treatment for kidney stones. Today, in addition to Dornier, other large manufacturers of medical equipment such as Siemens and Storz have ESWL devices that have treated millions of patients with urinary tract stones (7).

ESWL is routinely used in University Hospital Center Zagreb since 1987. Since 2013, all procedures are performed on the Siemens Lithostar device. It is organized as an outpatient procedure. Patients first come to our urinary tract stone center, where a medical history is taken, a physical examination is performed, and medical documentation is reviewed. If there is an indication for ESWL, patients are informed about ESWL treatment and they are scheduled for it. Depending on the number of patients and the capacity of the institution, up to 5 procedures per day are carried out. There is a visible increase in a number of procedures each year, with the exception of the 2020, during the COVID-19 pandemic.

The success of ESWL depends on the size and location of the stone, as well as the composition. The last determinant is the properties of the lithotripter device itself. The result also depends on the habitus of the patient and the stone-skin distance. There is no consensus on the maximum energy applied and the number of shock waves (8). Higher energy can be applied to the ureteral stones, while the energy applied to kidney stones is lower. Lowering shock wave frequency to 60-90/min improves stone-free rates (SFR), and also lowers tissue damage (9). Reported complication rates vary between the studies, the most common being *steinstrasse* (4%-7%), regrowth of residual fragments (21%-59%), and renal colic (2%-4%) (10-12). Asymptomatic hematoma occurs in 4%-19%, while symptomatic occurs in less than 1% of cases (13). In this research, we didn't analyze exact complication rates, because of a vast number of patients and the fact that many patients came and are returned to the urology departments of other hospitals from Zagreb or from all over Croatia. However, we can state that the procedure is well tolerated by the patients, and the renal hematoma that requires hospitalization is a rare event. In the last year, we only have two cases of hematoma, and neither required intervention. Repeated sessions are feasible and often needed, even within one day for ureteral stones (14).

Although ESWL is a valuable modality for the treatment of urolithiasis, with low complication rates and additional costs, it requires good patient selection. The first criterion is stone visibility on X-ray. In our study, in 10% of cases, the EWSL could not be performed, because of the invisibility of stones on X-rays. This could be because of the radiotransparency of the stones due to their composition, meteorism, or because of spontaneous expulsion. The second criterion is the total stone burden and

position. Intake of oral anticoagulants is also a contraindication, as well as uncontrolled hypertension. Other contraindications are pregnancy, urinary tract infections, and aneurysms of the aorta, renal or iliac vessels. Patients with ureteral stones larger than 10 mm could also be eligible for ESWL, but faster stone-free status could be achieved with a more invasive approach. Kidney stones larger than 20 mm are usually not good candidates for ESWL. For patients who do not meet the criteria, a more invasive endoscopic approach is required. In UHC Zagreb, we perform all kinds of operative treatment for urolithiasis, ureteroscopy (URS), flexible ureterorenoscopy (FURS), percutaneous nephrolithotomy (PCNL), and endoscopic combined intrarenal surgery (ECIRS) which is a combination of PCNL and FURS. In isolated cases, we also use laparoscopic pyelolithotomy, while the open approach is rarely used.

Urolithiasis is a high-prevalence and high-recurrence disease. For many patients a non-invasive extracorporeal shock wave lithotripsy is the treatment modality of choice, offering good results with low complication rate. For patients with larger stones and higher stone burden, one of the more invasive methods could be a better choice. A good selection is needed in order to successfully treat patients with urolithiasis.

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References

1. Wimpissinger F, Türk C, Kheyfets O, Stackl W. The silence of the stones: asymptomatic ureteral calculi. The Journal of urology. 2007;178:1341-4; discussion 4. Epub 2007/08/21. doi: 10.1016/j.juro.2007.05.128.
2. Ray AA, Ghiculete D, Pace KT, Honey RJ. Limitations to ultrasound in the detection and measurement of urinary tract calculi. Urology. 2010;76:295-300. doi: 10.1016/j.urology.2009.12.015.
3. Heidenreich A, Desgrandschamps F, Terrier F. Modern approach of diagnosis and management of acute flank pain: review of all imaging modalities. European urology. 2002;41:351-62. Epub 2002/06/21. doi: 10.1016/s0302-2838(02)00064-7.
4. El-Nahas AR, El-Assmy AM, Mansour O, Sheir KZ. A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock wave lithotripsy: the value of high-resolution noncontrast computed tomography. European urology. 2007;51:1688-93; discussion 93-4. doi: 10.1016/j.eururo.2006.11.048.
5. Dornier MedTech. Available at: https://www.dornier.com/history/. Accessed Nov 20th 2023.
6. Chaussy C, Schmiedt E, Jocham D, Brendel W, Forssmann B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. J Urol. 1982;127:417-420.
7. Storz Medical. Available at: https://www.storzmedical.com/en/. Accessed Nov 20th 2023.
8. López-Acón JD, Budía Alba A, Bahílo-Mateu P, Trassierra-Villa M, de Los Ángeles Conca-Baenas M, de Guzmán Ordaz-Jurado D, et al. Analysis of the Efficacy and Safety of Increasing the Energy Dose Applied Per Session by Increasing the Number of Shock Waves in Extracorporeal Lithotripsy: A Prospective and Comparative Study. Journal of endourology. 2017;31:1289-94. doi: 10.1089/end.2017.0261.
9. Moon KB, Lim GS, Hwang JS, Lim CH, Lee JW, Son JH, et al. Optimal shock wave rate for shock wave lithotripsy in urolithiasis treatment: a prospective randomized study. Korean journal of urology. 2012;53:790-4. Epub 2012/11/28. doi: 10.4111/kju.2012.53.11.790.
10. Tan YM, Yip SK, Chong TW, Wong MY, Cheng C, Foo KT. Clinical experience and results of ESWL treatment for 3,093 urinary calculi with the Storz Modulith SL 20 lithotripter at the Singapore general hospital. Scand J Urol Nephrol. 2002;36:363-7. doi: 10.1080/003655902320783872.
11. Osman MM, Alfano Y, Kamp S, Haecker A, Alken P, Michel MS, et al. 5-year-follow-up of patients with clinically insignificant residual fragments after extracorporeal shockwave lithotripsy. European urology. 2005;47:860-4. doi: 10.1016/j.eururo.2005.01.005.
12. Sayed MA, el-Taher AM, Aboul-Ella HA, Shaker SE. Steinstrasse after extracorporeal shockwave lithotripsy: aetiology, prevention and management. BJU international. 2001;88:675-8. doi: 10.1046/j.1464-4096.2001.02435.x.
13. Dhar NB, Thornton J, Karafa MT, Streem SB. A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. The Journal of urology. 2004;172:2271-4. doi: 10.1097/01.ju.0000143459.03836.2d.
14. Abdelbary AM, Al-Dessoukey AA, Moussa AS, Elmarakbi AA, Ragheb AM, Sayed O, et al. Value of early second session shock wave lithotripsy in treatment of upper ureteric stones compared to laser ureteroscopy. World journal of urology. 2021;39:3089-93. doi: 10.1007/s00345-020-03560-x.

CAR T Cell Therapy in Hematology: Navigating Toxicities and Deciphering Patient Experiences Through Patient-Reported Outcomes

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Abstract:

This review examines the role of Patient-Reported Outcomes (PROs) in measuring toxicities of Chimeric Antigen Receptor T Cell Therapy (CAR T) for hematological malignancies. While highlighting the complex task of understanding the pathophysiology of CAR T's unique adverse events (AEs), the discussion focuses on the need for precise characterization of the diverse symptomatology associated with individual CAR T syndromes and the importance of capturing patient experiences with these side effects using PRO instruments. This review underscores the continuous search for an ideal PRO tool that is effective in detecting both early changes and late toxicities; stressing the importance of monitoring PROs soon after therapy to gather data on acute toxicity, enabling timely interventions that could reduce symptom severity. The assessment of PROs at later stages is also highlighted as crucial for evaluating long-term quality of life (QoL), especially in terms of neurocognitive effects. The narrative review identifies a gap in current PRO tools not specifically tailored for CAR T therapy and calls for further research to develop a comprehensive set of symptoms for monitoring in various studies. Such efforts are vital for improving our understanding of therapy tolerability as well as for improving the treatment of these side effects. This would also enable the comparison of different CAR T products based on their response rates.

Keywords: Immunotherapy, Adoptive, Patient Reported Outcome Measures, Hematologic Neoplasms, Drug-Related Side Effects and Adverse Reactions

Sažetak:

CAR T stanična terapija u hematologiji: upravljanje toksičnostima i dešifriranje iskustava pacijenata putem ishoda koje su prijavili pacijenti

U ovom preglednom radu istražujemo ulogu Patient-Reported Outcomes (PROs) u analizi i upravljanju toksičnošću terapije CAR T stanicama u liječenju hematoloških malignih bolesti. CAR T stanična terapija otvara nove horizonte u liječenju, ali istovremeno predstavlja izazov zbog svojih specifičnih i varijabilnih nuspojava. Ovim radom pokušali smo ukazati na važnost razumijevanja patofiziologije različitih sindroma koji proizlaze iz primjene ove terapije, usmjeravajući se na bazična i klinička istraživanja. Posebno naglašavamo važnost preciznog dokumentiranja iskustava pacijenata s nuspojavama, što je ključno za razvoj i unaprjeđenje optimalnih PRO instrumenata. Ovi alati su esencijalni za učinkovito prikupljanje podataka o kratkoročnoj toksičnosti, što može značajno doprinijeti prevenciji i

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pravovremenom liječenju nuspojava, kao i za razumijevanje dugotrajnih posljedica terapije, uključujući procjenu dugoročne kvalitete života (QoL) pacijenata, s fokusom na neurokognitivne ishode. Suočeni smo s izraženim nedostatkom PRO alata koji su specifično prilagođeni potrebama pacijenata liječenih CAR T staničnom terapijom. Iz tog razloga, neophodno je intenziviranje znanstvenih napora usmjerenih na razvoj odgovarajućeg i sveobuhvatnog seta PRO alata, koji bi bio implementiran u kliničkim studijama i u svakodnevnoj kliničkoj praksi. Takav napredak ključan je za produbljivanje našeg razumijevanja tolerancije ove inovativne terapije, poboljšanja liječenja, te potencijalne prevencije ponekad fatalnih nuspojava koje mogu nastati u liječenju određenih pacijenata CAR T staničnom terapijom.

Ključne riječi: Imunoterapija, adoptivna, mjerenje ishoda koje su prijavili pacijenti, hematološke neoplazme, nuspojave i nuspojave povezane s lijekovima

Introduction - Brief Overview of CAR T-cell Therapy:

With the recent success of Chimeric Antigen Receptor T- Cell Therapy (CAR T), many researchers have delved into understanding the mechanisms and characteristics that determine this modality's efficacy and toxicity. The concept of chimeric T cell receptors dates back 35 years to Dr. Yoshikazu Kurosawa and Dr. Zelig Eshhar's teams, who pioneered the redirection of T cells to target antigens in cancer treatment. (1, 2) CAR-T therapy uses modified T cells to target antigens on tumor cells, leading to their elimination and tumor clearance. These T cells, often derived from the patient (autologous) or a donor (allogeneic), are equipped with a Chimeric Antigen Receptor (CAR) to bind specific antigens. The evolution of CAR-T began with first-generation CARs, featuring a basic T-cell activating domain. Second generation CARs added costimulatory domains to enhance function and longevity, and third-generation CARs incorporated multiple domains for improved signaling and anti-tumor effects. Fourth-generation CARs further advanced by modulating the tumor environment via specific cytokine secretion. (3-5)

Current Status in Hematologic Malignancy

CAR T marks a significant advancement for treatment of hematologic malignancies, demonstrating remarkable efficacy, particularly in relapsed/refractory (R/R) B-cell malignancies. Currently, CD19 and B-cell maturation antigen (BCMA) stand as the predominant tumor-associated targets in this therapeutic approach. The US Food and Drug Administration (FDA)'s first approval for CAR T was for tisagenlecleucel (tisa-cel), granted in 2017, in treatment of pediatric and young adults up to 25 years of age with B-cell acute lymphoblastic leukemia (B-ALL) resistant to treatment or in second or subsequent relapse with reported overall response rates of over 80%. Since this approval, six CAR T-cell therapies have been approved. Four of these, targeting the CD19 antigen, are used for treating B-cell lymphomas (diffuse large B-cell lymphoma - DLBCL, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma - PMBL, follicular lymphoma - FL, mantle cell lymphoma - MCL and ALL). These products are axicabtagene ciloleucel (axi-cel), tisa-cel, lisocabtagene maraleucel (liso-cel) and brexucabtagene autoleucel (brexu-cel). The other two, targeting BCMA, are used for treatment of multiple myeloma (MM) - idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel). (6, 7) The emergence of novel toxicities associated with CAR T products has underscored the importance of PROs in capturing and understanding these unique adverse events. This patient-centric approach is vital for a holistic understanding of the efficacy and safety of CAR T, ensuring that treatment advancements truly align with patient well-being. As such, PROs are instrumental in shaping the development, evaluation, and refinement of these innovative therapies. In this narrative review we concentrate on the challenges posed by toxicities in CAR T for hematological malignancies, emphasizing the use of PROs. There is a limited amount of such reviews and research focusing on PROs in the context of CAR T. This review seeks to fill this gap, offering a contribution to a field where extensive analysis is currently sparse.

Overview of toxicities:

With CAR-T being a novel therapeutic approach, clinicians and patients alike have adjusted to a learning curve of a new class of toxicities introduced called immune effector cell (IEC)-associated toxicities. The most frequently observed adverse events (AEs) from CAR T, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), continue to pose challenges to the broader application of this type of treatment and in everyday clinical practice since they require close inpatient monitoring by a multidisciplinary team of specialists. Additional AEs associated with CAR T include cytopenias, infections, tumor lysis syndrome (TLS), hypogammaglobulinemia, immune effector cell (IEC) associated HLH-like syndrome (IEC-HS), infusion-related reactions and anaphylaxis, secondary malignancies, and even graft-versus-host disease (GVHD). Data about the long-term consequences of therapy is particularly lacking, and in that aspect, PROs play an

especially important role. This is of particular importance, since CAR T is now being introduced earlier in the treatment algorithm (8).

CRS

The American Society for Transplantation and Cellular Therapy (ASTCT) defines CRS as "a supraphysiological response following any immunotherapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells" (9). It is a type of non-antigen-specific toxicity that arises from intense immune system activation. CRS is a common occurrence in most patients with ALL, with prevalence varying widely, ranging from 25% to 100%, depending on severity.(10, 11) CRS is the most common complication associated with CAR T. However, it occurs less frequently in patients receiving CAR T for other conditions like NHL and MM.(12)
As the name suggests, CRS revolves around the role of cytokines and its pathogenesis is not fully understood nor predictable. The term cytokine storm was first used in a scientific article on graft-*versus*-host disease (GvHD) over 30 years ago, marking the beginning of our understanding of this phenomenon (13). CRS is triggered by the release of specific cytokines, including interferon-gamma, interleukin-1 (IL-1), IL-6, IL-10, TNF-alpha and many others, primarily by activated T cells or tumor cells. This surge in proinflammatory cytokines leads to a widespread systemic inflammatory reaction, involving not only T cells but also macrophages, monocytes, dendritic cells and endothelial cells. (14, 15) The gasdermins (GSDME), pore-forming effector proteins that cause a lytic pro-inflammatory type of cell death also play a role in CRS, and animal experiments have shown that knocking down GSDME, destroying macrophages, or blocking the activation of GSDME prevents the development of CRS. (16, 17) CRS is not limited to patients undergoing cellular immunotherapy but can also affect those treated with bispecific antibodies and haploidentical allogeneic stem cell transplantation. Interestingly, a similar syndrome, akin to CRS, has been observed in patients with infectious diseases and became more widely known during the H5N1 influenza virus pandemic as well as during recent COVID19 pandemic. (18, 19)
The severity of CRS has been linked to several factors, including disease burden, quantity of CAR T-cells administered, level of T cell activation, specific molecular configuration of the CAR such as the costimulatory domain, type and intensity of lymphodepletion (LD) carried out before infusion. (20-22) Clinically, CRS is diagnosed by the presence of fever (≥38.0°C), which may be accompanied by varying degrees of hypotension, hypoxia, capillary leak and/or other signs of organ dysfunction, typically occurring between 1-14 days following CAR-T infusion. (9, 23). Originally, CRS severity was assessed using National Cancer Institute's Common Terminology for Adverse Events (NCI CTCAE) version 4.03, but this method proved inadequate for evaluating this specific adverse effect of new cancer treatment. Subsequently, alternate scales like the Penn scale and the Lee scale were introduced. The ASTCT, aiming for a standardized approach, recommended a grading system for CRS, drawing on insights from a diverse group of experts. This system is designed for application in various clinical trials and settings following treatment approval. This consensus' approach is based largely on the type of interventions that are required for patient management and grades patients into 4 groups – grade 3 and 4 requiring ICU care. (9, 24, 25) Laboratory markers can also be useful when attempting to identify the onset of CRS in a clinical setting. However, all of these markers, such as C-reactive protein (CRP), ferritin, however are non-specific and not reliable markers for diagnosing CRS. (26)

ICANS

Another major IEC-related toxicity is neurotoxicity referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS often presents as neurologic dysfunction, and can start with subtle changes such as word-finding difficulties, disorientation, issues with language comprehension and expression/expressive aphasia, difficulties with precise hand movements, tremors and drowsiness, but progress to more significant manifestations such as seizures and motor weakness.(27) The incidence of ICANS, similarly to CRS, demonstrates substantial variability, evidenced by reported frequencies ranging from 2% to 70%.(28, 29) Neurological manifestations usually commence between 3 to 6 days following CAR T infusion (30, 31). Factors indicative of a higher likelihood of developing ICANS include younger patient age, diagnosis of B-ALL, significant disease burden in the bone marrow, higher CAR T-cell dose, any prior neurological comorbidities, as well as the use of CAR T-cells that incorporate CD28 costimulatory domains.(31, 32) The underlying mechanisms of the pathophysiology of ICANS are still not well understood. In animal models, pathophysiology is hypothesized to involve endothelial cell activation and subsequent disruption of the blood-brain barrier, culminating in direct neuronal injury. Evidence supports the occurrence of vascular permeability in patients with severe ICANS. Furthermore, there are documented alterations in the angiopoietin (ANG)–TIE2 axis, a regulatory mechanism for endothelial cell activity under normal physiological conditions, that are also seen with sepsis.(33, 34) Additional evidence indicates the accumulation of von Willebrand Factor (vWF) multimers in patients experiencing severe ICANS, leading to coagulopathy (35). This process is compounded by the action of multiple pro-inflammatory cytokines. Extensive clinical research has demonstrated a significant correlation between augmented serum levels of a range of cytokines and the increased propensity for ICANS onset, including IL-2, IL-6, IL-10, IL-15 and GM-CSF.(28, 31, 34) Furthermore, in pathophysiology of ICANS, the antigens expressed by CNS cells are potentially also important. A recent

study revealed that human brain mural cells express CD19. This finding suggests that an OTOT effect might play a role in the neurotoxicity linked with CD19 CAR T-cells. However, ICANS has been reported in CAR T-cell treatments targeting not only CD19, suggesting that the occurrence of ICANS is not solely attributable to the specific target antigen, indicating the likelihood of an alternative mechanism at play.(36-38) As well as for CRS, ASTCT issued guidelines for grading ICANS based on several criteria, including the immune effector cell-associated encephalopathy (ICE) score, alterations in consciousness level, seizure occurrences, motor symptoms, and the presence of cerebral edema.(9)

Cytopenias

Post-CAR T cytopenia represents a multifaceted medical issue, demanding a holistic approach in management. Terminology related to post-CAR T cytopenias includes Persistent Cytopenia after T-cell Therapy (PCTT), CAR-T-OPENIA, and Immune Effector Cell Associated Hematotoxicity (ICAHT), with classifications typically following NCI-CTCAE v5.0. (39-41) A joint effort by EHA and EBMT led to the development of best practice recommendations and a classification system for ICAHT, based on the depth and duration of neutropenia, for both early and late cytopenia, with 30 days post-infusion being the cutoff between the two. (41) Determining the precise incidence of cytopenias post-CAR T remains challenging due to its variable range, although early cytopenias are more common than late-onset ones (42). A 2021 study by Rejeski et al. introduced the CAR-HEMATOTOX risk score, a tool for identifying patients at increased risk for prolonged cytopenias and severe infectious complications following CAR T. This study identified baseline cytopenias, high tumor burden, and elevated serum/plasma inflammatory markers as significant indicators of post-CAR T cytopenia. (43) CAR-T-cell infusion is typically preceded by LD chemotherapy, usually with agents like fludarabine and cyclophosphamide, which account for most early cytopenias. As LD chemotherapy is non-myeloablative, blood counts often recover rapidly. (44, 45) The etiology of late-onset cytopenias in CAR T-cell treatment is however multifactorial and complex. It may result from direct bone marrow inhibition by CAR T-cells or secondary to elevated inflammatory cytokine levels, as well as from bone marrow failure triggered by the immune system, as occurs in IEC-HS or due to the immune consequences of infections. Additionally, it is noteworthy that in both standard care and clinical trial settings for CD19- and BCMA-directed CAR T therapies, there is a significant association between prolonged cytopenia and severe manifestations, specifically grade 3 to 4 CRS or ICANS.(46)

CAR-HLH/ IEC-HS

To improve patient outcomes and establish a framework for investigating and comprehending the HLH-like syndrome in CAR T patients, a panel was initiated under the auspices of the ASTCT (47). Following CAR T, toxicities resembling hemophagocytic lymphohistiocytosis (HLH) occur, which are now identified as immune effector cell (IEC) associated HLH-like syndrome (IEC-HS). HLH is generally classified into two types: primary (genetic or inherited) and secondary (acquired). While familial (primary) HLH, a significant subtype of HLH in children, can also manifest in young adults, secondary HLH (sHLH) is overwhelmingly more prevalent in adults.(48, 49) sHLH in the context of CAR T has been reported with an incidence of about 3-4% (50). The pathogenesis of IEC-HS is likely attributable to dysregulated T-cell activation and an overly intense hyperinflammatory response after CAR T-cell infusion. The ASTCT panel ultimately defined IEC-HS as the emergence of a pathological and biochemical hyperinflammatory syndrome characterized by symptoms of macrophage activation/HLH, resulting from IEC therapy, and as a condition that is associated with the development or worsening of cytopenias, high ferritin levels, coagulopathy with low fibrinogen, and/or elevated liver enzymes. (47) Both CRS and IEC-HS display signs such as cytopenias, high ferritin levels, coagulation disorders, and elevated triglyceride levels. While patients with severe CRS often exhibit HLH-like symptoms, IEC-HS can present later, often emerging as CRS symptoms are resolving. Criteria for diagnosing IEC-HS are characterized by mentioned clinical and laboratory indicators, such as increased ferritin levels, emergence post-resolved CRS or escalating inflammatory response despite CRS treatment, liver enzyme elevation, low fibrinogen levels, histopathological evidence of hemophagocytosis, cytopenias, fever, and other signs and symptoms of organ failure. Different studies of various CAR T therapies have suggested different ferritin cutoff values as a criterion for the diagnosis of IEC-HS. (51-53) Due to the challenges in defining specific cutoffs, the ASTCT avoided setting exact ferritin levels in their criteria. However, a significant increase or rapid escalation in ferritin levels is essential for diagnosing IEC-HS. If inflammation persists with normal ferritin values, it should prompt the exploration of other possible causes. Clinically, while fever is a key diagnostic criterion for HLH in HLH-2004 diagnostic guidelines and can be observed in IEC-HS, ASTCT omitted fever from the proposed diagnostic criteria for IEC-HS in order to prevent confusion, as it is crucial to distinguish it from the onset or resurgence of CRS. (47, 49) Cytokine profiling could offer more understanding of the pathophysiology and diagnosis of IEC-HS, although this might be affected by previous CRS and treatments. In the future, integrating cytokine profiling into diagnostic procedures for IEC-HS could be beneficial and warrants further exploration. A study by Lichenstein et al. demonstrated that patients receiving CD22 CAR T cells who developed IEC-HS exhibited distinct cytokine patterns over time in comparison with CRS, specifically with cytokines like IFNy, IL-1β, IL-6, IL-18, its binding protein, and MIP-1α. (53) The ASTCT panel

has also suggested a grading system for IEC-HS, primarily based on the NCI-CTCAE. This system is designed to aid in evaluating the severity of clinical and laboratory manifestations. However, unlike the CRS grading system, it does not include treatment approaches in its assessment criteria.(47)

Long Term Effects

The prevention and management of delayed toxicities are becoming increasingly recognized as crucial elements in the care of patients who have been treated with CAR T. While the early toxicities of CAR T, such as CRS and ICANS, are well-documented syndromes in the literature, there is a noticeable absence of consolidation of knowledge on the observed and potential delayed effects of CAR T. The most common late effects of CAR T are hypogammaglobulinemia (B-cell depletion), prolonged cytopenias, infections, neurological and psychiatric disorders, secondary malignancies, and rarely some autoimmune issues. Late effects are usually defined as those that appear or persist 90 days after therapy. The most frequently observed delayed effect among late effects is hypogammaglobulinemia, a predictable OTOT consequence of CD19 targeted CAR T. In several key CD19 CAR T studies, reports indicated that the incidence of hypogammaglobulinemia varied between 44 to 83%. (10, 54-56) Patients who received BCMA-targeted CAR T cells have also exhibited prolonged depletion of immunoglobulins, which is also not unexpected considering that BCMA is expressed on healthy plasma cells as well, but since it is not expressed on B-cells earlier in the cell's differentiation trajectory, this suggests that targeting BCMA is less likely to lead to hypogammaglobulinemia compared to targeting CD19.(57-59) It is important to note that the frequency of hypogammaglobulinemia varies among studies because it is influenced by various other factors, such as previous immunotherapies (e.g., rituximab) or pre-existing hypogammaglobulinemia. Hypogammaglobulinemia and prolonged cytopenias can elevate the susceptibility to late-emerging infectious complications. In a phase 1–2 clinical trial by Hill et al., 133 adult patients with relapsed or refractory CD19+ ALL, CLL, or NHL, received LD chemotherapy followed by CAR T. These patients, having an extensive treatment history, displayed significant immune compromise, evidenced by 26% having hypogammaglobulinemia and 12% neutropenia at baseline. Post-infusion, the infection incidence between 29 and 90 days was lower than that in the initial 28-day period. During this later phase, 23 infections (19 microbiologically confirmed) were recorded in 14% of patients, with viral infections being most prevalent (9%), followed by bacterial infections (6%).(60) Similarly, a study from the Fred Hutchinson Cancer Research Center assessed late infections following CD-19 directed CAR T in B-cell NHL and CLL patients and reported at least one infection in 61% of these patients, most frequently occurring in the respiratory tract. A vast 80% of these patients received treatment outside of hospital settings, with a mere 5% necessitating admission to the ICU. Bacterial agents were implicated in 60% of cases with identified causative organisms, followed by viral infections at 31%, and fungal infections accounting for 9%. (55)

The Role of PROs in CAR T cell Therapy

Patient-reported outcomes (PROs), which consist of patients' self-reported symptoms and functional status without external interpretation, play a crucial role in assessing novel therapies and enhancing patient care. PRO measures are now widely recognized as outcomes that supplement traditional survival endpoints.(61) These measures are instrumental in evaluating symptom burden, functional status and health-related quality of life (HRQoL) but there are also three somewhat new applications of PROs that include evaluating adverse events, research on comparative effectiveness, and quality assessment, also known as performance evaluation.(62) It has become evident that PROs provide a more accurate measure of treatment toxicity, or more accurately tolerability, than outcomes reported by clinicians and this is important also in the context of CAR T, especially in monitoring long-term consequences or in early phase trials. (63, 64) A variety of PRO measures exist but their abundance complicates comparisons across studies and populations. What is also obvious in CAR T-cell trials is that numerous investigators have concentrated on the prevalence of particular syndromes, yet often overlook the patient experience concerning isolated symptomatic manifestations. These symptoms may vary in persistence, occasionally being transient, yet at times they represent early indicators of potentially highly morbid syndromes, necessitating timely recognition. Consequently, there is a compelling need to focus greater attention on PROs and the experiential accounts of patients enduring IEC-related toxicities, as well as the potentially long-lasting repercussions of these therapeutic interventions.

Navigating the Selection of Domains and Instruments for Optimal Measurement of Patient-Reported Outcomes (PROs)

Numerous instruments exist for assessing PROs, typically falling into two main types: general and disease-specific measures. Widely utilized general measures encompass tools like the Medical Outcomes Trust Short-Form-36 (SF-36), Euro-QoL EQ-5D, and the Patient-Reported Outcomes Measurement Information System (PROMIS). In the realm of oncology, frequently employed cancer-specific measures in both research and clinical settings include the Functional Assessment of Cancer Therapy-General (FACT-G) and the EORTC-Quality of Life Questionnaire (EORTC-QLQ-C30). When designing a study involving patients undergoing CAR T cell therapy, the selection of PRO domains should be based on the specific disease and the therapy's impact. For instance, different domains might be of importance in MM versus other B-cell malignancies. But as

we have previously emphasized, numerous factors related to the product and to the patient/disease influence the intensity of therapy toxicity, and ideally, all elements should be considered when constructing a study that also measures PROs. It has been proposed that researchers in cancer clinical trials, now extending to those encompassing CAR T, should focus on three specific measures of clearly defined concepts: symptomatic adverse events, physical function, and disease-specific symptoms. These elements are vital in determining how a therapy affects HRQoL. (65) In 2014 The Symptom Management and HRQoL Steering Committee of the NCI defined a core set of 12 fundamental PRO-relevant symptoms to aid in designing cancer clinical trials (66). However, there's a growing necessity to expand on the foundational research by Reeve and colleagues and the currently proposed core set of items to be used in cancer clinical trials. (66) This expansion is essential not just in the context of CAR T but also in the broader spectrum of oncology, particularly in light of the increasing variety of new anticancer drugs, each with its distinct range of toxicities. Implementing a consistent core questionnaire for assessing PROs in individuals undergoing CAR-T is crucial to minimize variability and enable comparisons across different studies. The PROMIS, an initiative by the NIH, aims to standardize the measurement of common PROs in clinical research. Beyond general health surveys, PROMIS provides various item banks focused on key disease-related symptoms such as fatigue, neuropathy, dyspnea, and cognitive deficits, enabling the creation of tailored, hypothesis-specific instruments.(67, 68) An additional exciting and valuable resource for enhanced evaluation of treatment toxicity is the patient-reported outcomes version of the CTCAE (PRO-CTCAE). This tool encompasses about 10% of the items found in the CTCAE, featuring 78 symptomatic adverse events. Specific relevant adverse events can be selectively included in a study. (69) However, an objective approach to item selection from a library is needed. The challenge is to identify a core list of common symptomatic toxicities aligned with modern treatment approaches such as CAR T, that can be used ad-hoc, and further research addressing this problem is ongoing from multiple stakeholders' perspectives. (Figure 1)

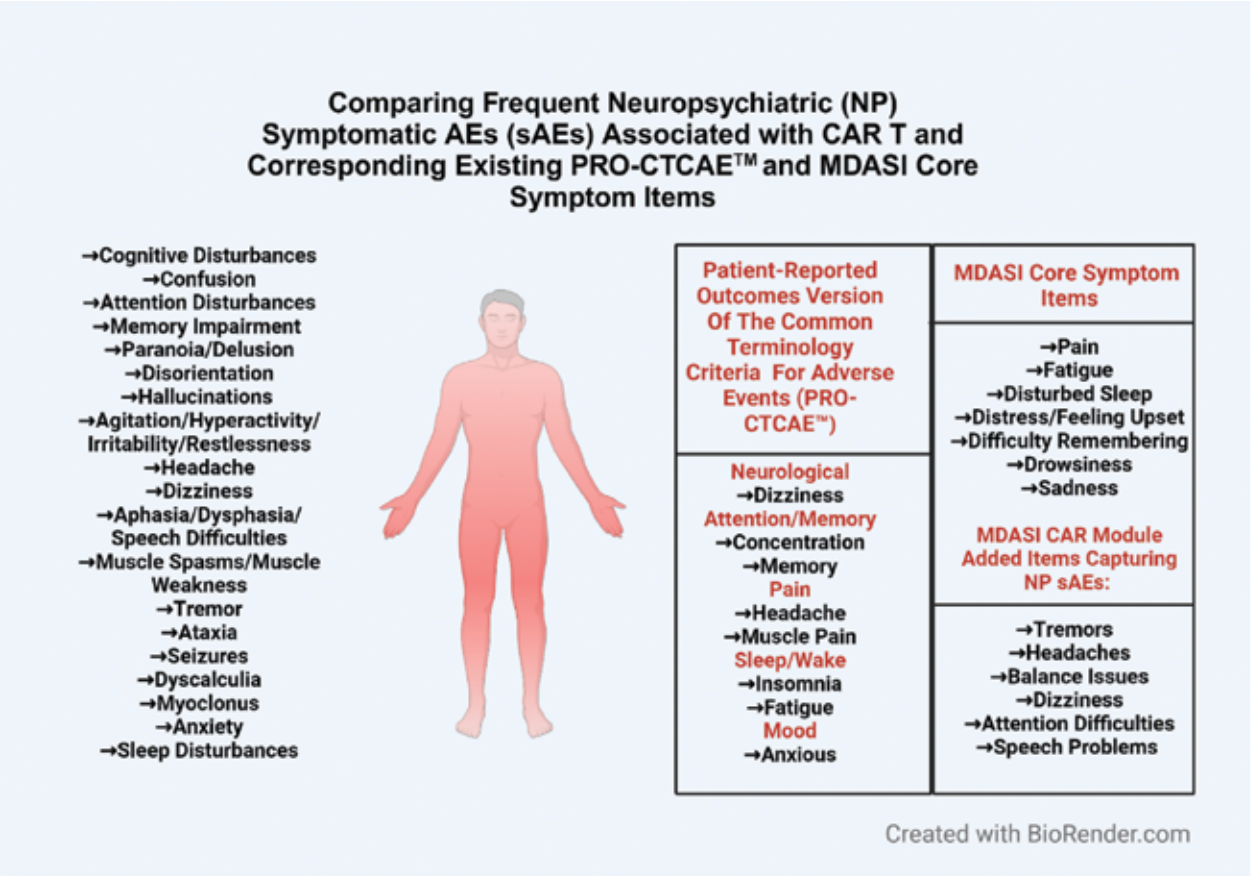

Figure 1: Comparative overview of neuropsychiatric symptomatic adverse events (NP sAEs) associated with CAR T, aligned with the corresponding items from the PRO-CTCAE™ and the core symptoms set of the MDASI. The left section itemizes frequent NP sAEs, and the right section lists currently existing related PRO-CTCAE™ items alongside MDASI core symptoms and additional NP sAEs added in the new MDASI CAR Module. (69, 70)

Complexity of PRO evaluation in CAR T

The acute toxicities frequently manifesting post CAR T cell infusion, notably CRS and ICANS, present a formidable challenge in patient care due to their potential severity and profound impact on patient health and QoL. The task of capturing these side effects through PROs is rendered complex by the acute nature and intricacies of these symptoms. Patients in critical condition, grappling with these adverse effects, may find it difficult to self-report their experiences, particularly when facing cognitive impairments or intense physical discomfort that impede effective communication. A crucial aspect to consider is the temporal variation of these symptoms; the emergence and evolution of side effects such as CRS and ICANS can differ, ranging from immediate post-infusion reactions to delayed onset of weeks. This necessitates an adaptable and dynamic methodology in PRO assessment to precisely monitor these fluctuations over time. Considering the critical nature of these side effects, integrating PRO data collection with clinical care is paramount for ensuring patient safety and reducing data collection burdens. Employing a flexible, and possibly daily, approach in gathering PRO data, such as utilizing PRO-CTCAE right after CAR T cell infusion, offers a strategic advantage. It could also enable healthcare providers to rapidly receive alerts about any worsening of symptoms, thereby facilitating more immediate and effective medical interventions. When focusing on long-term effects of CAR T, capturing those is a complex task, given the unique characteristics of this treatment and the diseases it targets. This process extends well beyond the scope of traditional therapies, necessitating a prolonged period of follow-up to fully understand the long-term outcomes, with an emphasis on neurological consequences. The importance of tracking these effects lies in providing comprehensive patient care and gaining a deeper understanding of the therapy's full impact. A significant aspect of long-term monitoring is the assessment of HRQoL, influenced both by the therapy and underlying disease. Utilizing PRO measures is essential in both contexts, as they offer insights into the patient perspective on their health and the effects of the treatment over time. The effectiveness of long-term monitoring relies heavily on robust data collection and management systems. The employment of electronic health records (EHRs), electronic patient-reported outcomes (ePROs), and telemedicine could be a key in facilitating this process, ensuring that the long-term effects of CAR T are captured accurately and comprehensively.

PROs in CAR T Clinical Trials

Despite existing research, there remains a notable scarcity of published data on the use of PROs in CAR T context. A panel from the Centers for Medicare & Medicaid Services (CMS) endorsed the effectiveness of four validated measurement tools: PRO-CTCAE, MD Anderson Symptom Inventory (MDASI), EORTC-QLQ-C30, and PROMIS. This endorsement reflects a scientific consensus on the reliability and validity of these instruments in assessing PROs in the CAR T clinical setting. (71) The scoping review by Efficace et al, on PROs in CAR T cell therapy for hematologic malignancies identified 14 studies that included PRO measures important for understanding the patient perspective on the impact of CAR T cell therapy. The EQ-5D and PROMIS-29 were the most frequently used PRO measures and were employed in 6 (42.9%) and 5 (35.7%) of these studies, respectively. The authors emphasized the importance of longitudinal monitoring of patient experiences in order to learn more about the tolerability of this new therapy.(72) The integration of PROs in early-phase clinical trials, particularly within advanced cancer cohorts, represents a challenge, yet, emerging evidence robustly underscores the viability of PRO assessment in these contexts, revealing its capacity to generate data that is not only clinically relevant but also of good quality. (Table 1) The ELIANA and JULIET studies assessed tisa-cel's impact on HRQoL in pediatric/young adult patients with R/R B-ALL and adult patients with R/R DLBCL, respectively. In ELIANA significant and ongoing HRQoL improvements post-tisa-cel infusion, using PedsQL and EQ-5D VAS were observed, with reduced benefits in patients with severe CRS or neurotoxicity. Conversely, JULIET study reported substantial, enduring HRQoL enhancements in adult DLBCL patients, measured by FACT-Lym and SF-36. The ZUMA-2 and ZUMA-3 studies evaluated the impact of brexu-cel on HRQoL in adults with R/R MCL and ALL, respectively. Wang et al. observed in R/R MCL patients a temporary HRQoL decline at week 4 post-brexu-cel infusion, with a subsequent return or improvement at 3 and 6 months, as measured by EQ-5D scores. Shah et al. found that most evaluable adult R/R ALL patients experienced stable or improved HRQoL over time post-infusion, with a notable increase from the third month. In the KarMMa study, patients with triple-class exposed R/R MM receiving ide-cel as fourth-line or later treatment reported significant improvements in most PROs by the first month, including pain and disease symptoms. These enhancements, covering aspects like fatigue, physical and cognitive functioning, HRQoL, and disease symptoms, were sustained from the second through the ninth month, as measured by the EORTC QLQ-C30 and QLQ-MY20. Moreover, patients' baseline HRQoL scores, initially worse than the general population, aligned with or exceeded those of the general population from one to three months and persisted through the eighteenth month. (56, 73-76) The Efficace et al. research unveiled an important gap: only a few studies have delved into data on PROs in the two-week window post CAR T-cell infusion and the critical long-term phase, surpassing the one-year mark. This paucity stands in stark contrast to existing research underscoring the criticality of longitudinal PRO data to unearth latent symptoms or functional impairments that might only surface months, if not years, after therapy. This illuminates a significant frontier awaiting further exploration.

Table 1. FDA-approved CAR T cell therapies – Prevalent Toxicity and PROs used.

Product Name	FDA Approval for Current Indications	Reference	Indication	No. of Evaluable Patients	CRS	Neurological Events/ Neurotoxicities	CRS Grading	Neurotoxicity Grading	PRO Instruments
Tisagenlecleucel	2017	(10)	Patients up to 25 years of age with B-ALL that is refractory or in second or later relapse	75	77%	40%	NCI CTCAE v4.03 (specific symptoms) and Penn/CHOP scale	NCI CTCAE v4.03	PedsQL and EQ-5D, EQ-VAS
Axicabtagene Ciloleucel	2017	(28)	Adult patients with R/R LBCL after 2 or more lines of systemic therapy, including DLBCL, NOS, PMBL, high grade B-cell lymphoma and DLBCL arising from FL	108	93%	64%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03	EQ-5D, MMSE
Tisagenlecleucel	2018	(78)	Adult patients with R/R LBCL after 2 or more lines of systemic therapy, including DLBCL, NOS, high grade B-cell lymphoma and DLBCL arising from FL	93	58%	21%	NCI CTCAE v4.03 (specific symptoms) and Penn scale	NCI CTCAE v4.03	FACT-Lym and SF-36
Brexucabtagene Autoleucel	2020	(81)	Adult patients with R/R MCL	68	91%	63%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03	EQ-5D and VAS score
Lisocabtagene Maraleucel	2021	(80)	Adult patients with LBCL, DLBCL, NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, PMBL, and FL grade 3B with refractory disease to first-line chemoimmunotherapy or relapse within 12 months, or who are not eligible for HSCT or with R/R disease after 2 or more lines of systemic therapy	269	42%	30%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03	n/a

Table 1. FDA-approved CAR T cell therapies – Prevalent Toxicity and PROs used.

Product Name	FDA Approval for Current Indications	Reference	Indication	No.of Evaluable Patients	CRS	Neurological Events/ Neurotoxicity	CRS Grading	Neurotoxicity Grading	PRO Instruments
Axicabtagene Ciloleucel	2021	(77)	Adult patients with R/R FL after 2 or more lines of systemic therapy	148	82%	59%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03	n/a
Idecabtagene Vicleucel	2021	(83)	Adult patients with R/R MM after 4 or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody	128	84%	18%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03	EORTC-QLQ-C30, EQ-5D-5L, EORTC-QLQ-MY20
Ciltacabtagene Autoleucel	2022	(82)	Adult patients with R/R MM after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody	97	95%	21%	NCI CTCAE v 5.0 (specific symptoms) and ASTCT consensus grading	NCI CTCAE v 5.0 and ASTCT consensus grading	(EORTC)-QLQ-C30, EQ-5D-5L, PGIC, PGIS, single items from EORTC QLQ-MY20
Tisagenlecleucel	2022	(79)	Adult patients with R/R FL after 2 or more lines of systemic therapy	97	47%	36%	NCI CTCAE v4.03 (specific symptoms) and Lee scale	NCI CTCAE v4.03 and ASTCT ICANS consensus grading	SF-36v2, FACT-Lym and EQ-5D-3L

In the dynamic landscape of CAR T, the systematic tracking of PROs emerges as a pivotal tool, particularly for capturing the nuances of late-onset toxicities, such as neurocognitive deficits, thus charting new territories in patient-centric medical research. Up to now, to our knowledge, only one PRO instrument has been developed specifically for patients treated with CAR T. Wang et al. conducted a cross-sectional study with the goal of creating and validating a PRO tool specifically designed to measure symptom burden and daily functioning in patients who have undergone CAR T-cell therapy. This instrument, MDASI-CAR, is an extension of the established MDASI. The MDASI-CAR represents a pioneering effort in developing a treatment-specific PRO assessment tool for CAR T patients. The research led to the identification and inclusion of 10 critical symptoms – tremors, fever/chills, headaches, balance problems, dizziness, attention issues, speech difficulties, coughing, sexual dysfunction, and diarrhea – into the existing MDASI framework, forming the final version of the MDASI-CAR instrument. (70)

Conclusion

CAR T represents a significant advancement in treatment of hematological malignancies, introducing a range of unique adverse events whose frequency and severity vary considerably. The complexity of understanding and managing this therapy's toxicities constitutes a serious challenge in the medical field.
A deeper insight into the pathophysiology of these side effects is also crucial, demanding an effort in both basic and clinical research. This research is vital to determine why certain patients experience specific side effects and it would help in prevention, earlier recognition, and treatment of these side effects. Moreover, the diverse symptomatology associated with individual CAR-T syndromes, each with its own frequency, requires more precise characterization. It underscores the need for a systematic approach to patient care, emphasizing the importance of directly understanding patients' experiences with these side effects. To this end, the consistent application of PRO instruments across clinical studies is essential. Healthcare professionals continue to search for an optimal PRO tool capable of identifying early and late-stage toxicities. It is crucial to closely monitor PROs shortly after therapy to gather information on acute toxicity. This monitoring enables timely interventions to reduce symptom severity and potentially prevent the escalation of CRS and ICANS to more severe grades. Assessing PROs at later stages is equally vital for evaluating long-term QoL, particularly in relation to neurocognitive effects.
Current PRO tools, most not originally tailored for CAR T-cell therapy, highlight a significant gap in our research methodologies, necessitating further exploration to establish a core set of symptoms, following on Reeve's set. Such a set would be valuable in tracking patient experiences in clinical trials and would provide important and needed information on the tolerability of the therapy as well as enable comparisons of different CAR T products with similar response rates.

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References

1. Kuwana Y, Asakura Y, Utsunomiya N, Nakanishi M, Arata Y, Itoh S, et al. Expression of chimeric receptor composed of immunoglobulin-derived V regions and T-cell receptor-derived C regions. Biochem Biophys Res Commun. 1987;149(3):960-8.
2. Gross G, Waks T, Eshhar Z. Expression of Immunoglobulin-T-Cell Receptor Chimeric Molecules as Functional Receptors with Antibody-Type Specificity. P Natl Acad Sci USA. 1989;86(24):10024-8.
3. Wang J, Jensen M, Lin Y, Sui X, Chen E, Lindgren CG, et al. Optimizing adoptive polyclonal T cell immunotherapy of lymphomas, using a chimeric T cell receptor possessing CD28 and CD137 costimulatory domains. Hum Gene Ther. 2007;18(8):712-25.
4. Abken H. The fourth generation of CARs: TRUCKs can activate the innate response towards tumors. Transfus Med Hemoth. 2017;44:28-.
5. Chmielewski M, Abken H. TRUCKs: the fourth generation of CARs. Expert Opin Biol Th. 2015;15(8):1145-54.
6. Berdeja JG, Madduri D, Usmani SZ. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study (vol 398, pg 314, 2021). Lancet. 2021;398(10307):1216-.
7. Munshi NC, Anderson LD, Shah N, Jagannath S, Berdeja JG, Lonial S, et al. Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): Initial KarMMa results. Journal of Clinical Oncology. 2020;38(15).
8. Albanyan O, Chavez J, Munoz J. The role of CAR-T cell therapy as second line in diffuse large B-cell lymphoma. Ther Adv Hematol. 2022;13.
9. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Tr. 2019;25(4):625-38.
10. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. New Engl J Med. 2018;378(5):439-48.
11. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-84.
12. Frey N, Porter D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. Biol Blood Marrow Transplant. 2019;25(4):e123-e7.
13. Ferrara JLM, Abhyankar S, Gilliland DG. Cytokine Storm of Graft-Versus-Host Disease - a Critical Effector Role for Interleukin-1. Transplant P. 1993;25(1):1216-7.
14. Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. Biomark Res. 2018;6:4.
15. Freyer CW, Porter DL. Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies. J Allergy Clin Immun. 2020;146(5):940-8.
16. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Reviews. 2019;34:45-55.
17. Broz P, Pelegrín P, Shao F. The gasdermins, a protein family executing cell death and inflammation. Nat Rev Immunol. 2020;20(3):143-57.
18. Huang KJ, Su IJ, Theron M, Wu YC, Lai SK, Liu CC, Lei HY. An interferon-gamma-related cytokine storm in SARS patients. J Med Virol. 2005;75(2):185-94.
19. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. Microbiol Mol Biol R. 2012;76(1):16-32.
20. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
21. Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6(224):224ra25.
22. Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood. 2015;125(26):4017-23.
23. Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017;130(21):2295-306.
24. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Correction to: Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. J Hematol Oncol. 2018;11(1):81.
25. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.
26. Siglin J, Bukhari A, Lutfi F, Holtzman NG, Shanholtz C, Yared JA, et al. C-reactive protein: not always a reliable marker of ongoing cytokine release syndrome in CAR-T therapy following IL-6 blockade. Leuk Lymphoma. 2020;61(9):2280-2.
27. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez

C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.
28. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. New Engl J Med. 2017;377(26):2531-44.
29. Klinger M, Zugmaier G, Nägele V, Goebeler ME, Brandl C, Stelljes M, et al. Adhesion of T Cells to Endothelial Cells Facilitates Blinatumomab-Associated Neurologic Adverse Events. Cancer Research. 2020;80(1):91-101.
30. Rubin DB, Danish HH, Ali AB, Li K, LaRose S, Monk AD, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. Brain. 2019;142:1334-48.
31. Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov. 2018;8(8):958-71.
32. Park JH, Santomasso B, Riviere I, Senechal B, Wang XY, Purdon T, et al. Baseline and early post-treatment clinical and laboratory factors associated with severe neurotoxicity following 19-28z CAR T cells in adult patients with relapsed B-ALL. Journal of Clinical Oncology. 2017;35.
33. Page AV, Liles WC. Biomarkers of endothelial activation/dysfunction in infectious diseases. Virulence. 2013;4(6):507-16.
34. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2022;22(2):85-96.
35. Schwameis M, Schörgenhofer C, Assinger A, Steiner MM, Jilma B. VWF excess and ADAMTS13 deficiency: a unifying pathomechanism linking inflammation to thrombosis in DIC, malaria, and TIP. Thromb Haemostasis. 2015;113(4):708-18.
36. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018;24(1):20-+.
37. Garfall AL, Lancaster E, Stadtmauer EA, Lacey SF, Dengel K, Ambrose DE, et al. Posterior Reversible Encephalopathy Syndrome (PRES) after Infusion of Anti-Bcma CAR T Cells (CART-BCMA) for Multiple Myeloma: Successful Treatment with Cyclophosphamide. Blood. 2016;128(22).
38. Parker KR, Migliorini D, Perkey E, Yost KE, Bhaduri A, Bagga P, et al. Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies. Cell. 2020;183(1):126-+.
39. Nahas GR, Komanduri KV, Pereira D, Goodman M, Jimenez AM, Beitinjaneh A, et al. Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT). Leukemia Lymphoma. 2020;61(4):940-3.
40. Taneja A, Jain T. CAR-T-OPENIA: Chimeric antigen receptor T-cell therapy-associated cytopenias. EJHaem. 2022;3(Suppl 1):32-8.
41. Rejeski K, Subklewe M, Aljurf M, Bachy E, Balduzzi A, Barba P, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142(10):865-77.
42. Fried S, Avigdor A, Bielorai B, Meir A, Besser MJ, Schachter J, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transpl. 2019;54(10):1643-50.
43. Rejeski K, Perez A, Sesques P, Hoster E, Berger C, Jentzsch L, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499-513.
44. Sidana S, Hosoya H, Jensen A, Liu LWC, Goyal A, Hovanky V, et al. Bendamustine vs. fludarabine/cyclophosphamide lymphodepletion prior to BCMA CAR-T cell therapy in multiple myeloma. Blood Cancer J. 2023;13(1).
45. Turtle CJ, Hanafi LA, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8 and CD4 CD19-specific chimeric antigen receptor-modified T cells. Science Translational Medicine. 2016;8(355).
46. Jain T, Knezevic A, Pennisi M, Chen YX, Ruiz JD, Purdon TJ, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Advances. 2020;4(15):3776-87.
47. Hines MR, Knight TE, McNerney KO, Leick MB, Jain T, Ahmed S, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transpl Cell Ther. 2023;29(7).
48. Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2015;125(19):2908-14.
49. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-31.
50. Sandler RD, Tattersall RS, Schoemans H, Greco R, Badoglio M, Labopin M, et al. Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol. 2020;11.
51. Teachey DT, Bishop MR, Maloney DG, Grupp SA. Toxicity management after chimeric antigen receptor T cell

therapy: one size does not fit 'ALL'. Nat Rev Clin Oncol. 2018;15(4):218.
52. Kennedy VE, Wong CS, Huang CY, Kambhampati S, Wolf J, Martin TG, et al. Macrophage activation syndrome-like (MAS-L) manifestations following BCMA-directed CAR T cells in multiple myeloma. Blood Advances. 2021;5(23):5344-8.
53. Lichtenstein DA, Schischlik F, Shao L, Steinberg SM, Yates B, Wang HW, et al. Characterization of HLH-like manifestations as a CRS variant in patients receiving CD22 CAR T cells. Blood. 2021;138(24):2469-84.
54. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncology. 2019;20(1):31-42.
55. Cordeiro A, Bezerra ED, Hirayama AV, Hill JA, Wu QV, Voutsinas J, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. Biol Blood Marrow Tr. 2020;26(1):26-33.
56. Schuster SJ, Tam CS, Borchmann P, Worel N, McGuirk JP, Holte H, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncology. 2021;22(10):1403-15.
57. Zhao WH, Wang BY, Chen LJ, Fu WJ, Xu J, Liu J, et al. Four-year follow-up of LCAR-B38M in relapsed or refractory multiple myeloma: a phase 1, single-arm, open-label, multicenter study in China (LEGEND-2). J Hematol Oncol. 2022;15(1).
58. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med. 2004;199(1):91-7.
59. Wat J, Barmettler S. Hypogammaglobulinemia After Chimeric Antigen Receptor (CAR) T-Cell Therapy: Characteristics, Management, and Future Directions. J Aller Cl Imm-Pract. 2022;10(2):460-6.
60. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen XY, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131(1):121-30.
61. Res FCDE, Res FCDE, Res FCBE, Res FCBE, Hlth FCDR. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Out. 2006;4.
62. Basch E. New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment. Annu Rev Med. 2014;65:307-17.
63. Basch E, Jia XY, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse Symptom Event Reporting by Patients vs Clinicians: Relationships With Clinical Outcomes. Jnci-J Natl Cancer I. 2009;101(23):1624-32.
64. Atkinson TM, Li YL, Coffey CW, Sit L, Shaw M, Lavene D, et al. Reliability of adverse symptom event reporting by clinicians. Quality of Life Research. 2012;21(7):1159-64.
65. Kluetz PG, Slagle A, Papadopoulos EJ, Johnson LL, Donoghue M, Kwitkowski VE, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms. Clin Cancer Res. 2016;22(7):1553-8.
66. Reeve BB, Mitchell SA, Dueck AC, Basch E, Cella D, Reilly CM, et al. Recommended Patient-Reported Core Set of Symptoms to Measure in Adult Cancer Treatment Trials. Jnci-J Natl Cancer I. 2014;106(7).
67. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-94.
68. Garcia SF, Cella D, Clauser SB, Flynn KE, Lad T, Lai JS, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: A patient-reported outcomes measurement information system initiative (vol 25, pg 5106, 2007). Journal of Clinical Oncology. 2008;26(6):1018-.
69. Dueck AC, Mendoza TR, Mitchell SA. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (vol 1, pg 1051, 2015). Jama Oncol. 2016;2(1):146-.
70. Wang XS, Srour SA, Mendoza T, Whisenant M, Subbiah I, Gonzalez E, et al. Development and validation of a patient-reported outcome measure to assess symptom burden after chimeric antigen receptor T-cell therapy. Brit J Haematol. 2023;201(4):738-46.
71. C H. CMS panel expresses confidence in patient-reported outcomes tools. HEM/ONC Today. 2018;19(18):10; 2018.
72. Efficace F, Cannella L, Sparano F, Giesinger JM, Vignetti M, Baron F, et al. Chimeric Antigen Receptor T-cell Therapy in Hematologic Malignancies and Patient-reported Outcomes: A Scoping Review. Hemasphere. 2022;6(12).
73. Laetsch TW, Myers GD, Baruchel A, Dietz AC, Pulsipher MA, Bittencourt H, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. Lancet Oncology. 2019;20(12):1710-8.
74. Maziarz RT, Waller EK, Jaeger U, Fleury I, McGuirk J, Holte H, et al. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv. 2020;4(4):629-37.

75. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491-502.
76. Delforge M, Shah N, Miguel JS, Braverman J, Dhanda DS, Shi L, et al. Health-related quality of life with idecabtagene vicleucel in relapsed and refractory multiple myeloma. Blood Advances. 2022;6(4):1309-18.
77. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.
78. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
79. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325-+.
80. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-52.
81. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020;382(14):1331-42.
82. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigendirected chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-24.
83. Munshi NC, Anderson LD, Jr., Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-16.

Cardiovascular comorbidities in epileptology

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Abstract:

Epilepsy is one of the most common neurological diseases affecting around 50 million people worldwide. Modern scientific and professional literature recognizes comorbidities as an integral part of epilepsy, with the goal of defining optimal treatment. A series of studies from 2002 to date have confirmed a high prevalence of heart diseases in all age groups of adult patients with epilepsy, and nearly three times higher risk of malignant arrhythmias and sudden cardiac death, compared to the general population. Currently, research is increasingly being focused on elucidating the long-term connection between epilepsy and the cardiovascular system, and in 2020 the term ''epileptic heart" was first introduced, describing a heart and coronary vasculature damaged by chronic epilepsy. Plausible pathophysiological mechanisms include the cardiotoxic effects of catecholamines and repeated hypoxemia, but also the use of antiseizure medications (ASMs) associated with hyperlipidemia and arrhythmogenic effects, which could make an additional contribution to the electromechanical dysfunction of the heart. People over 60 years of age make up the largest group of patients with newly diagnosed epilepsy and represent a particular challenge for epileptologists, due to the frequent presence of multimorbidity and polypharmacy, especially in the domain of the cardiovascular system. The International League Against Epilepsy (ILAE) Task Force on Epilepsy in the elderly proposed guidelines that state that clinicians need to approach an elderly person as they would a woman of childbearing potential, and emphasize the importance of considering factors such as adverse effects and pharmacokinetic interactions when choosing ASMs, as well as the necessity for an individualized, multidisciplinary and patient-oriented approach. In addition, recent studies draw attention to the need for a routine cardiological assessment when treating patients with epilepsy, and highlight the importance of electrocardiogram (ECG) in determining the initial cardiovascular risk, as well as monitoring the impact of epileptic seizures and ASMs on the structural integrity of the heart and its vasculature.

Keywords: Epilepsy, Cardiovascular system, Antiseizure medications, Heart

Sažetak:

Kardiovaskularni komorbiditeti u epileptologiji

Epilepsija je jedna od najčešćih neuroloških bolesti od koje boluje oko 50 milijuna ljudi diljem svijeta. Suvremena znanstvena i stručna literatura prepoznaje komorbiditete kao sastavni dio epilepsije, s ciljem definiranja optimalnog liječenja. Niz studija od 2002. godine do danas potvrdio je visoku preva-

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lenciju srčanih bolesti u svim dobnim skupinama odraslih bolesnika s epilepsijom te gotovo tri puta veći rizik od malignih aritmija i iznenadne srčane smrti u odnosu na opću populaciju. Trenutačno se istraživanja sve više usmjeravaju na rasvjetljavanje dugoročne povezanosti epilepsije i kardiovaskularnog sustava, a 2020. godine prvi put je uveden pojam „epileptično srce" koji opisuje oštećenje srca i koronarne vaskulature uzrokovano kroničnom epilepsijom. Vjerojatni patofiziološki mehanizmi uključuju kardiotoksične učinke katekolamina i ponovljenu hipoksemiju, ali i upotrebu antiepileptičnih lijekova (AEL) povezanih s hiperlipidemijom i aritmogenim učincima, koji bi mogli dati dodatni doprinos elektromehaničkoj disfunkciji srca. Osobe starije od 60 godina čine najveću skupinu bolesnika s novodijagnosticiranom epilepsijom i predstavljaju poseban izazov za epileptologe, zbog česte prisutnosti multimorbiditeta i polifarmacije, posebice u domeni kardiovaskularnog sustava. Radna skupina Međunarodne lige protiv epilepsije (ILAE) za epilepsiju u starijih osoba predložila je smjernice u kojim se navodi da starije osobe treba tretirati kao žene reproduktivne dobi te se naglašava važnost razmatranja čimbenika kao što su nuspojave i farmakokinetičke interakcije pri odabiru AEL, kao i nužnost individualiziranog, multidisciplinarnog i pacijentu orijentiranog pristupa. Osim toga, novije studije skreću pozornost na potrebu za rutinskom kardiološkom procjenom pri liječenju bolesnika s epilepsijom i naglašavaju važnost elektrokardiograma (EKG) u određivanju početnog kardiovaskularnog rizika, kao i praćenja utjecaja epileptičkih napadaja i AEL na strukturni integritet srca i njegove vaskulature.

Ključne riječi: Epilepsija, Kardiovaskularni sustav, Antiepileptični lijekovi, Srce

Introduction

Epilepsy is one of the most common neurological diseases that affects about 50 million people in the world (1). Medicine has come a long way from the belief that having epilepsy means only seizures, so today modern scientific and professional literature considers comorbidities as an integral part of epilepsy, with the goal of defining optimal treatment (2). Epilepsy as a single disease is rare and about 50% of adult patients with epilepsy have at least one other associated condition, while that percentage is even higher in children (3, 4). The most common comorbidities are psychiatric disorders, mainly depression and anxiety, but numerous somatic disorders such as neurological, cardiovascular, gastrointestinal, endocrinological, and respiratory diseases are often present (3, 5, 6, 7). Here, we review the present state of knowledge of intertwined relationships between epilepsy and cardiovascular comorbidities and discuss new opportunities for improvement in clinical care.

Epidemiology

A series of studies from 2002 to date have confirmed a high prevalence of heart diseases (62-82%) in all age groups of adult patients with epilepsy, which present a major cause of death in this population (8, 9, 10). The Amsterdam Resuscitation Studies (ARREST) included more than 3000 subjects and they reported that the risk of fatal arrhythmias and cardiac arrest was almost 3-fold greater in people with epilepsy compared to the general population, which was further increased if the patients had symptomatic epilepsy (11, 12). Sudden cardiac death (SCD) constitutes a 4.5-fold greater risk for premature death in patients with epilepsy compared to sudden unexpected death in epilepsy (SUDEP), which by definition excludes all known causes of mortality, including cardiac comorbidities. In a community-based study, Stecker and colleagues determined that in about two-thirds of the cases of SCD in patients with epilepsy, there was no apparent temporal relationship between a seizure and the cardiac event (13). Post-mortem findings suggest that, at least in some cases, SCD and SUDEP present two overlapping entities (14). Zack and Luncheon reported that patients with epilepsy developed heart diseases, such as angina pectoris, coronary heart disease, and myocardial infarction, at an accelerated rate than individuals without epilepsy, with the greatest difference, percentage-wise, observed in patients between 45 and 64 years of age (15). Epidemiological studies have also shown that the incidence of myocardial infarction was greater in patients with epilepsy (16, 17).

Structural cardiovascular abnormalities and arrhythmias in epilepsy

Up til now, transient changes in cardiac function during interictal or peri-ictal phases, such as ictal tachycardia, ictal asystole, and postictal asystole, have been extensively studied (18, 19). However, in line with previous observations, research is increasingly being focused on elucidating the long-term connection between epilepsy and the cardiovascular system. In 2020 Verrier and colleagues first proposed the concept of the ''epileptic heart", defined as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and

hypoxemia leading to electrical and mechanical dysfunction". Interictal autonomic dysfunction, such as decreased heart rate variability (HRV), as well as repeated seizures, especially generalized tonic-clonic seizures (GTCS), cause an excess of catecholamines and myocardial ischemia that lead to electrical instability and arrhythmogenesis with a potentially fatal effect (14). Echocardiographic studies found that patients with temporal lobe epilepsy exhibited higher left ventricle stiffness, left ventricle filling pressure, and greater left atrial volume as well as markers of autonomic dysfunction than healthy matched controls (20). Liu et al reported altered echocardiography parameters reflecting systolic and diastolic dysfunctions in patients with epilepsy without any underlying cardiovascular disease, compared to healthy controls, such as decreased left ventricular ejection fraction (LVEF) and prolonged isovolumic relaxation time (IVRT), which are associated with cardiovascular morbidity (21). A higher burden of cardiovascular risk factors observed in patients with epilepsy could additionally contribute to structural heart disease, including obesity, physical inactivity, smoking, and poor metabolic profile (22, 23, 24). Recent molecular findings based on animal studies have revealed that epilepsy might secondarily lead to acquired cardiac channelopathies which can further increase arrhythmogenesis (25). In addition to numerous investigations on sudden cardiac events that support the concept of ''epileptic heart", in 2023 Wang and colleagues published the first study focused on investigating the connection between epilepsy and the long-term risk of cardiac arrhythmias (26). They revealed a higher risk of all cardiac arrhythmias in people with epilepsy, including atrial fibrillation, bradyarrhythmias, ventricular arrhythmias, and other types of arrhythmias. The risk was even higher in those using anti-seizure medications (ASMs). In a large survey with over 1.4 million patients with epilepsy done by Desai et al, it was found that nearly one-quarter of patients had some cardiac arrhythmias, with atrial fibrillation being the most common one (27).

Antiepileptic therapy and the cardiovascular system

ASMs also play an important role in the pathogenesis of cardiac conditions in epilepsy by several mechanisms. They have been described as independent risk factors for SCD even in individuals without epilepsy (28, 29). Sodium channel-blocking agents, such as carbamazepine, phenytoin, lacosamide, and lamotrigine, have been studied the most, and numerous studies have described their side effects like arrhythmias or conduction abnormalities (28, 30). Wang et al concluded that the use of carbamazepine and valproic acid carried the highest risk of cardiac arrhythmias of all ASMs (26). They are also known to cause weight gain which induces metabolic syndrome, further increasing cardiovascular risk. Moreover, enzyme-inducing ASMs, such as carbamazepine, phenobarbitone, and phenytoin, negatively affect lipid profiles which results in accelerated atherosclerosis and a higher risk of cardiac ischemic disease (31, 32). Renoux and colleagues showed that the use of inhibiting ASMs was associated with a decreased risk of myocardial infarction (33). Additionally, studies have found that both adults and children taking ASMs had higher carotid intima-media thickness and epicardial adipose tissue thickness compared to the healthy control group (34, 35). In pharmacoresistant patients, vagus nerve stimulation (VNS) presents a frequently used therapeutic method that has documented success in seizure reduction, although its exact mechanism of action is still unknown (36). VNS-induced cardiovascular complications have rarely been reported (37, 38, 39). Conversely, the current state of knowledge suggests that VNS exhibits a significant cardioprotective effect by two separate mechanisms: affecting the central nervous system leading to seizure reduction, and direct influence on the heart leading to a decrease in its electrical instability (40).

ECG findings in epilepsy

Cardiac repolarization abnormalities are common in patients with epilepsy. This may be caused by structural cardiomyocyte lesions, changes in their ion channel expressions, and sympathovagal imbalance, manifested as decreased HRV, which has been described as one of the possible markers of increased risk for both SUDEP and SCD (41, 42). People with epilepsy express different ECG measures compared to healthy people. QT interval (corrected for heart rate QTc) prolongation and dispersion are more frequently seen in people with epilepsy, which is associated with an increased risk of ventricular arrhythmias (10, 43, 44). T wave alternans (TWA) is one of the most studied markers of cardiac repolarization. It is defined as a microvolt-level beat-to-beat fluctuation in ST-segment or T-wave morphology and is an important predictor of SCD (45, 46). 82% of patients with epilepsy have elevated TWA values that are dependent on the duration of epilepsy, meaning that patients with chronic epilepsy display higher TWA values compared to the newly diagnosed ones (46, 47). Furthermore, TWA is influenced by the pro and antiarrhythmic effects of drugs, as well as VNS which was shown to significantly reduce TWA (40).

ASMs, multimorbidity and polypharmacy

The highest incidence of developing new-onset epilepsy occurs in people aged 60 or more (48). The treatment of the elderly population represents a special challenge for epileptologists due to age-related changes in pharmacokinetics, as well as the frequent presence of multimorbidity and polypharmacy, especially in the domain of the cardiovascular system. These occurrences are an important factor when deciding on the most suitable treatment. Bruun and colleagues showed that more than two-thirds of patients (69%) with epilepsy, who were 65 or older, had six or more medications as part of their therapy regime, in addition to ASMs (49). About 30% of cases of newly diagnosed epilepsy

in the elderly are stroke-related, followed by other causes such as tumors, dementia, and trauma (50). ASMs display numerous interactions with other drugs frequently used by this population, such as antiarrhythmics, antihypertensives, statins, oral anticoagulants, and antiplatelet medications. This especially refers to potent hepatic enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and primidone, that can decrease the levels of concomitantly administered medications. The most significant interactions with the drugs from the ATC C drug section were described with ivabradine, ranolazine, felodipine, nicardipine, verapamil, hydrochlorothiazide, as well as simvastatin and atorvastatin (51). As previously mentioned, sodium channel blockers are known to potentially trigger or worsen conduction abnormalities and arrhythmias (28, 30). Valproate and pregabalin have been linked to heart failure exacerbation, and a preference for levetiracetam and lamotrigine in those conditions was given (52, 53). In the PROPOSE study conducted by Tanaka et al, it was concluded that newer-generation ASMs (levetiracetam, lacosamide, zonisamide, perampanel, gabapentin, topiramate) showed great advantages and superiority over older-generation ASMs (carbamazepine, valproate, phenytoin, phenobarbital, clonazepam, clobazam) in the secondary prevention of post-stroke epilepsy, due to better seizure control, less serious adverse effects and less interference with other drugs (54). The use of novel oral anticoagulants (NOACs) among adults with epilepsy has rapidly increased in the last decade (55). In the 2021 European Heart Rhythm Association Practical Guide, no relevant interactions with NOACs were described with lamotrigine, lacosamide, and zonisamide. However, the use of valproate was contraindicated due to reduced NOAC plasma levels, whereas levetiracetam and carbamazepine were advised to be used with caution and careful monitoring for bleeding, as summarized in Table 1 (56). Considering all the above, the International League Against Epilepsy (ILAE) Task Force on Epilepsy in the elderly issued practical guidelines that state that the elderly should be treated as women of reproductive age and emphasize the importance of considering factors such as adverse events and pharmacokinetic interactions when choosing an ASMs, as well as the necessity of an individualized, multidisciplinary and patient-oriented approach (57).

*Table 1. Interactions of NOACs with ASMs**

ASMs	Interactions with NOACs
Carbamazepine	
Lacosamide	
Lamotrigine	
Levetiracetam	
Valproate	
Zonisamide	

Legend for Table 1.

- No relevant interactions
- Use with caution
- Contraindicated

*Adapted from Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676.

Conclusion

Cardiovascular comorbidities in epilepsy are common and result in poorer clinical outcomes. Although they are gaining increasing importance, most of the underlying pathophysiological mechanisms are still unknown. Early identification and adequate treatment of cardiovascular disorders is imperative in the treatment of patients with epilepsy and requires a change in the way epilepsy is perceived by clinicians. Routine cardiological evaluations should be incorporated into the management of these patients. ECG can be a useful tool in the assessment of the initial cardiovascular risk, as well as in determining the impact of ASMs and epileptic seizures on heart function. Risk factors and comorbidities must be taken into account when choosing ASMs, whose potential adverse effects need to be closely monitored. The clinical care of patients with epilepsy needs to include a personalized and holistic approach.

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References

1. World Health Organization. (2023, February) Retrieved from: https://www.who.int/health-topics/epilepsy#tab=tab_1
2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58:512–521
3. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016;15:106–115.
4. Aaberg KM, Bakken IJ, Lossius MI, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics. 2016;138
5. Doherty AJ, Harrison J, Christian DL, Boland P, Harris C, Hill JE et al. Br. J. Neurosci. Nurs. 2022 18:2, 98-106.
6. Mula M, Kanner AM, Jetté N, Sander JW. Psychiatric Comorbidities in People With Epilepsy. Neurol Clin Pract. 2021 Apr;11(2):e112-e120
7. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia. 2012 Aug;53(8):1282-93.
8. Selassie AW, Wilson DA, Martz GU, Smith GG, Wagner JL, Wannamaker BB. Epilepsy beyond seizure: a population-based study of comorbidities. Epilepsy Res 2014;108:305–15.
9. Lamberts RJ, BlomMT,Wassenaar M, Bardai A, Leijten FS, de Haan G-J, et al. Sudden cardiac arrest in people with epilepsy in the community. Neurology 2015;85:212–8.
10. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. J Neurol Neurosurg Psychiatry 2015;86:309–13.
11. Bardai A, Lamberts RJ, Blom MT, Spanjaart AM, Berdowski J, et al. Epilepsy Is a risk factor for sudden cardiac arrest in the general population. PLoS ONE 2012;7(8)e42749.
12. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MCJM, Tan HL. Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications. Heart 2015;101:17–22.
13. Stecker EC, Reinier K, Uy-Evanado A, Teodorescu C, Chugh H, Gunson K et al. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. Circ Arrhythm Electrophysiol. 2013 Oct;6(5):912-6.
14. Verrier RL, Pang TD, Nearing BD, Schachter SC. The epileptic heart: concept and clinical evidence. Epilepsy Behav 2020; 105: 106946.
15. Zack M, Luncheon C. Adults with an epilepsy history, notably those 45-64 years old or at the lowest income levels, more often report heart disease than adults without an epilepsy history. Epilepsy Behav. 2018 Sep;86:208-210.
16. Brigo F, Lochner P, Nardone R, Manganotti P, Lattanzi S. Increased risk of stroke and myocardial infarction in patients with epilepsy: A systematic review of population-based cohort studies. Epilepsy Behav. 2020 Mar;104(Pt B):106307.
17. Janszky I, Hallqvist J, Tomson T, Ahlbom A, Mukamal KJ, Ahnve S. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy--the Stockholm Heart Epidemiology Program. Brain. 2009 Oct;132(Pt 10):2798-804.
18. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry. 2016 Jan;87(1):69-74.

19. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. 2014 Aug;23(7):496-505.
20. Fialho GL, Wolf P, Walz R, Lin K. Increased cardiac stiffness is associated with autonomic dysfunction in patients with temporal lobe epilepsy. Epilepsia. 2018 Jun;59(6):e85-e90.
21. Liu Z, Thergarajan P, Antonic-Baker A, Chen Z, Sparks PB, Lannin NA, Kwan P, Jones NC, Casillas-Espinosa PM, Perucca P, O'Brien TJ, Sivathamboo S. Cardiac structural and functional abnormalities in epilepsy: A systematic review and meta-analysis. Epilepsia Open. 2023 Mar;8(1):46-59.
22. Nazish S. Obesity and metabolic syndrome in patients with epilepsy, their relation with epilepsy control. Ann Afr Med. 2023 Apr-Jun;22(2):136-144.
23. Kobau R, Zahran H, Thurman DJ, Zack MM, Henry TR, Schachter SC et al. Centers for Disease Control and Prevention (CDC). Epilepsy surveillance among adults--19 States, Behavioral Risk Factor Surveillance System, 2005. MMWR Surveill Summ. 2008 Aug 8;57(6):1-20.
24. Vooturi S, Jayalakshmi S. Metabolic syndrome in people with epilepsy. *Epilepsy Behav* 2020; 106: 106992.
25. Li MCH, O'Brien TJ, Todaro M, Powell KL. Acquired cardiac channelopathies in epilepsy: Evidence, mechanisms, and clinical significance. Epilepsia. 2019 Sep;60(9):1753-1767.
26. Wang J, Huang P, Yu Q, Lu J, Liu P, Yang Ye et al. Epilepsy and long-term risk of arrhythmias. Eur Heart J. 2023 Sep 14;44(35):3374-3382.
27. Desai R, Rupareliya C, Patel U, Naqvi S, Patel S, Lunagariya A, *et al.* Burden of arrhythmias in epilepsy patients: a nationwide inpatient analysis of 1.4 million hospitalizations in the United States. *Cureus* 2017;**9**:e1550.
28. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MC, Tan HL. Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications. Heart. 2015 Jan;101(1):17-22.
29. Hookana E, Ansakorpi H, Kortelainen ML, Junttila MJ, Kaikkonen KS, Perkiömäki J et al. Antiepileptic medications and the risk for sudden cardiac death caused by an acute coronary event: a prospective case-control study. Ann Med. 2016;48(1-2):111-7.
30. Shmuely S, van der Lende M, Lamberts RJ, Sander JW, Thijs RD. The heart of epilepsy: Current views and future concepts. Seizure. 2017 Jan;44:176-183
31. Josephson CB, Wiebe S, Delgado-Garcia G, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT et al. Association of Enzyme-Inducing Antiseizure Drug Use With Long-term Cardiovascular Disease. JAMA Neurol. 2021 Nov 1;78(11):1367-1374.
32. Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: a narrative review. Seizure. 2014 Oct;23(9):677-84.
33. Renoux C, Dell'Aniello S, Saarela O, Filion KB, Boivin JF. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: a population-based cohort study. BMJ Open. 2015 Aug 12;5(8):e008365.
34. Calik M, Ozkan HY, Ethemoglu O, Koca B, Kazanasmaz H, Karacan N et al. The measurement of both carotid intima-media thickness and epicardial adipose tissue thickness in children with epilepsy receiving antiepileptic drug therapy. Epilepsy Behav. 2018 Aug;85:110-114.
35. Safarpour Lima B, Mohamadzadeh A, Dadras M, Mahdavi A, Mansouri B, Farazdaghi M. Carotid intima-media and epicardial adipose tissue thickness in adult patients with epilepsy taking anti-seizure medication and its long-term significance. Epilepsy Behav. 2021 Dec;125:108432.
36. Toffa DH, Touma L, El Meskine T, Bouthillier A, Nguyen DK. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. Seizure. 2020 Dec;83:104-123.
37. Dapic Ivancic B, Nankovic S, Vujevic A, Cajic I, Petelin Gadze Z. Case report of patient with bradycardia as a complication of VNS therapy and psychiatric worsening after turning VNS off. Neurol Sci. 2022 Jan;43(1):735-738.
38. Kato H, Fujimoto A, Okanishi T, Sugiura R, Ijima K, Enoki H. New onset syncopal events following vagus nerve stimulator implantation might be key to preventing vagus nerve stimulation-induced symptomatic bradycardia - A case report and review. Epilepsy Behav Case Rep. 2018 Apr 25;10:57-60.
39. Keithler A, Ashcroft C, Sabado R, et al. Be still my beating heart: Complete heart block and ventricular asystole caused by vagal nerve stimulation therapy. J Am Coll Cardiol. 2023 Mar, 81 (8_Supplement) 3912.
40. Verrier RL, Pang TD, Nearing BD, Schachter SC. The Epileptic Heart and the Case for Routine Use of the Electrocardiogram in Patients with Chronic Epilepsy. Neurol Clin. 2022 Nov;40(4):699-716.
41. Surges, R., Taggart, P., Sander, J.W. and Walker, M.C. (2010), Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. Epilepsia, 51: 738-744.
42. Surges R, Shmuely S, Dietze C, Ryvlin P, Thijs RD. Identifying patients with epilepsy at high risk of cardiac death: signs, risk factors and initial management of high risk of cardiac death. Epileptic Disord. 2021 Feb 1;23(1):17-39.
43. Kishk NA, Sharaf Y, Ebraheim AM, Baghdady Y, Alieldin N, Afify A, Eldamaty A. Interictal cardiac repolarization abnormalities in people with epilepsy. Epilepsy Behav. 2018 Feb;79:106-111.
44. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. Epilepsy Behav. 2013 Mar;26(3):421-6.

45. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility--consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol. 2011 Sep 20;58(13):1309-24.
46. Verrier RL, Nearing BD, Olin B, Boon P, Schachter SC. Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. Epilepsy Behav 2016;62:85
47. Pang TD, Nearing BD, Krishnamurthy KB, Olin B, Schachter SC, Verrier RL. Cardiac electrical instability in newly diagnosed/chronic epilepsy tracked by Holter and ECG patch. Neurology. 2019 Sep 3;93(10):450-458
48. Vu LC, Piccenna L, Kwan P, O'Brien TJ. New-onset epilepsy in the elderly. Br J Clin Pharmacol. 2018 Oct;84(10):2208-2217.
49. Bruun E, Virta LJ, Kälviäinen R, Keränen T. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. Epilepsy Behav. 2017 Aug;73:71-76.
50. Lee SK. Epilepsy in the Elderly: Treatment and Consideration of Comorbid Diseases. J Epilepsy Res. 2019 Jun 30;9(1):27-35.
51. Zaccara G, Lattanzi S, Cincotta M, Russo E. Drug treatments in patients with cardiac diseases and epilepsy. Acta Neurol Scand. 2020 Jul;142(1):37-49
52. Wynn E, Biskupiak J, Kim K, Munger MA. Pregabalin Use Increases the Risk of Acute Heart Failure in Patients With Heart Failure: A Population-Based Study. Circulation. 2022;146:A11912
53. Liang D, Gardella E, Kragholm K, Polcwiartek C, Sessa M. The Relationship Between Valproate and Lamotrigine/Levetiracetam Use and Prognosis in Patients With Epilepsy and Heart Failure: A Danish Register-Based Study. J Card Fail. 2022 Apr;28(4):630-638.
54. Tanaka T, Fukuma K, Abe S, Matsubara S, Motoyama R, Mizobuchi M et al. PROPOSE Study Investigators. Antiseizure medications for post-stroke epilepsy: A real-world prospective cohort study. Brain Behav. 2021 Sep;11(9):e2330.
55. Acton EK, Gelfand MA, Hennessy S, Xie SX, Pollard JR, Kasner SE et al. Trends in oral anticoagulant co-prescription with antiepileptic drugs among adults with epilepsy, 2010-2018. Epilepsy Behav. 2020 Dec;113:107550.
56. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676.
57. Piccenna, L, O'Dwyer, R, Leppik, I, Beghi, E, Giussani, G, Costa, C et al. Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly. Epilepsia. 2023; 64: 567–585.

Perioperative anaesthetic management of patient with amelia and phocomelia - case report

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Abstract:

Phocomelia is a congenital condition involving malformations of the arm and leg, resulting in a fin-like appendage. It is often caused by the mother's use of the drug thalidomide during pregnancy, with various mechanisms being proposed. There is no specific treatment for phocomelia or amelia, but in certain cases surgical intervention may be recommended to improve limb function or other functional outcomes. This case report concerns a ten-year-old female patient with congenital amelia of the upper extremities and phocomelia of the lower extremities who was admitted to the hospital for elective thoracic scoliosis surgery It is a demanding and long-term operation with estimated major blood loss. In addition, the prone position of the patient makes access difficult in case of resuscitation, and therefore the role of the anesthesiologist in the care of such patients is crucial in the perioperative period. When caring for such patients, there are many technical difficulties, starting with the monitoring of arterial pressure values. Furthermore, difficulties may arise related to peripheral venous access, which can be a great challenge, and the placement of a central venous catheter is sometimes indicated. Also, intubation can be difficult due to limited mobility of the cervical spine. Early and adequate preoperative assessment of the patient is essential for the induction and maintenance of safe anesthesia and postoperative care. The current review of the literature does not reveal strict recommendations on the optimal treatment of these patients. Due to all the above-mentioned difficulties, preoperative preparation and assessment are of key importance for the introduction and maintenance of safe anesthesia, as well as postoperative care.

Keywords: phocomelia, amelia, scoliosis, anaesthetic management, anaesthesia

Sažetak:

Perioperativna anestezиološka skrb pacijenta sa amelijom i fokomelijom - prikaz slučaja

Fokomelija je kongenitalno stanje koje uključuje malformacije ruku i nogu, što rezultira privjeskom poput peraje. Često je uzrokovana majčinom uporabom lijeka talidomida tijekom trudnoće, uz predložene različite mehanizme objašnjenja. Ne postoji specifično liječenje fokomelije ili amelije, ali u određenim slučajevima može se preporučiti kirurška intervencija za poboljšanje funkcije ekstremiteta ili drugih funkcionalnih ishoda. U ovom prikazu slučaja radi se o desetogodisnjoj bolesnici sa kongenitalnom amelijom gornjih ekstremiteta i fokomelijom donjih ekstremiteta koja je primljena je u bolnicu na elektivnu operaciju torakalne skolioze. Radi se o zahtjevnom i dugotrajnom operativnom zahvatu sa velikim procijenjenim gubicima krvi. Osim toga, potrbušni položaj bolesnika otežava pristup u slučaju reanimacije te je stoga uloga anesteziologa u zbrinjavanju ovakvih bolesnika ključna u perioperativnom razdoblju. Kod zbrinjavanja ovakvih bolesnika postoji mnogo tehničkih poteškoća počevši od monitoriranja vrijednosti arterijskog tlaka, a mogu se pojaviti poteškoće vezane uz periferni venski pristup

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što može predstavljati veliki izazov te je ponekad indicirano postavljanje centralnog venskog katetera. Također, intubacija može biti otežana zbog ograničene mobilnosti vratne kralježnice. Rana i adekvatna prijeoperacijska procjena bolesnika ključna je za indukciju i održavanje sigurne anestezije i postoperativne skrbi. Trenutačno pregledom literature ne nalaze se stroge preporuke o optimalnom liječenju ovih bolesnika. Zbog svih navedenih poteškoća, prijeoperacijska priprema i procjena od ključne su važnosti za uvođenje i održavanje sigurne anestezije, kao i postoperativne skrbi.

Ključne riječi: fokomelija, amelija, skolioza, anesteziološka skrb, anestezija

Introduction

Phocomelia is a congenital condition that involves malformations of human arms and legs which results in a flipper-like appendage, while amelia is congenital absence of arms or legs or both (1). A prominent cause of phocomelia is the mother's use of the drug thalidomide (which was marketed for treating anxiety and morning sickness) during pregnancy; however, the causes of most cases are to be determined (2). Various explanatory mechanisms have been proposed, including genetic mutations, teratogenic exposures during embryonic development as mentioned above and environmental influences (3). Aside from the teratogenicity of thalidomide, researchers have assumed that phocomelia may be caused by anomalous origins of the subclavian artery (4). There is no specific treatment for phocomelia nor amelia, but in certain cases, a surgical intervention may be recommended for improving limb function or other functional outcomes (5). The anesthetist faces a variety of difficulties, particularly when treating patients with phocomelia. Some of these challenges include difficulty in monitoring blood pressure, venous access, difficult intubation and fluid management. Also spinal abnormalities, such as spina bifida, scoliosis, and anterior fusion of the thoracic and lumbar vertebrae, may make spinal or epidural anesthesia more difficult (6).

Case report

A 10 year old patient with congenital amelia of upper extremities and phocomelia of lower extremities was admitted to the hospital for elective surgery of thoracic scoliosis. Besides, the patient had suffered from vesicoureteral reflux of 2nd grade as well as from urovaginal reflux. Phocomelia patients have mobility restrictions and require assistance in transport to theatre. Scoliosis surgery is a demanding and long-term operation with estimated major blood loss. A study conducted by Xuerong Yu and associates has shown that more than half of the patients (59.7%) undergoing scoliosis surgery had massive blood loss (7). In addition, the prone position of the patient makes access difficult in case of resuscitation, and therefore the role of the anesthesiologist in the care of such patients is crucial in the perioperative period. Before the operation was performed, the patient was assessed by anaesthesiologist and was assigned ASA III (American Society of Anesthesiologists score is a subjective assessment of a patient's overall health that is based on five classes) due to severe congenital malformation with orthopedic and urological comorbidities. Apart from that, her physical condition was overall satisfying. Past anesthetic procedures have passed without complications. However, due to her condition that affects total body surface and volume distribution, preoperative preparation and assessment is of key importance in inducing and maintaining safe anesthesia as well as postoperative care. The patient was pre-medicated by midazolam and accompanied to the operating room by medical staff. After checking the identity and documentation, non-invasive blood pressure (NIBP) was placed on the right leg appendage. Furthermore, electrocardiogram (ECG) electrodes were placed on the chest as part of standard anaesthetic monitoring as well as pulse oximeter for oxygen saturation (SpO2) measurement on the right ear. Standard monitoring was extended by bispectral index monitoring (BIS). Initially, the patient was cardiopulmonary compensated with preoperative blood pressure of 120/60 mmHg and heart rate of 70 beats per minute. Her oxygen saturation was 100% without oxygen therapy. Initial laboratory results including coagulation tests were in reference range, and no noted coagulation abnormalities were noted. Before the surgery started, a venous line had to be placed, but due to the lack of peripheral venous access, the external jugular vein on the neck was cannulated. After careful denitrogenation, general endotracheal anesthesia was induced, and airway secured by flexible endotracheal tube number 5.5 with cuff. After induction, a urinary catheter and nasogastric tube were inserted. Drugs used for induction were midazolam, propofol, sufentanil and vecuronium. The patient was put on mechanical ventilation in volume mode. Anesthesia was maintained with propofol continuously on perfusor by rate of 160 mg/h with vecuronium fractionated to keep the patient's muscles relaxed. The patient prophylactically received cefazolin 400 mg intravenously (iv) to prevent infection and tranexamic acid 250 mg iv to reduce intraoperative bleeding. Surgery was performed in the prone position. During the procedure, the patient was tachycardic up to 170 beats per minute, and hypotensive down to 80/40 mmHg. Volume was compensated with crystalloids and erythrocyte concentrate. She has lost

about 350 ml of blood. Intraoperative autotransfusion device was used and by so, 75 ml of blood was returned into the patient's bloodstream. Postoperatively, the patient was intubated, sedated and transported to the pediatric Intensive care unit (ICU). Soon after arrival, she was extubated, and during the further course of her stay was hemodynamically and respiratorily stable. The patient has received two doses of erythrocyte concentrate, as well as the necessary analgesia and sedation. She was parenterally hydrated with a glucose-electrolyte solution, but oral intake of food and liquids has not been started. Hemodynamically and respiratorily stable, she was transferred to the Orthopedic ICU, where cardiorespiratory monitoring was maintained regularly, antibiotic prophylaxis, analgesia and sedation were administered. The patient is furthermore transferred to the Ward, where she was bandaged regularly, and physical therapy was started under the supervision of physiotherapist. During her hospital stay, the patient started sitting in a wheelchair while the wound healing was satisfactory. The patient subjectively felt well and was discharged successfully from the hospital.

Discussion

There are currently no recommendations in literature regarding the optimum management of these patients. A variety of corrective surgical procedures may be undertaken for malformations associated with amelia and phocomelia. According to the definition of the Scoliosis Research Society, scoliosis is any lateral curvature of the spine in the frontal plane whose Cobb angle is greater than 10 degrees. There are a number of classifications of scoliosis. Considering the etiology, they can be divided into primary (idiopathic) and secondary. In childhood idiopathic are more common, and depending on the age of appearance, are divided into idiopathic infantile scoliosis that occurs in the first three years of life, juvenile scoliosis that occurs from the fourth to the tenth year life and adolescent that appear after the tenth year of life. The most common deformations (over 80% of deformities) are adolescent idiopathic scoliosis. (8). "Early onset scoliosis" is the term for scoliosis of idiopathic or secondary etiology that occurs before the age of ten. Severe curves and rapid progress can cause disorders of lung development, ventilation disorders, heart decompensation and respiratory insufficiency (9). In the treatment of early-onset scoliosis, a combination of conservative and, if necessary, surgical treatment is used. Conservative methods include physical therapy, plaster bandages, and orthotic hello traction. Surgical treatment for scoliosis is indicated, in general, for the curves exceeding 45 or 50 degrees by the Cobb's method. Larger the curve progress it is more difficult to treat. Posterior fusion with instrumentation has been a standard of the surgical treatment for scoliosis, while anterior instrumentation surgery has been a choice of treatment for the thoracolumbar and lumbar scoliosis because better correction can be obtained with shorter fusion levels (10). Due to the current advances in care, there are increasing numbers of adults affected by phocomelia that present with medical conditions that require emergency interventions (6). The challenges facing the anaesthesiologist, especially when dealing with patients who present phocomelia as part of a syndrome, are numerous and include difficulty in monitoring blood pressure. It may be impossible to measure the blood pressure non-invasively due to the absence of limbs or if they are attached to the trunk via very short appendages. Invasive blood pressure monitoring may itself be very challenging, too. The choice of arteries available is sometimes limited to the femoral and axillary arteries which may be aberrant in course and caliber causing major difficulties in accessing them. Alternative approaches for assessment of cardiovascular status to enable fluid management may need to be discussed, including non-invasive cardiac output monitoring. Furthermore, difficulties can occur regarding venous access; this can present a huge challenge as only central veins may be accessible. Early involvement of the anaesthetic team should be considered to secure central venous access or a peripherally inserted central catheter (PICC) in these patients, preferably on the day prior to the surgical procedure and in a high dependency environment. In these cases, ultrasound can be very helpful and is highly recommended (11). Also, intubation can be difficult due to the limited neck movement because of possible cervical spine abnormalities. Problems regarding regional techniques can be encountered as well due to the spinal deformities including anterior fusion of thoracic and lumbar vertebrae, spina bifida and scoliosis. It may make spinal or epidural anaesthesia more challenging (6). In cases where airway abnormalities are evident or when a difficult airway is expected, advanced planning, specialist instruments, and appropriately trained medical staff must be available. Also, some forms of phocomelia have been associated with micrognathia. The need for transfusion is usually dictated by the surgical procedure, but it should be mentioned that due to a reduced skeletal muscle mass which acts as a vascular reservoir, the need for blood transfusions may be increased (6). As already mentioned, appropriate preparation for difficult venous access must be addressed and central venous access should be considered.

Conclusion

Phocomelia is an extremely rare birth defect that falls under the broader category of congenital limb malformations, while amelia is the congenital absence of arms or legs or both. Perioperative anaesthetic management faces a variety of difficulties during treatment of these groups of patients. Some of the challenges include difficulty in monitoring blood pressure, venous access, difficult intubation and fluid management. Due to all of the above mentioned difficulties, preoperative preparation and assessment is of key importance in inducing and maintaining safe anesthesia as well as postoperative care.

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Conflict of interess
No conflict of interest to declare.

Ethical approval
For every elective and urgent procedure in our Hospital, it is required to obtain an informed consent form. The patient had signed the informed consent form and therefore gave the Hospital permission to perform procedures as well as use the data for scientific purposes with strong protection of personal information.

References
1. Hooper, G.; Tytherleigh-Strong, G. (2003). "The Classification of Phocomelia". Journal of Hand Surgery (British and European Volume). 28B (3): 215–217.
2. Amar, Emmanuelle (2011). "Phocomelia: A Worldwide Descriptive Epidemiologic Study in a Large Series of Cases From the International Clearinghouse for Birth Defects Surveillance and Research, and Overview of the Literature". American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 15 (4): 305–320. doi:10.1002/ajmg.c.30320. PMC 4427055. PMID 22002800.
3. Davis DD, Kane SM. Phocomelia. [Updated 2022 Jun 21]. In: StatPearls [Internet]; [cited 2023 Nov 17] Available from: https://www.ncbi.nlm.nih.gov/books/NBK559212/
4. Van der Horst RL, Gotsman MS. Anomalous origin of the subclavian artery associated with phocomelia. S Afr Med J. 1971 Dec 18;45(48):1397-9. PMID: 5136042.
5. National Organization fore Rare Disorders. [Internet]; [cited 2023 Nov 17] . Available from: https://rarediseases.org
6. Orphan Anesthesia. [Internet]; [cited 2023 Nov 17] . Available from: https://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/phocomelia/1645-phocomelia-2-1/file.html
7. Yu X, Xiao H, Wang R, Huang Y. Prediction of massive blood loss in scoliosis surgery from preoperative variables. Spine (Phila Pa 1976). 2013 Feb 15;38(4):350-5. doi: 10.1097/BRS.0b013e31826c63cb. PMID: 22872215.
8. Scoliosis Research Society. [Internet]; [cited 2023 Nov 17] . Available from: https://www.srs.org/
9. Ruiz G, Torres-Lugo NJ, Marrero-Ortiz P, Guzmán H, Olivella G, Ramírez N. Early-onset scoliosis: a narrative review. EFORT Open Rev. 2022 Aug 4;7(8):599-610. doi: 10.1530/EOR-22-0040. PMID: 35924646; PMCID: PMC9458941.
10. Maruyama, T., Takeshita, K. Surgical treatment of scoliosis: a review of techniques currently applied. Scoliosis 3, 6 (2008). https://doi.org/10.1186/1748-7161-3-6
11. Lamperti, M., Bodenham, A.R., Pittiruti, M. et al. International evidence-based recommendations on ultrasound-guided vascular access. Intensive Care Med 38, 1105–1117 (2012). https://doi.org/10.1007/s00134-012-2597-x

The reality of a real-world stroke patient – extended time window, low ASPECTS, and a good outcome

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Abstract:

Mechanical thrombectomy (MT) is recommended in patients with anterior large vessel occlusion from 6 to 24 hours after stroke onset in selected patients with baseline ischemia defined by Alberta stroke program early CT score (ASPECTS) ≥ 6. Recent studies have shown that carefully selected patients with lower ASPECTS 3-5 and even with ASPECTS 0-2 could benefit from MT.

A 45-year-old patient was admitted to our emergency department 14 hours after the stroke onset. The neurological assessment revealed severe dysarthria, gaze palsy to the right, and severe left arm and leg palsy. His National Institutes of Health Stroke Scale (NIHSS) score was 10. The emergent brain CT scan showed large right middle cerebral artery territory infarction with right internal carotid artery and right M2 segment occlusion on CT angiography. The ASPECTS was 2. CT perfusion showed a good core/penumbra mismatch ratio in temporal/peri-insular parts and basal ganglia. The MT was performed 14 hours after the stroke onset with a TICI 2b score. The treatment was complicated by the progression of severe brain edema and brain herniation which required emergent decompressive craniectomy. The patient was discharged to the neurorehabilitation center after 26 hospital days with an NIHSS 10. On the last outpatient visit, after three months, the patient scored 5 on NIHHS and 3 on the 3-month Modified Rankin Score.

Our patient was successfully treated by MT despite a low ASPECTS and extended time window. Further randomized control trials are necessary to define which subgroup of these patients can benefit from MT.

Keywords: ASPECTS, extended time window, large baseline ischemia, mechanical thrombectomy

Sažetak:

Realnost pacijenta s moždanim udarom u stvarnom svijetu – produženi vremenski prozor, niski ASPECTS i dobar ishod

Mehanička trombektomija (MT) indicirana je za liječenje okluzije velike krvne žile u prednjem moždanom krvotoku u proširenom vremenskom prozoru (6 do 24h nakon nastanka simptoma) za bolesnike koji su zadovoljili neuroradiološke kriterije, definirane prema Alberta stroke program Early CT score (ASPECTS) bodovnom sustavu kao ≥ 6. Nove studije su pokazale kako MT poboljšava ishod u bolesnika koji imaju niski ASPECTS 3-5, pa čak i vrlo niski ASPECTS 0-2.

Bolesnik u dobi od 45 godina dovezen je u hitnu službu zbog akutnog moždanog udara 14 sati nakon početka simptoma. Pri pregledu je bio teško dizartričan s parezom pogleda u lijevo te teškom parezom lijevih ekstremiteta. The National Institutes of Health Stroke Scale (NIHSS) je iznosio 10. Hitni CT mozga pokazao je ishemijske promjene u opskrbnom području desne srednje moždane arterije (ACM) uz ASPECTS 2, a CT angiografija okluziju desne karotidne arterije i desne ACM. CT perfuzija je

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pokazala povoljan omjer jezgre i penumbre temporalno, periinzularno i u bazalnim ganglijima. MT je učinjena 14 sati nakon početka simptoma sa TICI 2b rezultatom. Liječenje je komplicirano razvojem moždanog edema radi čega je učinjena hitna dekompresijska kranijektomija. Bolesnik je otpušten na neurorehabilitaciju s NIHSS 10 i s The Modified Rankin Score-om (mRS) 4. Tri mjeseca nakon moždanog udara, bolesnik ima lakšu hemiparezu lijevih ekstremiteta. NIHHS iznosi 5, a mRS nakon tri mjeseca 3.
Bolesnik je uspješno liječen MT u proširenom vremenskom prozoru unatoč niskom ASPECTS-u. Potrebna su daljnja istraživanja kako bi se ustvrdilo koji bolesnici s niskim ASPECTS-om mogu imati dobar ishod nakon MT.

Ključne riječi: ASPECTS, mehanička trombektomija, opsežne ishemijske promjene, prošireni vremenski prozor

Introduction

Mechanical thrombectomy (MT) is a standard of care in acute ischemic stroke patients with large vessel occlusion (LVO) in anterior circulation in the early period (up to 6 hours) after the stroke onset. (1) MT is also recommended for selected patients presenting late (between 6 and 24 hours after the stroke onset) who meet specific advanced imaging criteria. (2) According to current guidelines, only patients with < 1/3 middle cerebral artery (MCA) territory involvement on CT/MRI are eligible for MT, thus all patients with large core infarcts, defined by Alberta Stroke Program Early CT score (ASPECTS) as < 6 are not suited for MT. (3,4)
Recent trials aimed to widen indications for MT in patients who did not meet these criteria by expanding the time window, using different imaging modalities but mostly focusing on whether MT is beneficial in patients with anterior LVO stroke presenting with a large baseline ischemia. Although some of them did not show any or at least no clear benefit of MT in patients with ASPECTS < 6, (5,6) according to the results of big RCTs (7-10) MT is safe and effective in patients with ASPECTS < 6. (7-10) Even though the studies mainly focused on patients presenting in a late time window with ASPECTS 3-5, (11) some trials showed a good functional outcome after MT in some patients with ASPECTS of 2 and even less than 2. (11,12)
We present a case of a patient with anterior LVO stroke and ASPECTS 2 in whom MT was performed in extended time window.

Case report

A 45-year-old male patient with no previous medical history and premorbid modified Rankin score (mRS) 0 was admitted to Sestre Milosrdnice University Hospital Center at about 10 am with severe dysarthria, gaze palsy to the right, central paresis of the left facial nerve, moderate left arm paresis, and severe left leg paresis. The NIH Stroke Scale (NIHSS) score was 10. The patient felt slight left arm and leg weakness the day before admission at about 9 pm but went to sleep regardless. On the day of admission, at about 9 am, his girlfriend noticed that he had some speech difficulties, so she called the ambulance.
The emergent brain CT scan showed right middle cerebral artery (MCA) infarction with ASPECTS of 2. The cerebral CT angiography (CTA) showed right internal carotid artery (ICA) occlusion with hypoperfusion in M1 and distal occlusion in the M2 segment. The collateral flow was improved. (Figure 1) CT perfusion showed mismatch ratio in temporal/ peri-insular parts and basal ganglia, and in frontal cranial/cortical segments. The MT was performed 14 hours after the stroke onset with a TICI 2B score. Maneuvers with stent retrievers revealed underlying dissection in cervical segment of the right ICA as a probable cause of stroke. (Figure 2)
The CT scan done eight hours after the procedure showed fronto-temporooccipital (FTO) hyperdensity, meaning either hemorrhage or extravasation of contrast, and loss of grey-white differentiation in the affected area. (Figure 3) The CT scan done 24 hours after MT showed an extensive hypodensity in the right MCA territory with a shift of midline structures to the left and regressive dynamic of FTO hyperdensity. On the third hospital day, the patient started to deteriorate in the state of consciousness scoring a 12 on NIHSS and a 10 on Glasgow Coma Scale (GCS). He was intubated and mechanically ventilated. The control CT scan was performed showing severe brain edema, midline shift to the left, brain herniation, and left ventricle enlargement due to CSF obstruction. (Figure 4) An emergent decompressive craniectomy was performed. Seven days after the procedure, the patient started to neurologically improve. He was extubated and scored 15 on GCS and 10 on NIHSS. Two consecutively performed CT scans, on the 7th and 15th day post craniectomy revealed a regressive dynamic of edema with some subarachnoid hemorrhage at the craniectomy site and well-demarcated subacute ischemia in the right cerebral hemisphere. (Figure 5)

Figure 1. CT angiography showing acute ischemia in the right MCA territory, right ICA and MCA occlusion and good collateral flow

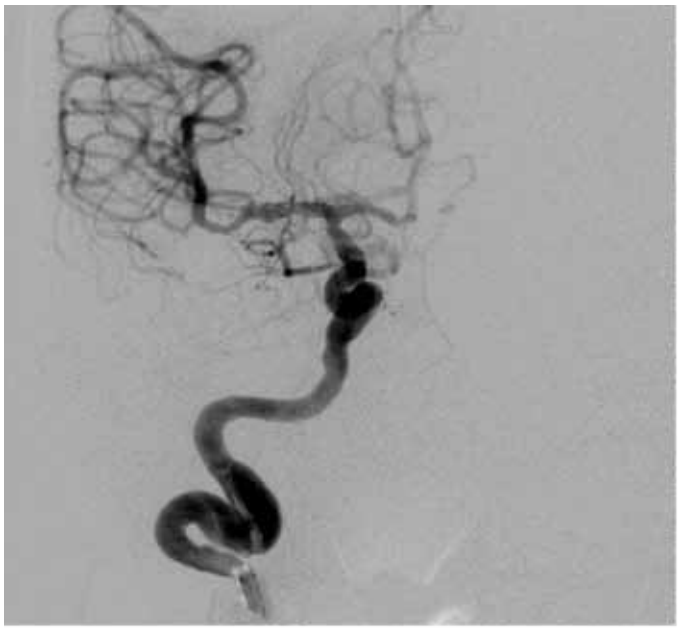

Figure 2. MT procedure done with a TICI 2b score- frontal branch of the M2 opened by stent-retriever, parietal branch remains closed

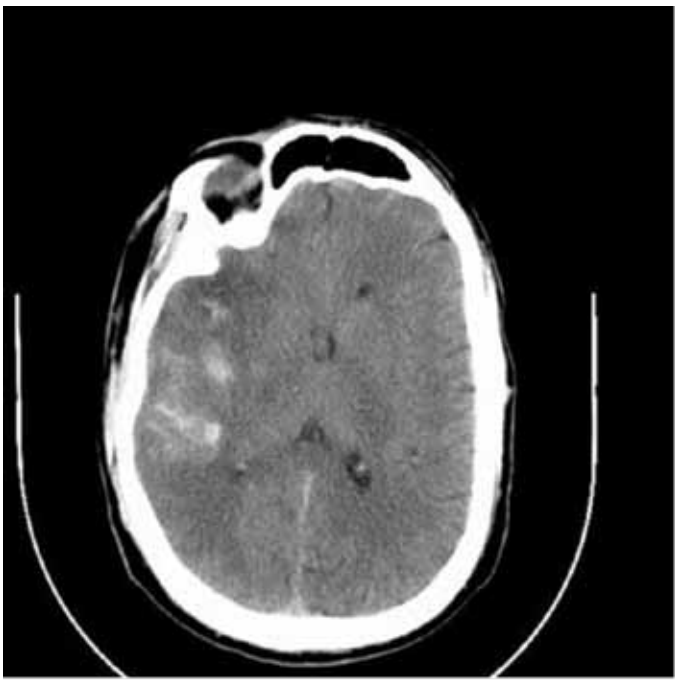

Figure 3. CT scan 8 hours after MT showing right FTO extravasation of contrast/ hemorrhage and loss of grey/white matter differentiation in the right temporal lobe

Figure 4. CT scan on 3rd hospital day - severe progression of brain edema and brain herniation

Figure 5. CT scan 15 days post craniectomy - regressive dynamic of edema and well-demarcated subacute ischemia in the right cerebral hemisphere

The control CTA showed dissection flap in the extracranial part of the right ICA in the C2 segment, without blood flow limitation. The results of neurosonology, Holter ECG, transthoracic, and transesophageal heart ultrasound were normal. His blood pressure and blood sugar were normal.
The patient was treated with antiplatelets, LMH, analgesics, antiulcer medication, antiedematous drugs, and hypolipemic drugs. Speech therapy and neurorehabilitation were performed through all phases of stroke recovery.
The patient was discharged to the neurorehabilitation center after 26 hospital days, with NIHSS 10 and mRS 4. He was prescribed acetylsalicylic acid, pantoprazole, atorvastatin, and dietary supplements.
In the latest outpatient visit, three months after the stroke onset, the neurological assessment revealed mild dysarthria, mild left leg paresis, moderate left arm paresis, and supranuclear left facial nerve palsy. His NIHSS was 5 and a 3-month mRS 3.

Discussion

Our patient presented in an extended time window from stroke onset with acute ischemic changes in >1/3 MCA territory and ASPECTS of 2, thus he did not meet current guidelines for reperfusion therapy. Considering age, no relevant medical history, and neuroimaging results, we decided to perform MT 14 hours after stroke symptoms. The reperfusion was successful with a TICI 2b score.
There are published research on performing MT in a subgroup of patients with ASPECTS < 6 in early and extended time and a some of them showed benefit of MT even in patients with ASPECTS <3. (12,13)
Successful recanalization (TICI ≥2b) is a predictor of a good functional outcome regardless of whether the patients are treated in an early or late time window according to Almallouhi et.al. (13) Moreover, this study on 2345 stroke patients showed that every 5th patient with ASPECTS 2-5 would benefit from MT if successful recanalization was achieved. (13) In another study from the German Stroke Registry on 1700 patients, 22% of patients with baseline ASPECTS <6 successfully treated with MT achieved independence with mRS scores 0 to 2 at 90 days. Most of the patients were younger, had moderate stroke symptoms, and had no relevant premorbid disability. (14) Similar results with a good functional outcome of mRS 0-2 were shown in patients with baseline ASPECTS 3-5 if MT was performed in a time window of up to 17.6 hours. (15) The RESCUE-Japan-LIMIT study on 203 anterior LVO patients with ASPECTS 3-5 showed better functional outcomes (mRS 0-3) in 31% of patients treated with MT compared to 12.7% of them in the medical care group. (16) In the SELECT trial in 31% of patients with ASPECTS ≤5 who underwent MT functional independence was achieved. (8) The Angel-ASPECT and TENSION studies conducted on patients with ASPECTS 3-5 have shown similar results. (11) TESLA study on patients with baseline ASPECTS 2-5 found greater rates of mRS 0-3 in patients who underwent MT than in those medically treated, with some greater rate of symptomatic intracranial hemorrhage (sICH), but not altering the functional outcome. (12)
Symptomatic intracranial hemorrhage occurred in 6% of patients treated with thrombectomy versus 5% of patients with medical treatment alone in the TENSION trial. (10) The SELECT trial found similar rates of sICH in MT and medically treated groups of patients. (11) While the Japan-LIMIT study did not show the difference in rates of sICH in patients with ASPECTS 4-5, there was a greater rate of sICH in MT patients with baseline ASPECTS of ≤ 3. (16) Based on the prompt regressive dynamic of changes shown on consecutive CT scans the hyperdensity seen in our patient was most likely contrast extravasation. He did develop a small subarachnoid hemorrhage but because of a craniectomy procedure.
The severe cerebral edema and neurological worsening in our patient can be explained by extensive ischemic brain changes found in MCA strokes in medically treated patients but also in 22% of patients treated with MT because of reperfusion. (12) Whether the final core volume and edema evolution would be the same if our patient wasn't treated with MT is hard to predict. It was shown that MT in patients with large core infarcts is as-

sociated with a significant reduction in final infarct volumes and even lowers the rates of neurosurgical procedures. (8,17) It is also hard to estimate how much good collateral flow contributed to our patient's outcome. None of the 6 RCTs included collateral flow status as inclusion/exclusion criteria when performing MT in patients with low baseline ASPECTS. (7-10,11,16)
Some research on patients with a large baseline core infarct defines good functional outcome as a more commonly used score of 0-2, (14,15) while some RTCs defined it as 3-month mRS 0-3. (8,12) Considering our patient's final neurological state and possible complications if not treated, we consider his 3-month mRS 3 as a satisfying functional outcome.

Conclusion

Our case shows that selected patients with ASPECTS 0-2 could benefit from MT performed in an extended time window. Nevertheless, the approach to every patient is individual. Further well-designed RCTs are necessary to define selection criteria for this subgroup of patients, not to exclude but include as many as patients possible who would benefit from MT.

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References

1. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke [published correction appears in N Engl J Med. 2015 Jan 22;372(4):394]. N Engl J Med. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587
2. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic StrokeEndorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J. 2019;4(1):6-12. doi:10.1177/2396987319832140
3. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973
4. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442
5. Jovin TG, Nogueira RG, Lansberg MG, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. Lancet. 2022;399(10321):249-258. doi:10.1016/S0140-6736(21)01341-6
6. Virtanen P, Tomppo L, Martinez-Majander N, et al. Thrombectomy in Acute Ischemic Stroke in the Extended Time Window: Real-Life Experience in a High-Volume Center. J Stroke Cerebrovasc Dis. 2022;31(8):106603. doi:10.1016/j.jstrokecerebrovasdis.2022.106603
7. Yoshimura S, Sakai N, Yamagami H, et al. Endovascular Therapy for Acute Stroke with a Large Ischemic Region. N Engl J Med. 2022;386(14):1303-1313. doi:10.1056/NEJMoa2118191
8. Sarraj A, Hassan AE, Abraham MG, et al. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. N Engl J Med. 2023;388(14):1259-1271. doi:10.1056/NEJMoa2214403
9. Huo X, Ma G, Tong X, et al. Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. N Engl J Med. 2023;388(14):1272-1283. doi:10.1056/NEJMoa2213379
10. Bendszus M, Fiehler J, Subtil F, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct: multicentre, open-label, randomised trial. Lancet. 2023;402(10414):1753-1763. doi:10.1016/S0140-6736(23)02032-9
11. Ren Z, Huo X, Kumar JI, et al. Review of Current Large Core Volume Stroke Thrombectomy Clinical Trials: Controversies and Progress. Stroke: vascular and interventional neurology. 2022;2(5). doi:https://doi.org/10.1161/svin.121.000330
12. Kobeissi H, Adusumilli G, Ghozy S, et al. Endovascular thrombectomy for ischemic stroke with large core volume: An updated, post-TESLA systematic review and meta-analysis of the randomized trials [published online ahead of print, 2023 Jun 28]. Interv Neuroradiol. 2023;15910199231185738. doi:10.1177/15910199231185738
13. Almallouhi E, Al Kasab S, Hubbard Z, et al. Outcomes of Mechanical Thrombectomy for Patients With Stroke Presenting With Low Alberta Stroke Program Early Computed Tomography Score in the Early and Extended Window. JAMA Netw Open. 2021;4(12):e2137708. Published 2021 Dec 1. doi:10.1001/jamanetworkopen.2021.37708
14. Deb-Chatterji M, Pinnschmidt H, Flottmann F, et al. Predictors of independent outcome of thrombectomy in stroke patients with large baseline infarcts in clinical practice: a multicenter analysis. J Neurointerv Surg. 2020;12(11):1064-1068. doi:10.1136/neurintsurg-2019-015641
15. Broocks G, Hanning U, Bechstein M, et al. Association of Thrombectomy With Functional Outcome for Patients With Ischemic Stroke Who Presented in the Extended Time Window With Extensive Signs of Infarction. JAMA Netw Open. 2022;5(10):e2235733. Published 2022 Oct 3. doi:10.1001/jamanetworkopen.2022.35733
16. Uchida K, Shindo S, Yoshimura S, et al. Association Between Alberta Stroke Program Early Computed Tomography Score and Efficacy and Safety Outcomes With Endovascular Therapy in Patients With Stroke From Large-Vessel Occlusion: A Secondary Analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism-Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT) [published correction appears in JAMA Neurol. 2022 Dec 12;:]. JAMA Neurol. 2022;79(12):1260-1266. doi:10.1001/jamaneurol.2022.3285
17. Rebello LC, Bouslama M, Haussen DC, et al. Endovascular Treatment for Patients With Acute Stroke Who Have a Large Ischemic Core and Large Mismatch Imaging Profile. JAMA Neurol. 2017;74(1):34-40. doi:10.1001/jamaneurol.2016.3954

Non-steroidal anti-inflammatory drugs exacerbated respiratory disease – a condition overlooked by anesthesiologist

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Abstract:

NSAID-exacerbated respiratory disease (N-ERD) is a chronic eosinophilic, inflammatory disorder of the respiratory tract occurring in patients with asthma and/or chronic rhinosinusitis with nasal polyps (CRNwNP), symptoms of which are exacerbated by NSAIDs, including acetylsalicylic acid (ASA). The clinical reaction to NSAID develops within 30-180 min and it is manifested by upper and/or lower airway symptoms. The majority of N-ERD patients suffer from moderate to severe asthma. A diagnosis of N-ERD is fundamentally based on the patient's history. N-ERD is suspected in patients having a history of upper/lower respiratory reactions after ingestion of ASA/NSAIDs or suffering from asthma along with chronic rhinosinusitis and nasal polyps. In this paper 57 years old women with history of well controlled asthma, allergic rhinitis and allergy to ASA is presented. After surgical procedure of total knee arthroplasty, during intensive care unit (ICU) stay, ketoprofen was administrated. Soon after, the patient develops symptoms such as dyspnea with decreased oxygen saturation (SpO2) and heaviness in stomach followed by appearance of swelling and itching of elbows and feet. After administrated therapy patient's condition was improved. NSAIDs are frequently used analgesics and antipyretics that should be used with caution in patients who suffer from asthma.

Keywords: Acetylsalicylic acid, Asthma, Chronic rhinosinusitis with nasal polyps, Non steroidal anti-inflammatory drugs exacerbated respiratory disease

Sažetak:

Respiratorna bolest uzrokovana nesteroidnim protuupalnim lijekovima – često previđeno stanje

Respiratorna bolest uzrokovana nesteroidnim protuupalnim lijekovima (engl. N-ERD) je kronični eozinofilni upalni poremećaj dišnog puta koji se pojavljuje kod bolesnika s astmom i/ili kroničnim rinosinusitisom s nosnom polipozom (engl.CRNwNP), a čiji se simpotmi pogoršavaju primjenom nesteroidnih protuupalnih lijekova (engl. NSAID), uključujući acetilsalicilnu kiselinu (engl. ASA). Klinička reakcija uzrokovana primjenom nesteroidnih protuuplanih lijekova razvija se unutar 30-180 minuta i uobičajeno se očituje simptomima od strane gornjegi/ili donjeg dišnog puta. Većina bolesnika koji imaju od N-ERD boluje od umjerenog do teškog oblika astme. Dijagoza N-ERDa temelji se uglavnom na pacijentovoj povijesti bolesti. Na N-ERD treba posumnjati kod bolesnika koji imaju anamnezu reakcije gornje/donjeg dišnog puta nakon primjene ASA-e/NSAID-a ili boluju od astme s kroničnim rinosinusitisom i nosnim polipima. U ovom radu prezentirana je 57-godišnja bolesnica s anamnezom dobro kontrolirane astme, alergijskim rinitisom i alergijom na ASA-u. Nakon kirurškog zahvata totalne endoproteze koljena, a tokom boravka u jedinici intenzivnog liječenja (engl ICU), primjenjen je ketoprofen. Ubrzo nakon toga bolesnica je razvila simptome kao što su dispneja sa smanjenjenom saturacijom krvi kisikom (SpO2) i težinom u želucu nakon kojih se pojavilo oticanje i

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svrbež laktova i stopala. Nakon primjenjene terapije stanje bolesnice se poboljšalo. Može se zaključiti das u NSAID-I često korišteni analgetici i antipiretici koji trebaju biti primjenjivani s oprezom kod bolesnika koji imaju astmu.

Ključne riječi: Acetilsalicilna kiselina, Kronični rinosinusitis s nosnom polipozom, Nesteroidni protuupalni lijekovi, Respiratorna bolest uzrokovana nesteroidnim protuupalnim lijekovima

Introduction

Although acetylsalicilyc acid (ASA) intolerance is well known for more than hundred years, fifty years later Samter at al. were first who described non-steroidal anti- inflammatory drugs - exacerbated respiratory disease (N-ERD), clinical syndrome that typically includes hypersensitivity to aspirin and other non-steroidal anti- inflammatory drugs (NSAIDs).[1]

N-ERD is a chronic eosinophilic, inflammatory disorder of the respiratory tract occurring in patients with asthma and/ or chronic rhinosinusitis with nasal polyps (CRNwNP), symptoms of which are exacerbated by NSAIDs, i ASA.[2,3] The prevalence of N-ERD in general population is unknown, respiratory symptoms following NSAID intake have been reported by 1,8% of the European population.[2,4] The incidence of N-ERD varies from 5.5%- 12.4% in adult asthmatic and increase to 14.9% in patients with more severe asthma.[2,5] This syndrome remains a diagnostic and therapeutic challenge. Despite the morbidity and relatively high prevalence of this syndrome, the initial cause and the underlying mechanism remain incompletely explained.

In patients with N-ERD, the clinical reaction to aspirin or other NSAID is manifested by upper and/ or lower airway symptoms, which develop within 30-180 min.[6,7] The reaction usually starts with nasal congestion and /or rhinorrhea, followed by wheezing, coughing, and shortness of breath. Symptoms may appear much faster, progressing rapidly to severe bronchospasm or even leading to death, especially in patients with unstable asthma.[8] A subgroup of N-ERD patients will develop pronouncing flushing, urticarial, and/ or gastrointestinal symptoms.[8,9]

The majority of N-ERD patients suffer from moderate to severe asthma, although some patients may present with a mild asthma phenotype.[10,11] Clinical presentation of upper airway disease in N-ERD patients are usually symptoms such as nasal blockage, nasal congestion or stiffness, facial pain or pressure and nasal discharge/ postnasal drip.[12,13] Partial loss of smell or anosmia occurs more frequently in N-ERD patients.[12,14] Recurrence of nasal polyps after surgery is more frequent in N-ERD than NSAIDs tolerant CRNwNP patients.[13]

A diagnosis of NERD is fundamentally based on the patient's history. N-ERD is suspected in patients having a history of upper/ lower respiratory reactions after ingestion of ASA/ NSAIDs or suffering from asthma along with chronic rhinosinusitis and nasal polipes.[15]Even though up to date there there is a lot of knowledge about diagnosis and treatment of N-ERD, there are still gaps that should be addressed in the future. In this paper the case of patient who developed N-ERD is presented.

Case report

A 57 year old women was admitted to the hospital for planned surgical procedure of total knee arthroplasty. The patient had a history of well controlled asthma, allergic rhinitis and allergy to ASA. Postoperatively, during Intensive care unit (ICU) stay, ketoprofen was administrated. Soon after administration of ketoprofen, dyspnoea with decreased oxygen saturation (SpO_2) and heaviness in stomach has occured. The therapy with dexamethasone and chlorpyramine intravenously (iv) and inhalations of salbutamol was immediately started. Two hours later, erythema, swelling and itching of elbows and feet appeard. After administration of 125 mg of methylprednisolone iv, the symptoms partially regressed. A CT angiography was performed and there were no signs of pulmonary thromboembolism. The CT has shown confluent zones of ground glass changes and bilatelar narrow zones of lung parenchyma consolidation. There was no significant pericardial or pleural effusion. In consultation with pulmonologist, further therapy was prescribed: oxygenation through Venturi mask and depending on results of repeated acid-base status analysis, it was suggested to take in consideration usage of non invasive ventilation (NIV). In addition to latter one, it was recommended to administer 40 mg of methylprednisolone once per day in duration of seven days, salmeterole/ fluticasone inhalation 3 times per day, bilastine 1-2 tablets once daily, cefepime 2 g iv twice daily, as well as radiological and laboratory control.

Discussion

N-ERD is a unique and often clinically severe disease affecting a subgroup of adults with asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions with exposure to all cyclooxygenase 1 (COX-1) - inhibiting nonsteroidal anti-inflammatory drugs. It is heterogenous disorder with various clinical manifestations. Pathophysiology of N-ERD is complex. Two major patho-

genic mechanisms are: overproduction of cysteinyl leukotrienes with dysregulation of arachidonic acid metabolism and increased type 2 eosinophilic inflammation affected by genetic mechanisms.[15,16] According to the literature review in patients with N-ERD, the clinical reaction to ASA or other NSAIDs is developed within 30-180 min. It usually starts with nasal congestion and/or rhinorrhea, followed by wheezing, coughing, and shortness of breath. The majority of N-ERD patients suffer from moderate to severe asthma, although some patients may present with a mild asthma phenotype. In this case, patient with known history of asthma with allergic rhinitis and history of allergy to ASA was treated with ketoprofen. Symptoms appeared within 120 minutes after administration of ketoprofen. Patient presented with respiratory insufficiency, gastrointestinal symptoms and skin erythema, swelling and itching. After administrationon oxygen therapy, bronchodilatators, intravenous and inhaled corticosteroids, the patient's general condition has improved.

N-ERD may be optional diagnose when a clear history of multiple reactions develops within 1-2 hours after ingestion of NSAID, manifesting with respiratory symptoms in patient with adult-onset asthma and recurrent nasal polyposis. However, the reliance exclusively on a history may result in either under diagnosis or over diagnosis of NSAIDs hypersensitivity. In certain cases, a challenge test with ASA or culprit drug is necessary to establish the diagnosis.[2,3] Reliable *in* vitro biomarkers have yet not been identified.[15] The successful management of patient with N-ERD requires a collaboration among several specialist as well as pharmacological and non-pharmacological measures.

Conclusion

Ketoprofen and other NSAIDs are frequently used analgesics and antipyretics that should be used with caution in patients who suffer from asthma. A diagnosis of NERD is fundamentally based on the patient's history. The complete avoidance of culprit drugs is essential. Patients with N-ERD require comprehensive diagnostic and therapeutic approaches and pose a significant challenge for a physician.

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References

1. Samter M. Intolerance to Aspirin. Ann Intern Med. 1968 May 1;68(5):975.
2. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. BMJ. 2004 Feb 21;328(7437):434.
3. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013 Oct 5;68(10):1219–32.
4. Makowska JS, Burney P, Jarvis D, Keil T, Tomassen P, Bislimovska J, et al. Respiratory hypersensitivity reactions to NSAIDs in Europe: the global allergy and asthma network (GA ² LEN) survey. Allergy. 2016 Nov;71(11):1603–11.
5. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. <scp>NSAID</scp> -exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015 Jul 7;70(7):828–35.
6. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2017 Jul;5(4):1061-1070.e3.
7. Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. Respirology. 2005 Sep 26;10(4):477–84.
8. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D2: A dominant mediator of aspirin-exacerbated respiratory disease. Journal of Allergy and Clinical Immunology. 2015 Jan;135(1):245–52.
9. Hope AP, Woessner KA, Simon RA, Stevenson DD. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. Journal of Allergy and Clinical Immunology. 2009 Feb;123(2):406–10.
10. Schatz M, Hsu JWY, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. Journal of Allergy and Clinical Immunology. 2014 Jun;133(6):1549–56.
11. Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleecker ER, Borish L. Aspirin sensitivity and severity of asthma: Evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. Journal of Allergy and Clinical Immunology. 2005 Nov;116(5):970–5.
12. Mullol J, Picado C. Rhinosinusitis and Nasal Polyps in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am. 2013 May;33(2):163–76.
13. Kowalski M, Bienkiewicz B, Pawliczak R, Kordek P. Nasal Polyposis in Aspirin-Hypersensitive Patients with Asthma (Aspirin Triad) and Aspirin-Tolerant Patients. Allergy & Clinical Immunology International - Journal of the World Allergy Organization. 2003;15(06):246–50.
14. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA2LEN study. Allergy. 2011 Sep;66(9):1216–23.
15. Woo SD, Luu QQ, Park HS. NSAID-Exacerbated Respiratory Disease (NERD): From Pathogenesis to Improved Care. Front Pharmacol. 2020 Jul 28;11.
16. Rhyou HI, Nam YH, Park HS. Emerging Biomarkers Beyond Leukotrienes for the Management of Nonsteroidal Anti-inflammatory Drug (NSAID)-Exacerbated Respiratory Disease. Allergy Asthma Immunol Res. 2022;14(2):153.

Preoperative assessment of patient with APECED syndrome

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Abstract:

Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) or autoimmune polyglandular syndrome type 1 (APS-1) is a rare autosomal recessive genetic disease due to mutations in the AIRE (AutoImmune REgulator) gene. A 40 year old female patient who suffers from the above mentioned condition was admitted to the hospital due to ureterolithiasis and hydronephrosis of the left kidney. When a patient suffers from an autoimmune disease such as APECED syndrome, preoperative preparation and assessment is of key importance in inducing and maintaining safe anaesthesia. Regarding the major role that the adrenal gland plays in adaptive response to stress, a careful evaluation of corticoid therapy, both chronic and supplemental, was performed. In patients with primary adrenal insufficiency, the major clinical features of adrenal insufficiency are consequences of cortisol deficiency and also volume depletion and hypotension, resulting mainly from mineralocorticoid deficiency as well. Therefore, when patients with impaired hypothalamo-pituitary-adrenal (HPA) axis undergo a surgical procedure, a state of enhanced stress, preoperative preparation must be done in terms of administration of high doses of hydrocortisone to enable the patients organism to cope with very high stress as surgical stimuli as well as maintaining euvolemic and electrolyte balance.
This case has shown that comprehensive preoperative preparation and assessment of patients with primary immune deficiencies can minimize surgical complications and optimize patient outcomes. It is of key importance to predict and address potential metabolic disturbances when people with this or similar conditions that include impairment in HPA axis undergo surgical procedure because lack of preoperative optimization can lead to severe complications during surgery as well as in postoperative period.

Keywords: APECED, autoimmune disease, anaesthesia, preoperative

Sažetak:

Preoperativna priprema bolesnika sa APECED sindromom

Autoimuna poliendokrinopatija-kandidijaza-ektodermalna-distrofija (APECED) ili autoimuni poliglandularni sindrom tip 1 (APS-1) je rijetka autosomno recesivna genetska bolest uzrokovana mutacijama u genu AIRE (AutoImmune REgulator). Bolesnica stara 40 godina koja boluje od navedenog stanja primljena je u bolnicu zbog ureterolitijaze i hidronefroze lijevog bubrega. Kada osoba boluje od autoimune bolesti kao što je APECED sindrom, preoperativna priprema i procjena su od ključne važnosti za indukciju i održavanje sigurne anestezije. S obzirom na glavnu ulogu koju nadbubrežna žlijezda ima u adaptivnom odgovoru na stres, provedena je pažljiva procjena terapije kortikoidima, kako kronične tako i dopunske. U bolesnika s primarnom insuficijencijom nadbubrežne žlijezde, glavna klinička obilježja insuficijencije nadbubrežne žlijezde posljedica su nedostatka kortizola, a

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također i deplecije volumena i hipotenzije, što je također posljedica nedostatka mineralokortikoida. Stoga, kada pacijenti s oštećenom hipotalamo-hipofizno-nadbubrežnom (HPA) osovinom prolaze kroz kirurški zahvat, koji je stanje pojačanog stresa, mora se obaviti preoperativna priprema u smislu primjene visokih doza hidrokortizona kako bi se organizam bolesnika mogao nositi s vrlo visokim stres kao kirurški podražaj kao i održavanje euvolemijske i ravnoteže elektrolita.
Ovaj je slučaj pokazao da sveobuhvatna prijeoperacijska priprema i procjena bolesnika s primarnim imunološkim nedostatkom može minimizirati kirurške komplikacije i optimizirati ishode bolesnika. Od ključne je važnosti predvidjeti i riješiti potencijalne metaboličke poremećaje kada se osobe s ovim ili sličnim stanjima koja uključuju oštećenje HPA osi podvrgnu kirurškom zahvatu jer nedostatak preoperativne optimizacije može dovesti do teških komplikacija tijekom operacije kao iu postoperativnom razdoblju.

Ključne riječi: APECED, autominuna bolest, anestezija, preoperativno

Introduction

Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) or autoimmune polyglandular syndrome type 1 (APS-1) is a rare autosomal recessive genetic disease due to mutations in the AIRE (AutoImmune REgulator) gene. The clinical diagnosis is classically based on the presence of at least two of the three main components: chronic mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency (1). It causes a loss in central immune tolerance, failure to eliminate autoreactive T cells in the thymus, and their escape to the periphery (2).
Hereby is presented preoperative assessment and anaesthetic approach in the case of a female patient with APECED syndrome who was admitted to the Urology department for operative treatment of ureterolithiasis associated with second degree hydronephrosis of left kidney.

Case report

A 40 year old female patient was admitted to the hospital due to ureterolithiasis and hydronephrosis of left kidney. The patient had many clinical conditions associated with APECED syndrome such as Mb Addison, hypoparathyroidism, liver lesions, keratoconjunctivitis, diabetes mellitus type 1, onychomycosis, hyperlipidemia (3) and also underwent multiple surgeries regarding to colon perforation. The patient was assessed by anaesthesiologist and was assigned ASA III (American Society of Anesthesiologists score is a subjective assessment of a patient's overall health that is based on five classes) due to severe autoimmune syndrome combined with many comorbidities that are associated with the primary diagnosis. Apart from that, her physical condition was satisfying. She was cardiopulmonary compensated with preoperative blood pressure of 140/80 mmHg and heart rate of 50 beats per minute. Past anaesthetic procedures have passed without complications. Nevertheless, when a patient suffers from an autoimmune disease such as APECED syndrome, preoperative preparation and assessment is of key importance in inducing and maintaining safe anaesthesia as well as postoperative care. Regarding the major role that the adrenal gland plays in adaptive response to stress, which was hindered due to Mb Addison, a careful evaluation of corticoid therapy, both chronic and supplemental, was performed. In patients with primary adrenal insufficiency, the major clinical features of adrenal insufficiency are consequences of cortisol deficiency and also volume depletion and hypotension, resulting mainly from mineralocorticoid deficiency as well (4). Her chronic steroid therapy was continued preoperatively, consisting of 15 mg of hydrocortisone and 50 mcg of fludrocortisone. Additionally, another 100 mg of hydrocortisone was given intravenously on the day of surgery and the first postoperative day.
Regarding diabetes mellitus, the patient was on chronic insulin regimen that included long acting insulin (Degludec) before bedtime and fast acting insulin (Aspart) right after meals during the day. The dose of long acting insulin was halved the day before and fast acting insulin was omitted on the day of surgery. Blood glucose levels were often measured starting on admission to avoid hypo- or hyperglycemia, and safe target range was achieved with fast acting insulin. After careful preoperative preparation, the patient arrived at the operating room. Standard noninvasive monitoring was set up and the patient was preoxygenated with 100% oxygen by mask. After an anaesthetic induction with midazolam, sufentanil, propofol and rocuronium, the patient was intubated on the first attempt. As mentioned before, after induction, 100 mg was administered of SoluCortef (hydrocortisone). The monitoring was then extended in the way that SedLine was connected as well as invasive blood pressure (a. radialis lat. dex.). Intravascular euvolemic was maintained with crystalloids. Otherwise, the intraoperative course was uneventful. After the procedure, the neuromuscular blockade was reversed, the patient was awakened, extubated and sent to the Urology de-

partment. In the aftermath, the patient has successfully recovered and returned to her original chronic therapy regimen.

Discussion

APECED syndrome is an autoimmune disease, caused by mutations in the AIRE gene that codes for a protein called the autoimmune regulator. Those mutations reduce or eliminate the function of the autoimmune regulator protein that helps the body distinguish its own proteins and cells from those of foreign invaders (such as bacteria, fungi, and viruses). This reaction, which is known as autoimmunity, results in inflammation and can damage otherwise healthy cells and tissues (5). This causes damage to, among others, adrenal glands and patients with APECED syndrome usually suffer from Addison disease. Therefore, those patients are usually given hydrocortisone as part of their chronic therapy.

Primary adrenal insufficiency (Addison's disease) is due to adrenocortical disease, while secondary and tertiary adrenal insufficiency are due to disorders of the pituitary gland (ACTH secretion) or the hypothalamus (CRH secretion). Primary adrenal insufficiency is associated with both cortisol and mineralocorticoid deficiency. In contrast, secondary and tertiary adrenal insufficiency are associated with cortisol, but not mineralocorticoid deficiency, because aldosterone is regulated primarily by the renin-angiotensin system, which is independent of the hypothalamus and pituitary.

In this case cortisol and aldosterone cannot be secreted normally. Cortisol has a number of effects on the body that are thought to be carried out in order to help the body deal with a stressor that lasts longer than a few minutes. It acts to increase circulating levels of glucose in your blood as well. As glucose is a crucial energy source for our cells, this also provides our body extra energy to deal with the stressor. Also, cortisol acts during the experience of a serious stressor to inhibit processes that are deemed to be of lesser importance at the time (6). Clinical manifestations of mineralocorticoid deficiency include hyponatremia, hypovolemia, hypotension, hyperkalemia, and metabolic acidosis (7).

When patients with impaired HPA axis need to undergo a surgical procedure, which is a state of enhanced stress, preoperative preparation must be done in terms of administration of high doses of hydrocortisone to enable the patients organism to cope with very high stress as surgical stimuli as well as maintaining euvolemic and electrolyte balance.

Conclusion

This case has shown that comprehensive preoperative preparation and assessment of patients with primary immune deficiencies can minimize surgical complications and optimize patient outcomes. It is of key importance to predict and address potential metabolic disturbances when people with this or similar conditions that include impairment in hypothalamo-pituitary-adrenal (HPA) axis undergo surgical procedure because lack of preoperative cortisol optimization and poor glycemia regulation can lead to severe complications during surgery as well as in postoperative period. The use of stress doses of glucocorticoids has become a common perioperative practice for patients on glucocorticoid therapy.The current approach is to determine glucocorticoid coverage based upon the patient's history of glucocorticoid intake, as well as the type and duration of surgery.

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Conflict of interess

No conflict of interess to declare

Ethical approval

For every elective and urgent procedure in our Hospital, it is required to obtain an informed consent form. The patient had signed the informed consent form and therefore gave the Hospital permission to perform procedures as well as use the data for scientific purposes with strong protection of personal information.

References

1. Fierabracci A, Arena A, Toto F, Gallo N, Puel A, Migaud M, Kumar M, Chengappa KG, Gulati R, Negi VS, Betterle C. Autoimmune polyendocrine syndrome type 1 (APECED) in the Indian population: case report and review of a series of 45 patients. J Endocrinol Invest. 2021 Apr;44(4):661-677. doi: 10.1007/s40618-020-01376-5. Epub 2020 Aug 7. PMID: 32767280.
2. Kluger N, Jokinen M, Krohn K, Ranki A. Gastrointestinal manifestations in APECED syndrome. J Clin Gastroenterol. 2013 Feb;47(2):112-20. 10.1097/MCG.0b013e31827356e1. PMID: 23314667.
3. Ferre EM, Rose SR, Rosenzweig SD, Burbelo PD, Romito KR, Niemela JE, Rosen LB, Break TJ, Gu W, Hunsberger S, Browne SK, Hsu AP, Rampertaap S, Swamydas M, Collar AL, Kong HH, Lee CR, Chascsa D, Simcox T, Pham A, Bondici A, Natarajan M, Monsale J, Kleiner DE, Quezado M, Alevizos I, Moutsopoulos NM, Yockey L, Frein C, Soldatos A, Calvo KR, Adjemian J, Similuk MN, Lang DM, Stone KD, Uzel G, Kopp JB, Bishop RJ, Holland SM, Olivier KN, Fleisher TA, Heller T, Winer KK, Lionakis MS. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. JCI Insight. 2016 Aug 18;1(13). pii: e88782.
4. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 1980; 17:118.
5. Constantine GM, Lionakis MS. Lessons from primary immunodeficiencies: Autoimmune regulator and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Immunol Rev. 2019 Jan;287(1):103-120. doi: 10.1111/imr.12714. Review. Citation on PubMed or Free article on PubMed Central
6. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009 Jul;5(7):374-81. doi: 10.1038/nrendo.2009.106. Epub 2009 Jun 2. PMID: 194880737
7. Pharmacology and Physiology for Anesthesia (Second Edition) Foundations and Clinical Application, 2019, Pages 693-707

Case report of patient with SARS-CoV-2 infection, encephalopathy and psychiatric comorbidity

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Abstract:

Neurological and neuropsychiatric manifestations of the coronavirus disease 2019 (COVID-19) have been widely described, but yet the pathophysiology underlying these presentations is still unclear. COVID-19 encephalopathy is a common neurological manifestation of SARS-CoV-2 infection and has been associated with poorer outcomes so it is crucial to be recognized early for further decision making regarding medical procedures and treatment. That can be challenging since the brain MRI scan can be normal or nonspecific as well as the EEG reports and analysis of cerebrospinal fluid is unremarkable. It is especially challenging in patients with a prior psychiatric diagnosis because symptoms can overlap

We present the case of COVID-19 associated acute encephalopathy in patient with a history of organic delusional disorder who presented with symptoms of delirium, minimal speech production which progressed to mutism and stupor.

Due to the wide range and overlapping of clinical presentation, nonspecific diagnostic findings and unclear therapeutic goal retrospectively, multidisciplinary approach is important in patients with neuropsychiatric manifestation of SARS-CoV-2 infection.

Further investigation is paramount in order to determine the potential central nervous system effects of infection with SARS CoV 2 and the optimal therapeutic approach.

Keywords: COVID-19, SARS-CoV-2, Delirium, Encephalopathy, Mutism

Sažetak:

Prikaz slučaja pacijentice s infekcijom SARS-CoV-2, encefalopatijom i psihijatrijskim komorbiditetom

Neurološke i neuropsihijatrijske manifestacije infekcije koronavirusom(COVID-19) naširoko su opisane, no ipak su patofiziološki mehanizmi u podlozi ovih prezentacija još uvijek nejasni. Encefalopatija COVID-19 uobičajena je neurološka manifestacija infekcije SARS-CoV-2 i povezana je s lošijim ishodima pa je ključno rano prepoznavanje zbog daljnjeg odlučivanja o medicinskim postupcima i liječenju. To može biti izazovno budući da MR mozga može biti uredan ili nespecifično promjenjen, kao i EEG i analiza cerebrospinalne tekućine koji mogu biti bez posebnosti. Navedeno je osobito izazovno kod pacijenata s prethodnom psihijatrijskom dijagnozom jer se simptomi mogu preklapati. Predstavljamo slučaj akutne encefalopatije povezane s COVID-19 infekcijom kod pacijentice s anamnezom organskog sumanutog poremećaja koja se prezentirala simptomima delirija, minimalne govorne produkcije koja je napredovala do mutizma i stupora.

Zbog širokog raspona i preklapanja kliničke slike, nespecifičnih dijagnostičkih nalaza i nejasnog terapijskog cilja, multidisciplinarni pristup je važan u liječenju bolesnika s neuropsihijatrijskom manifestaci-

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jom SARS-CoV-2 infekcije. Daljnje istraživanje je ključno kako bi se odredili mogući učinci infekcije sa SARS CoV 2 na središnji živčani sustav i optimalan terapijski pristup.

Ključne riječi: COVID-19, SARS-CoV-2, delirij, encefalopatija, mutizam

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus from the same group of viruses as SARS-CoV-2 and Middle East respiratory syndrome coronavirus, responsible for the subsequently named coronavirus disease 2019 (COVID-19). This disease spread all over the world and caused a pandemic which caused great threat and disruption in the global health system. Although the symptoms are primarily respiratory this disease can be presented with neurological and neuropsychiatric(Garg 2020).

This case report describes a patient with a history of organic delusional disorder that developed symptoms of acute encephalopathy during SARS-CoV-2 infection.

Case Report

Mrs B. is a 58-year-old woman with a history of left amygdalohippocampectomy performed in 1984 as a treatment of pharmacoresistant epilepsy and organic delusional disorder as a consequence for many years. Patient's clinical presentation of organic delusional disorder is dominated by psychoorganically conditioned character changes, mild cognitive impairment and chronic paranoid delusions towards spouse. At baseline, she is living mostly independent, she is oriented and in adequate verbal contact.

Prescribed therapy included clozapine (daily dose 75 mg); clonazepam (daily dose 4 mg); gabapentin (daily dose 100 mg).

She was admitted to the emergency department complaining of fever, fatigue and cough which began 5 days earlier. At that visit, she was afebrile, and other vital signs were within normal limits. She was tested with polymerase chain reaction (PCR) test for SARS-CoV-2 and the test returned positive. A chest x-ray was performed which showed no acute cardiopulmonary abnormality. C-reactive protein slightly increased (14 mg/L) with white blood count within reference intervals. Other laboratory tests were unremarkable. After diagnostic workup the patient was discharged to home care.

After 2 days, on the seventh day from the onset of symptoms, she represented to the emergency department with deterioration of the general condition with acute changes in mental status including decreased speech output and disorientation. the C-reactive protein increased (48 mg/L) (and hepatic function tests were slightly increased (aspartate transaminase of 100 U/L, alanine transaminase of 52 U/L and gamma glutamyl transferase of 69 U/L)) . Others laboratory findings were within reference intervals. After examination and diagnostic processing she was admitted to the hospital.

Next day neurologist consultation was obtained. On neurology examination it was noted that she was disorientated, had tremor of the upper extremities with cogwheel rigidity in bilateral upper extremities. She had minimal speech production despite normal verbal output at baseline.

Laboratory finding which included thyroid function test, levels of vitamin B12 and folate, and electrolytes, were normal.

Non-contrast head computed tomography was performed which showed left temporal gliomalation after previous neurosurgical treatment

Lumbar puncture was performed. Results of cytological and biochemical cerebrospinal fluid (CSF) analysis were unremarkable. CSF cultures, neurotropic virus panel and CSF Listeria monocytogenes polymerase chain reaction (PCR) assay were negative. The CSF autoimmune panel for came back negative.

Electroencephalogram (EEG) showed residual changes due to left amygdalohippocampectomy without interictal epileptiform discharges.

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed stationary finding considering her earlier operation.

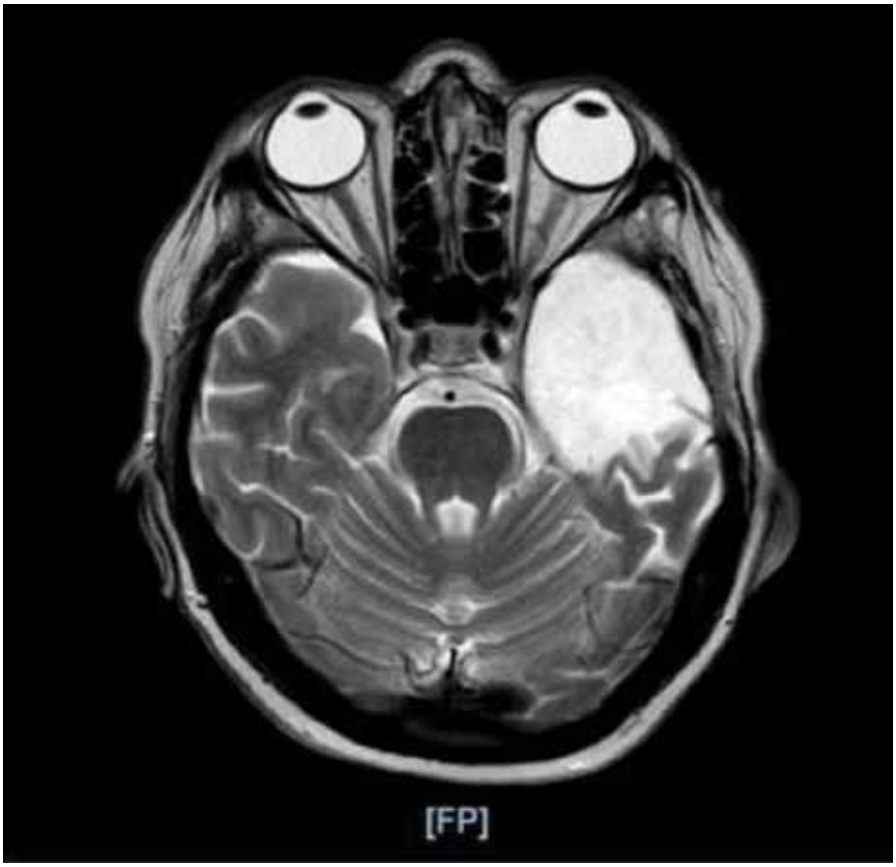

Figure 1. Magnetic resonance imaging showed stationary finding considering her earlier operation.

She was examined by a psychiatrist. It was noted that non-verbal eye contact was established, but without responding to inquiries. She was stuporous and mutistic with occasional rare restless behaviour. The rest of the mental status was difficult to assess due to the absence of verbal contact, but the impression was that the patient was confused and disorientated.
Considering the further development of the clinical presentation, it was concluded that the patient's diagnosis is encephalopathy (subsyndromal delirium with symptoms of catatonia).
She was given therapy which includes intravenous Methyprednisolone 250 mg for 3 days.
After receiving therapy, slight improvement was observed and after 20 days of hospital treatment patient was discharged to a nursing home. She was still mutistic, but the impression of the medical staff was that she was establishing better non-verbal eye contact and understood orders without reacting to them.
A follow-up was planned, but patient died within 1 month after discharge, and the exact cause of death was not determined.

Discussion

COVID-19 encephalopathy is frequent neurological manifestation, according to one study in 31.8% of 509 patients (Liotta et al. 2020) and can be presented in early stages of the SARS-CoV-2 infection, even as initial symptom (Al-Ramadan et al.2020). Further more, encephalopathy has been associated with poorer outcome compared with patients without encephalopathy.
Diagnosing COVID-19 encephalopathy can be challenging since the brain MRI scan can be orderly. According to a study involving 64 patients with COVID-19 and symptoms of encephalopathy, 46% of patients had a normal findings (Kremer et al. 2020). The EEG reports in COVID-19 patients showed normal or nonspecific results (Helms et.al 2020). So far, no study had described specific EEG abnormalities of the SARS-CoV-2 infection in the context of encephalopathy. The majority of currently reported EEGs showed generalized slowing, focal slowing, epileptiform discharges with seizures, and status epilepticus (Vellieux et al, 2021).
In vast majority of COVID19 assosiated encephalopathy patients, CSF was reported normal (Neumann et al. 2020).However, elevated CSF WBC, protein levels, and positive oligoclonal bands were described in case reports (Garg et al. 2021)
The therapeutic approach includes symptomatic therapy. One study described drastic regression of symptoms in patients with severe encephalopathy treated with methylprednisolone (Pugin et al. 2020). However, the role of glucocorticoids and immunomodulatory therapy still remains unclear.

Conclusion

Due to the broad spectrum and overlapping of clinical presentation, nonspecific diagnostic findings and unclear therapeutic approach, multidisciplinary collaboration is extremely important in patients with neuropsychiatric manifestation of SARS-CoV-2 infection.
Also, the assessment of clinical presentation in patient with psychiatric disorder should occur in the context of their known symptomatology. It is very important to ensure adequate communication between patient's family members and healthcare providers with the aim of distinguishing from previous symptoms in those with preexisting psychiatric condition.
Further research is needed in order to clarify the mechanism of occurrence and determine the most adequate therapeutic approach.

References

1. Al-Ramadan A, Rabab'h O, Shah J, Gharaibeh A : Acute and Post-Acute Neurological Complications of COVID-19. Neurol Int. 2021;13:102-119.
2. Garg RK: Spectrum of Neurological Manifestations in Covid-19: A Review. Neurol India 2020;68:560-572.
3. Garg RK, Paliwal VK & Gupta A.: Encephalopathy in patients with COVID-19: A review. J Med Virol 2021;93:206-222.
4. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C et al.: Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020;382:2268-2270.
5. Kremer S, Lersy F, Anheim M, Merdji H, Schenck M, Oesterlé H et al.: Neurologic and neuroimaging findings in patients with COVID-19: A retrospective multicenter study. Neurology 2020;95:e1868-e1882.
6. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, Koralnik IJ et al.: Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020;7:2221-2230.
7. Pugin D, Vargas MI, Thieffry C, Schibler M, Grosgurin O, Pugin J et al.: COVID-19-related encephalopathy responsive to high-dose glucocorticoids. Neurology 2020;95:543-546.
8. Stracciari A, Bottini G, Guarino M, Magni E & Pantoni L: "Cognitive and Behavioral Neurology" Study Group of the Italian Neurological Society. Cognitive and behavioral manifestations in SARS-CoV-2 infection: not specific or distinctive features?. Neurol Sci 2021;42:2273-2281.
9. Vellieux G, Sonneville R, Vledouts S, Jaquet P, Rouvel-Tallec A & d'Ortho MP: COVID-19-Associated Neurological Manifestations: An Emerging Electroencephalographic Literature. Front Physiol 2021;11:622466.

Epileptic seizure as the first manifestation of tuberculosis in a young male

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Abstract:

Introduction: Central nervous system tuberculosis is a life-threatening condition that usually presents with seizures. It is most frequently seen in low-to-middle income countries where tuberculosis is endemic.

Case report: A 23-year-old male from Nepal presented to the emergency department after a generalized seizure that lasted for several minutes, according to his colleagues. He was previously healthy, except for the minor weight loss and nausea a few weeks prior to this event. A multi-slice computed tomography (MSCT) of the brain showed multiple ring-enhancing lesions with surrounding edema. Magnetic resonance imaging was performed to further characterize the lesions. The differential diagnosis included neoplastic process, cerebral metastases and various infectious diseases. Antiepileptic therapy was administered during the hospitalization. MSCT of the thorax showed a conglomerate of enlarged lymph nodes in the right mediastinum. There was also an enlarged lymph node in the right supraclavicular fossa that was taken for surgical biopsy and the histologic analysis was performed. The Quantiferon test was positive and the analysis of the lymph nodes showed caseous necrosis as well as Langhans giant cells and the diagnosis of tuberculosis was confirmed. Antituberculotic treatment was started and the patient was referred to a specialized hospital for further evaluation and treatment.

Conclusion: The involvement of the central nervous system is rarely seen as the first manifestation of tuberculosis. However, most seizures caused by it will resolve after a successful treatment of the underlying CNS tuberculoma.

Keywords: Tuberculosis, Central Nervous System, Tuberculoma, Seizures

Sažetak:

Epileptički napad kao prva manifestacija tuberkuloze

Uvod: Tuberkuloza središnjeg živčanog sustava po život je opasno stanje koje se obično manifestira epileptičkim napadima. Najčešće se viđa u nisko i srednje razvijenim zemljama gdje je tuberkuloza endemska.

Prikaz slučaja: 23-godišnji muškarac iz Nepala primljen je u hitnu službu nakon generaliziranog toničko-kloničkog napada u trajanju od nekoliko minuta. Prethodno je bio zdrav, navodi se manji gubitka tjelesne težine i mučnine nekoliko tjedana prije ovog događaja. MSCT mozga pokazao je višestruke prstenaste lezije s postkontrastnom imbibicijom te s okolnim edemom. Učinjena je magnetska rezonancija za daljnju karakterizaciju lezija. Diferencijalno dijagnoza uključivala je neoplastični proces, metastaze i različite zarazne bolesti. Tijekom hospitalizacije započeta je antiepileptička terapija. MSCT toraksa pokazao je konglomerat povećanih limfnih čvorova u desnom medijastinumu. Također je bio povećan limfni čvor u desnoj supraklavikularnoj jami te je učinjena biopsija i patohistološka

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analiza istog. Quantiferonski test je bio pozitivan, a analiza limfnih čvorova pokazala je kazeoznu nekrozu kao i Langhansove gigantske stanice te je potvrđena dijagnoza tuberkuloze. Započeto je s antituberkuloznim liječenjem i bolesnik je upućena u specijaliziranu bolnicu na daljnju procjenu i liječenje. **Zaključak:** Zahvaćenost središnjeg živčanog sustava rijetko se vidi kao prva manifestacija tuberkuloze. Međutim,cnakon uspješnog liječenja tuberkuloma CNS-a postiže se adekvatna kontrola epileptičkih napada.

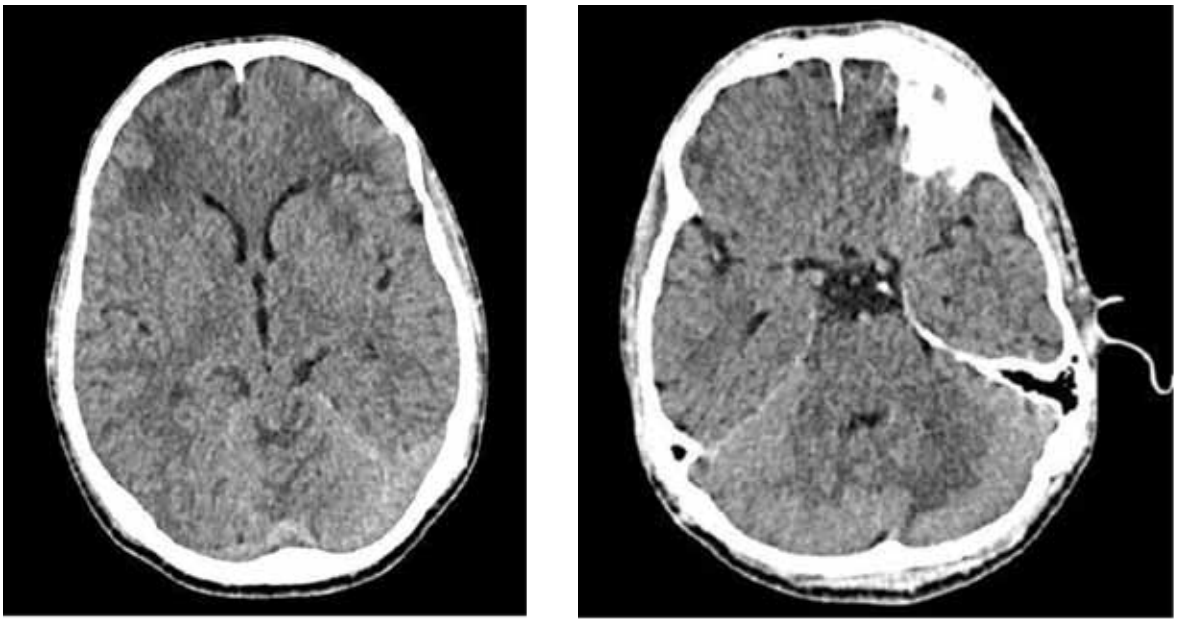
Ključne riječi: tuberkuloza, središnji živčani sustav, tuberkulom, epileptički napad

Introduction

Central nervous system (CNS) tuberculosis is a rare but extremely dangerous condition that is most frequently seen in low-to-middle income countries where tuberculosis is endemic. It carries high morbidity and mortality among all forms of tuberculosis. Among patients with tuberculosis, approximately 1 to 5 percent are complicated by CNS tuberculosis that may take three clinic-pathological forms: a diffuse form of tuberculous meningitis, a focal form of tuberculoma and spinal arachnoiditis (1). Tuberculoma have been reported to occur in 15% of all CNS tuberculosis cases (2). Patients with CNS tuberculoma can present with a new-onset focal or bilateral tonic-clonic seizures, evidence of systematic tuberculosis or some focal neurological deficit (1). Seizures may occur in 25% of patients with CNS tuberculoma (2). Since clinical, laboratory and radiology manifestation of CNS tuberculosis are nonspecific, its recognition is a challenge. However, an early and accurate diagnosis of CNS tuberculosis is crucial for survival. Treatment efficiency depends upon how early it is administered. Most seizures will resolve after successful treatment of the underlying CNS tuberculoma. Most patients with CNS tuberculoma can be managed nonoperatively, surgical excision is indicated when medical therapy fails.

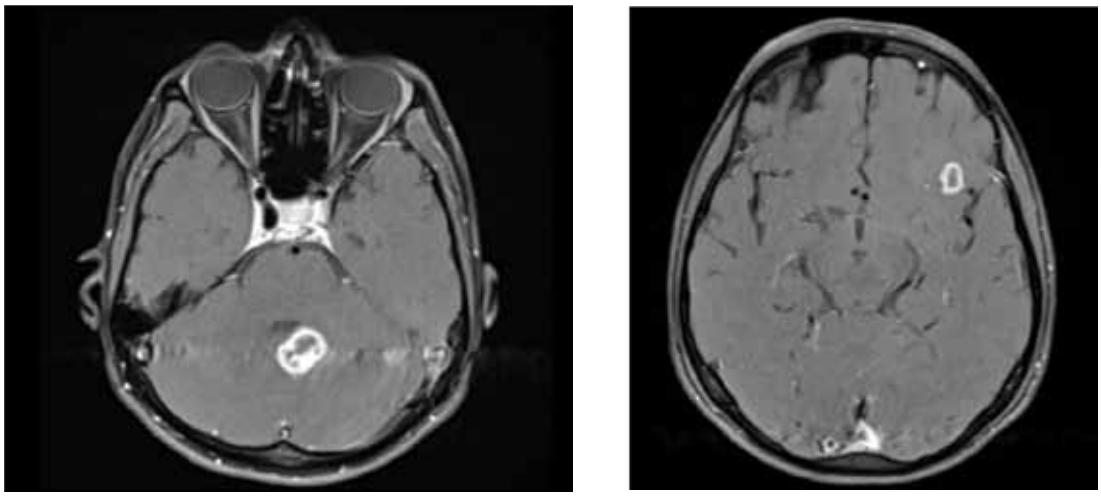
Case report

A young male, from Nepal, presented to our emergency department after loss of consciousness. According to the eyewitnesses, they observed tonic-clonic seizure of unknown onset. He temporarily lost bladder control and bit his tongue. Post-ictal confusion was noticed as well. He was previously healthy, except for the minor weight loss and nausea a few weeks prior to this event. Furthermore, neurological examination showed no neurological deficit. Routine blood tests were done and showed mild hypochromic microcytic anemia. A chest X-ray showed no abnormalities.

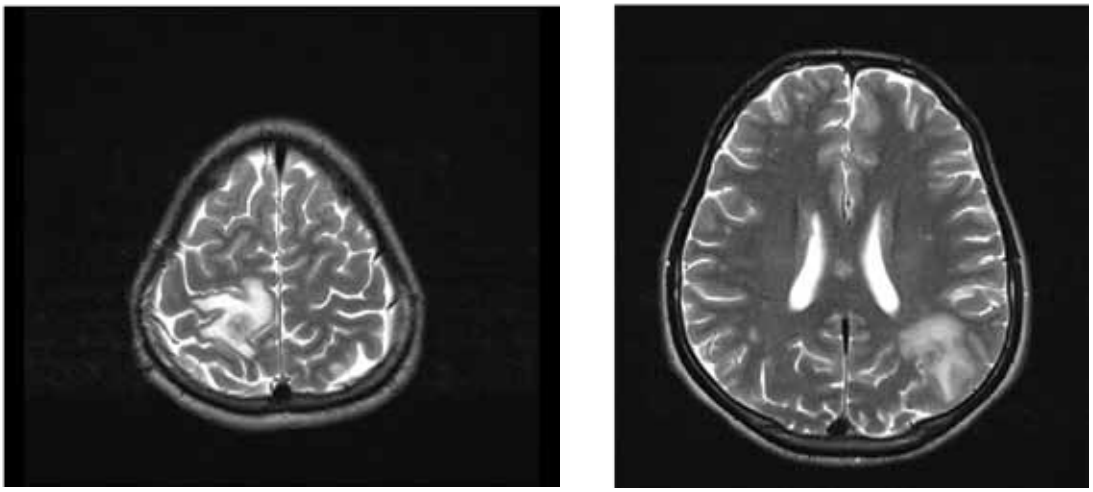


A noncontrast CT scan of the brain showed multiple supra- and infratentorial ring-enhancing lesions with perilesional edema.

In addition, MRI of the brain was preformed. Axial T2- weighted MRI revealed multiple cortico-subcortical isointense lesions supratentorially with the peripheral edema, which show post-contrast ring imbibition with central restriction of diffusion; lesion of the same properties is also seen in the left cereberal hemisphere paramedially and it compresses the 4th ventricle. There are also a few T2/FLAIR- weighted hyperintense lesions supratentorially that are predominantly in the subcortical white matter.



Axial T1-weighted MRI post contrast administration shows nodular lesions with significant ring enhancement after contrast administration.



Axial T2 weighted MRI shows a well circumscribed nodular lesions with a low intensity center on T" and peripheral hyperintensity.

EEG showed focal discharges over right electrodes. Furthermore, lumbar puncture was performed. CSF analysis demonstrated elevated protein concentration and hemato-liquor barrier deficiency. MSCT of thorax, abdomen and pelvis showed a conglomerate of enlarged lymph nodes in the right mediastinum with the central necrosis. Tree-in-bud pattern was described apically bilaterally as well. There was also an enlarged necrotic lymph node in the right supraclavicular fossa that was taken out for surgical biopsy and the histologic analysis was performed. The Quantiferon test was also positive. Surgical biopsy and histologic analysis of the lymph nodes showed caseous necrosis and characteristic Langhans giant cells. Serum and CSF analysis for toxoplasmosis was negative, as well as cysticercosis and serum cryptococcal antigen and the tests for tissue parasites. HIV test, as well as immunologic screening for possible immunodeficiencies were also negative. At the Department of Neurology initial antiedematous therapy was administered, as well as levetiracetam in dose of 500 mg twice a day for seizure prophylaxis. There were no new observed epileptic seizures. Antituberculotic treatment included isoniazide, rifampicin, ethambutol, pyrazinamide for 3 and a half months. Later, patient was referred to a specialized hospital for further evaluation and treatment. In addition, follow-up in the specialized hospital included lab exams (with a special attention to the liver enzymes) and chest X-rays. It is planned to do an additional MRI, EEG and neurological check-up. Treatment includes isoniazid and rifampicin for 3 more months until the next check-up.

Discussion

The involvement of the central nervous system is rarely seen as the first manifestation of tuberculosis. Children younger than 5 years and patients under immunosuppression have higer risk of the CNS involvement of TB. CNS tuberculosis is classified according to anatomical localization (intracranial and spinal). The most common presentation of CNS TB is meningitis (3). Tuberculoma is a rare presentation(<1% of all cases of CNS TB). CNS TB is associated with high mortality because it is hard to diagnose so the start of the treatment is delayed. The most important challenge in managing tuberculoma is its analysis and treatment. Differential diagnosis include intracranial abscess, cerebral metastases, primary lymphoma, meningeoma, glioma and other CNS infections (4). Histologically, tuberculoma consists of a necrotic caseous center surrounded by a capsule containing Langhans giant cells, lymphocytes and fibroblasts (4). Diagnostic procedures include physical examination, neuroimaging techniques (e.g.CT and MRI),extended laboratory blood analysis,CSF analysis and detection of other potentially affected sites (2). Characteristic CSF findings for CNS TB are lymphocytic pleocytosis with an average cell count around 200 cells/µl, moderate to severe proteinorachia and hypoglycorrhachia. It is crucial to perform the smear and the culture of CSF, although it is positive in less than half of patients (4). Treatment regimens include anti-tuberculous therapy and accompanying corticosteroid therapy (5). During the effective anti-tuberculous therapy, worsening of neuroradiological findings can be observed. In one study, more than 64% showed paradoxical deterioration on follow up MRI, but more than half of those patients were asymptomatic. Risk factors related to the development of epilepsy include young age, tuberculoma, cortical involvement, refractory seizures and residual lesions (5). Patients with seizures require antiepileptic drug therapy either as short-course or long- term therapy. Several studies concluded that early usage of antiepileptic drugs reduce risk of developing chronic epilepsy following TBM infection (6). Due to possible adverse drug reactions and potential complications of disease, along with uncertain optimal treatment regimen, it is necessary to monitor all patients during the treatment (5). In the treatment of tuberculosis, isoniazid inhibits the metabolism of carbamazepine, phenytoin and valproic acid, and also can cause toxicity. On the other hand, rifampicin reduces the concentration of carbamazepine, lamotrigine, phenobarbital , phenytoin and valproic acid. (7)

To conclude, CNS tuberculosis is a rare, but potentially fatal disease whose course can be altered by fast recognition and prompt administering of the right therapy.

References:

1. Letchuman V, Guillotte AR, Lundy PA, Dharia A, Lakis NS, Camarata PJ. Intracranial tuberculoma: a rare complication of extrapulmonary tuberculosis. Illustrative case. J Neurosurg Case Lessons. 2022 Jul 4;4(1):CASE2291. doi: 10.3171/CASE2291. PMID: 35855351; PMCID: PMC9257396.
2. Schaller MA, Wicke F, Foerch c, Weidauer S; Cental nervous system tuberculosis: etiology, clinical manifestation and neuroradiological features. Clin Neuuroradiol 2019;29-3-18
3. Navarro-Flores A, Fernandez-Chinguel JE, Pacheco-Barrios N, Soriano-Moreno DR, Pacheco-Barrios K. Global morbidity and mortality of central nervous system tuberculosis: a systematic review and meta-analysis. J Neurol. 2022 Jul;269(7):3482-3494.
4. Ana P Ramos, Jorge G Burneo, Seizures and epilepsy associated with central nervous system tuberculosis, Seizure: European Journal of Epilepsy, Volume 107, 2023, Pages 60-66, ISSN 1059-1311
5. Gupta M, Munakomi S. CNS Tuberculosis. [Updated 2023 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585138
6. Abdulaziz, A.T.A., Li, J. & Zhou, D. The prevalence, characteristics and outcome of seizure in tuberculous meningitis. Acta Epileptologica 2, 1 (2020)
7. Ruiz-Giménez J, Sánchez-Alvarez JC, Cañadillas-Hidalgo F, Serrano-Castro PJ; Andalusian Epilepsy Society. Antiepileptic treatment in patients with epilepsy and other comorbidities. Seizure. 2010 Sep;19(7):375-82. doi: 10.1016/j.seizure.2010.05.008. Epub 2010 Jun 15. PMID: 20554455.

Acute renal failure due to severe rhabdomyolysis provoked by a mild covid-19 infection in patient with LCHAD deficency- a case report

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Abstract:

Introduction: LCHAD (long-chain 3-hydroxy-acyl-CoA dehydrogenase) deficiency is an inherited fatty acid oxidation disorder in which the body is unable to break down certain fats resulting in hypoketotic hypoglycemia, myopathy, episodic rhabdomyolysis and neuropathy. Metabolic decompensation is often precipitated by infection or fasting.

Case report: A 26-year-old patient was admitted to the emergency department because of generalized myalgias. This is a patient with known congenital deficiency of long-chain 3- hydroxy-acyl- CoA dehydrogenase (LCHAD). He was diagnosed at the age of 3 years and regularly undergoes check-ups in specialized metabolic department. 10 days prior to the symptoms he had milder form of covid-19 infection with a persistent dry cough. Previously, he was vaccinated with two doses of the mRNA SARS-COV 2 vaccine. Initially laboratory findings at emergency department showed elevated levels of creatine kinase (46000 U/L) with normal renal function (egfr: 105 ml/min/1.73m2). Chest X-ray excluded pneumonia. Abundant hydration with intravenous infusions (0.9% NaCl, 5% glucose) was started, but during the observation the patient developed oliguria with urine output <10 ml/hour. Further laboratory findings showed acute kidney injury with worsening rhabdomyolysis (CK>80,000 U/L, egfr: 19 ml/min/1.73m2, creatinine: 369 umol/L). Due to the need for hemodialysis, he was hospitalized in the intensive care unit where dialysis procedures (CVVHD, CVVHDF) were continuously performed for 7 days until gradual decrease in creatinine and CK levels. In continuation he was carefully hydrated with infusions of 10% glucose and received a specially adapted diet to ensure sufficient caloric intake and to prevent catabolism. In total, he was 12 days on continuous hemodialysis and the renal function completely recovered after 3 weeks with the normalization of creatinine and CK values. Beside mild SARS-CoV-2 infection, we haven't founded any other cause of patient's metabolic decompensation.

Conclusion: Patients with LCHAD should be educated and controlled more often in the covid-19 pandemic, as even the mild form of SARS-CoV-2 infection can lead to a rapid metabolic decompensation and a possible fatal outcome.

Keywords: LCHAD deficiency, rhabdomyolysis, SARS-CoV-2, acute kidney failure

Sažetak:

Akutno zatajenje bubrega zbog teške rabdomiolize izazvane blagom infekcijom covid-19 u bolesnika s nedostatkom LCHAD-prikaz slučaja

Uvod: Nedostatak LCHAD (dugolančana 3-hidroksi-acil-CoA dehidrogenaza) je nasljedni poremećaj oksidacije masnih kiselina u kojem tijelo ne može razgraditi određene masti što rezul-

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tira hipoketotičkom hipoglikemijom, miopatijom, ponavljajućom rabdomiolizom i neuropatijom. Metabolička dekompenzacija često je uzrokovana prolongiranim gladovanjem ili infekcijom.
Prikaz slučaja: 26-godišnji pacijent javlja se u hitni prijem zbog generaliziranih mialgija. Riječ je o pacijentu s poznatim kongenitalnim nedostatkom LCHAD kojemu je dijagnoza postavljena u dobi od 3 godine. Redovito provodi kontrole kod vodećeg specijalista u Zavodu za bolesti metabolizma. Pacijent je 10-ak dana prije mialgija prebolio blaži oblik covid-19 infekcije s ostatnim suhim kašljem. Redovito je cijepljen s mRNA SARS-COV 2 cjepivom. Obradom u hitnoj službi verificirane su povišene razine kreatin kinaze (46000 U/L) uz urednu bubrežnu funkciju (npr. 105 ml/min/1,73 m2). RTG prsnog koša isključio je upalu pluća. Započeta je obilna hidracija intravenskim infuzijama (0,9% NaCl, 5% glukoza), no u kontrolnom intervalu pacijent razvija oliguriju s diurezom <10 ml/sat. Daljnji laboratorijski nalazi pokazali su akutnu ozljedu bubrega s pogoršanjem rabdomiolize (CK>80 000 U/L, egfr: 19 ml/min/1,73m2, kreatinin: 369 umol/L). Zbog potrebe za hemodijalizom hospitaliziran je u jedinici intenzivnog liječenja gdje je kontinuirano provođen postupak dijalize (CVVHD, CVVHDF) do postupnog pada vrijednosti kreatinina i CK. U nastavku je pažljivo hidriran infuzijama 10% glukoze uz prehranu posebno prilagođenom dijetom kako bi se osigurao dovoljan kalorijski unos i spriječio katabolizam. Pacijent je sveukupno proveo 12 dana kontinuirane dijalize, a do potpunog oporavka bubrežne funkcije došlo je za 3 tjedna. Osim blage SARS-CoV-2 infekcije, nismo pronašli nijedan drugi uzrok metaboličke dekompenzacije.
Zaključak: Bolesnike s LCHAD-om treba češće educirati i kontrolirati u pandemiji covid-19 infekcije jer i blaži oblik infekcije može dovesti do brze metaboličke dekompenzacije i mogućeg smrtnog ishoda.

Ključne riječi: nedostatak LCHAD, rabdomioliza, SARS-CoV-2, akutno zatajenje bubrega

Introduction

LCHAD (long-chain 3-hydroxyacyl-CoA dehydrogenase) deficiency belongs to the group of fatty acid oxidation disorders in which the body in unable to break down certain fats. They are categorized based upon the length of the fatty acid chain. Like most of metabolic diseased LCHADD (LCHAD deficiency) is inherited in an autosomal recessive way with a prevalence of 1:150 000(1). It is caused by a genetic variant in the HADHA gene that encodes alpha and beta subunits of mitochondrial trifunctional protein. Majority of cases is caused by p.(Glu510Gln) variant in *HADHA*, but genetic testing revealed novel variant c.1108G > A, p.(Gly370Arg) associated with late onset, moderate disease (2,3) . Severe neonatal form of the disease presents with recurrent hypoketotic hypoglycaemia, episodic rhabdomyolysis, myopathy and rapidly progressive cardiomyopathy. Surviving patients with LCHADD may develop slowly progressing peripheral neuropathy, pigmentary retinopathy and during illness recurrent rhabdomyolysis (1). Metabolic decompensation is often precipitated by infection or prolonged fasting. Treatment of LCHADD involves dietary fat restriction and MCT (middle-chain triglycerides) or triheptanoin supplementation in order to decrease plasma hydroxyacylcarnitine. Given the low proportion of fat in the diet, it is necessary to supplement essential fatty acids and fat-soluble vitamins in patients with LCHADD (4).

Case report

A 26-year-old patient was admitted to the emergency department because of generalized myalgias. This is a patient with known congenital deficiency of long-chain 3-hydroxy-acyl- CoA dehydrogenase (LCHAD). The disease was diagnosed at the age of three due to hypoketotic hypoglycaemia and elevated levels of creatine kinase (CK). He regularly undergoes check-ups in specialized metabolic department. Ten days prior to the symptoms he had milder form of covid-19 infection (low-grade fever) with a persistent dry cough. Previously, he was vaccinated with two doses of the mRNA SARS-COV 2 vaccine. Initially laboratory findings at emergency department showed elevated levels of CK (46000 U/L), ALT (305 U/L) with normal renal function (egfr: 105 ml/min/1.73m2). Chest X-ray excluded pneumonia. Abundant hydration with intravenous infusions (0.9% NaCl, 5% glucose) was started at the emergency department. During observation, in a time interval of 12 hours, the patient developed oliguria with urine output <10 ml/hour. Further laboratory findings showed acute kidney injury with worsening rhabdomyolysis (CK>80,000 U/L, egfr: 19 ml/min/1.73m2, creatinine: 369 umol/L). Due to the need for hemodialysis, he was hospitalized in the intensive care unit where dialysis procedures (CVVHD, CVVHDF) were continuously performed for 12 days until gradual decrease in creatinine and CK levels. In order to prevent

further catabolism, a detailed diet plan was organised in cooperation with nutritionist. He was carefully hydrated with infusions of 20% glucose and received a specially adapted carbohydrate rich diet with only 10% fats from long-chain triglycerides. Beside mild SARS-CoV-2 infection, we haven't founded any other cause of patient's metabolic decompensation.

Discussion

In patients with inborn errors of metabolism, it is important to avoid any factors that could precipitate metabolic crisis. Even a milder form of infection can be life-threatening for patients, as it was in the case of our patient. During the covid-19 pandemic, we encountered a major problem of inadequate treatment of metabolic patients due to large number of infected people. Wongkittichote and al. descripted a case of 23-years old female patient with LCHADD who developed acute respiratory failure and severe cardiomyopathy which progressed to multiple organ failure and death. She presented with nausea, dry cough and chest pain and tested positive for COVID-19. As well as our patient laboratory findings revealed rhabdomyolysis with acute kidney injury. She was relative stabile until day 11 when she suddenly developed respiratory arrest and hypotension due to cardiomyopathy. Despite all modalities of intensive treatment, a fatal outcome occurred (5). One of the most serious complications of LCHADD is cardiomyopathy, which occurs due to deposition of toxic acylcarnitines (6). Carefully monitoring patient's vital signs and ECG during metabolic crisis is necessary in order to avoid this complication. Despite the late recognition of the metabolic crisis, urgent dialysis procedures and sufficient caloric intake prevented further complication and lead to a fully recovery.

Conclusion

Patients with LCHADD should be educated and controlled more often in the covid-19 pandemic, as even the mild form of SARS-CoV-2 infection can lead to a rapid metabolic decompensation and a possible fatal outcome. It is necessary to educate medical doctors in the emergency departments about metabolic diseases and way of preventing catabolism to avoid fatal outcomes of patients with LCHADD.

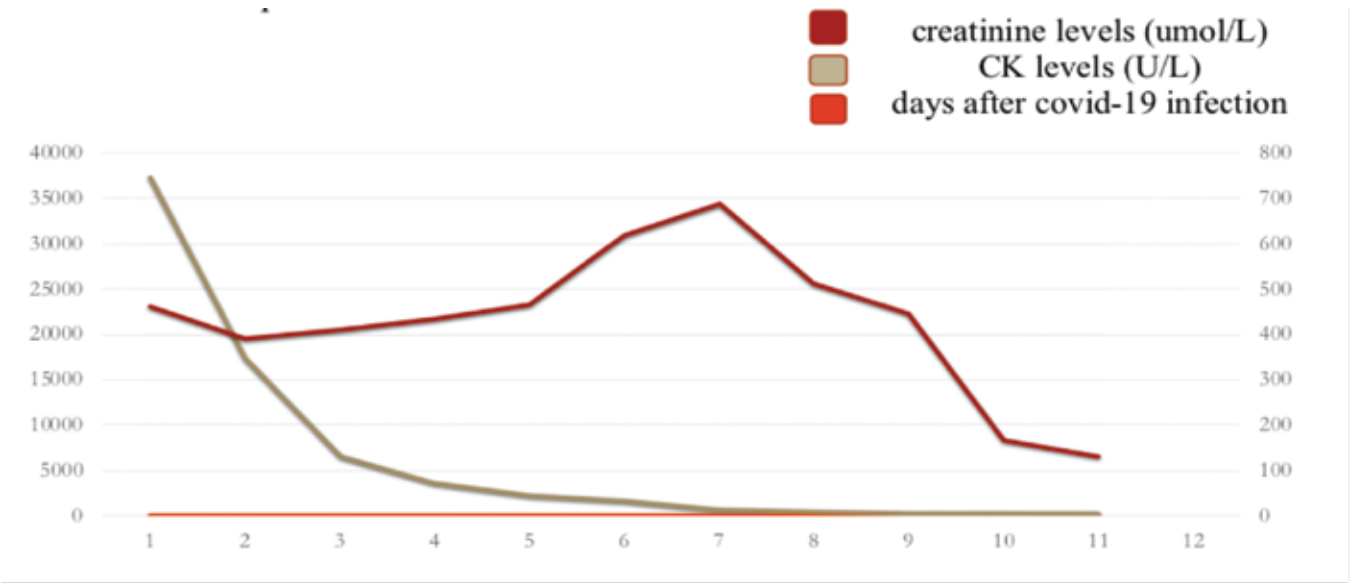

Figure 1. Dynamics of decreasing CK and creatinine levels during hospitalization and dialysis procedures

References:

1. Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency - PubMed [Internet]. [cited 2023 Nov 14]. Available from: https://pubmed.ncbi.nlm.nih.gov/36063482/
2. Tyni T, Pihko H. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Acta Paediatr [Internet]. 1999 [cited 2023 Nov 14];88(3):237–45. Available from: https://pubmed.ncbi.nlm.nih.gov/10229030/
3. Dessein AF, Hebbar E, Vamecq J, Lebredonchel E, Devos A, Ghoumid J, et al. A novel HADHA variant associated with an atypical moderate and late-onset LCHAD deficiency. Mol Genet Metab Rep [Internet]. 2022 Jun 1 [cited 2023 Nov 14];31. Available from: https://pubmed.ncbi.nlm.nih.gov/35782617/
4. Gillingham MB, Purnell JQ, Jordan J, Stadler D, Haqq AM, Harding CO. Effects of higher dietary protein intake on energy balance and metabolic control in children with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency. Mol Genet Metab [Internet]. 2007 Jan [cited 2023 Nov 14];90(1):64–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16996288/
5. Wongkittichote P, Watson JR, Leonard JM, Toolan ER, Dickson PI, Grange DK. Fatal COVID-19 infection in a patient with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: A case report. JIMD Rep [Internet]. 2020 Nov 1 [cited 2023 Nov 14];56(1):40–5. Available from: https://pubmed.ncbi.nlm.nih.gov/33204595/
6. Rocchiccioli F, Wanders RJA, Aubourg P, Vianey-Liaud C, Ijlst L, Fabre M, et al. Deficiency of long-chain 3-hydroxy-acyl-CoA dehydrogenase: a cause of lethal myopathy and cardiomyopathy in early childhood. Pediatr Res [Internet]. 1990 [cited 2023 Nov 14];28(6):657–62. Available from: https://pubmed.ncbi.nlm.nih.gov/2284166/

JAK 2 mutation positive polycythemia vera presenting as internal carotid artery dissection followed by dural sinus thrombosis

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Abstract:

Polycythemia vera is a stem cell disorder, often complicated by thrombotic and hemorrhagic events. We report a case of polycythemia vera in a 60-years-old man which presented with acute ischemic stroke. Computed tomography angiography of head and neck vessels was perfomed which revealed left internal carotid artery dissection. During his hospitalization his neurological status deteriorated and brain MRI, MRA and MRV showed right internal jugular vein, superior sagittal, sigmoid and transverse sinus thrombosis with hemorrhage in left frontal and parietal lobe. Repeated laboratory evaluation showed slightly elevated platelets and hematological consultation was requested. Results of sternal puncture suggested myeloproliferative disorder and JAK2 mutation was positive. Thrombus formation in the dural sinus is extremely rare in PV patients. To best of our knowledge this is the first case describing occurence of acute ischemic stroke, internal carotid artery dissection and dural sinus thrombosis in PV patient. It highlights the need of awareness of the association of PV and cerebrovascular disease and PV should be considered as a part of the differential diagnosis in patient with acute cerebrovascular event of otherwise unknown origin.

Keywords: Polycythemia vera, JAK 2 mutation, dural sinus thrombosis

Sažetak:

JAK2 pozitivna mautacija policitemije vere koja se manifestirala kao disekcija unutarnje karotidne arterija praćena trombozom duralnih sinusa.

Policitemija vera je mijeloproliferativa bolest koju karakterizira povećana sklonost trombozama i krvarenjima. U ovom radu prikazujemo 60- godišnjeg muškarca u kojeg se bolest prvotno prezentirala akutnim ishemijskim moždanim udarom. Učinjena je opširna obrada koja je uključivala kompjutoriziranu tomografsku *angiografiju* mozga i vrata kojom se verificirala disekcija lijeva unutranje karotidne arterije. Tijekom hospitalizacije dolazi do pogoršanja bolesnikova neurološkog statusa te je učinjen MR, MRA i MRV mozga kojima se opisuje tromboza desne unutarnje jugularne vene, superiornog sagitalnog, sigmoidnog i transverzalnog sinusa te krvarenje u lijevom frontalnom i parijetalnom režnju. Laboratorijskom obradom utvrđen je blago povišen broj trombocita te je učinjena daljnja hematološka obrada. Učinjena sternalna punkcija je upućivala na mijeloproliferativnu bolest te je pristigla pozitivna JAK 2 mutacija. Tromboza duralnih sinusa je iznimno rijetka u bolesnika s PV. Prema našim dosadašnjim saznanjima ovo je prvi slučaj u kojem je prisutan akutni ishemijski moždani udar, disekcija

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Crnjaković M, Vukorepa G, Devađija S. JAK 2 mutation positive polycythemia vera presenting as internal carotid artery dissection followed by dural sinus thrombosis.
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unutarnje karotidne arterije i tromboza duralnih sinusa u bolesnika s PV. Izradom ovog rada željeli smo naglasiti važnost povezanosti PV-a i cerebrovaskularnih bolesti te potrebu o razmatranju PV-a kao jedne od diferencijalnih dijagnoza u bolesnika s akutnim moždanim događajem nepoznate etiologije.

Ključne riječi: Policitemija vera, JAK 2 mutacija, tromboza duralnih sinusa

Dear Editor,

Polycythemia vera (PV) is a stem cell disorder, often complicated by thrombotic and hemorrhagic events (1). In most patients with PV and other myeloproliferative diseases (MPDs) mutation in *JAK2* is found (1). Thromboembolic events and cardiovascular disease are the major cause of morbidity and mortality in this population (1,2). Vascular complication such as arterial or venous thrombosis often leads to the diagnosis of PV (1,2). Acute stroke is the important cause of death and of long-term disability (3). Patients with PV are a unique subset of stroke patients, both for the pathophysiology and for management. Cerebral infarction and transient ischemic attacks are the most common neurological manifestation of PV, while cerebral hemorrhage, extra/intracranial dissection and dural sinus thrombosis have been rarely reported (4,5).

A 60-year-old right handed male was referred to our Department after being treated in local hospital for acute ischemic stroke presenting with mild right-sided hemiparesis, aphasia and right supranuclear facial palsy. His medical history included atrial fibrillation and was taking warfarin. Diagnostic work up showed acute ischemic lesion in left frontoparietal region as well as diffuse white matter lesions consistent with small vessel disease on brain magnetic resonance imaging (MRI). Computed tomography angiography (CTA) of head and neck vessels revealed left internal carotid artery dissection (ICAD). Thorough immunological work up was done with negative results and patient was switched to rivaroxaban. Suddenly, patient neurological status deteriorated and brain MRI, MRA and MRV were performed revealing right internal jugular vein, superior sagittal, sigmoid and transverse sinus thrombosis with hemorrhage in left frontal and parietal lobe.
Extensive diagnostic work up was performed including screening for occult malignant disease. Repeated laboratory evaluation showed slightly elevated platelets and hematological consultation was requested. Results of sternal puncture suggested MPD and JAK2 mutation was positive.

Patient was reffered to outpatient neurological and hematological follow up and was treated with venepunction, hydroxycarbamide and low molecular weight heparin which was eventually switched to dabigatran. His neurological symptoms improved with only discrete right hemiparesis on last outpatient visit.

We argue that PV is associated with endothelial dysfunction that may predispose to arterial disease and ICAD by promoting thrombosis, leucocyte adhesion, inflammation and proliferation of smooth muscle cells in the arterial wall (6). Thrombus formation in the dural sinus is extremely rare in PV patients. To best of our knowledge this is the first case describing co-occurence of both in PV patient. It highlights the need of awareness of the association of PV and cerebrovascular disease and should be considered as a part of the differential diagnosis in patient with acute cerebrovascular event of otherwise unknown origin.

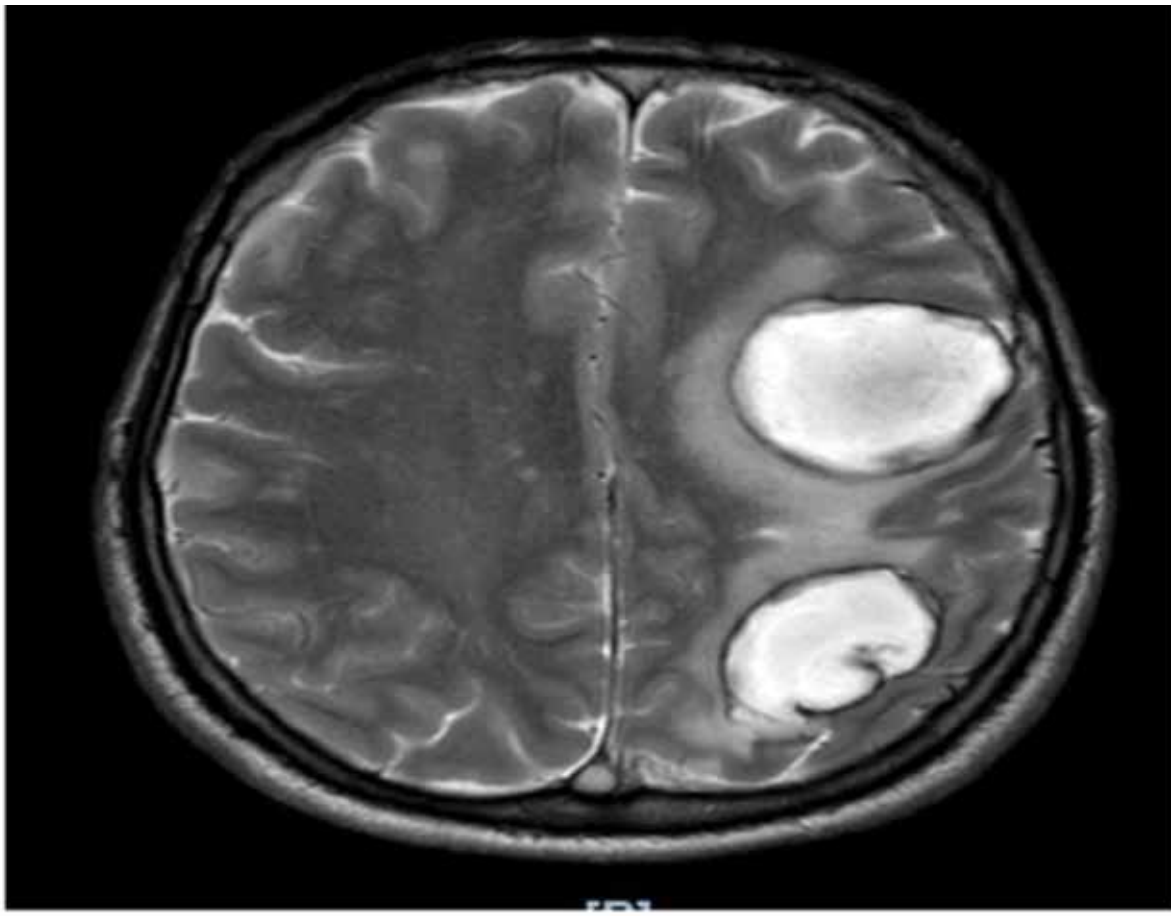


Figure 1: MRI showing two atypical subacute intracerebral hematoma in the left frontal and in the left parietal lobe

References:

1. Spivak JL. Polycythemia Vera. Curr Treat Options Oncol. 2018 Mar 7;19(2):12.
2. Griesshammer M, Kiladjian JJ, Besses C. Thromboembolic events in polycythemia vera. Ann Hematol. 2019 May;98(5):1071-1082.
3. Donkor ES. Stroke in the 21st Century:A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke Res Treat. 2018;2018:3238165.
4. Choi KS, Kim JM, Ryu JI, Oh YH. Concurrent Ruptured Pseudoaneurysm of the Internal Carotid Artery and Cerebral Infarction as an Initial Manifestation of Polycythemia Vera. J Korean Neurosurg Soc. 2015 Aug;58(2):137-40.
5. Zoraster RM, Rison RA. Acute embolic cerebral ischemia as an initial presentation of polycythemia vera: a case report. J Med Case Rep. 2013;7:131
6. Neunteufl T, Heher S, Stefenelli T, Pabinger I, Gisslinger H. Endothelial dysfunction in patients with polycythaemia vera. Br J Haematol. 2001 Nov;115(2):354-9.

Book review: Mind, Brain and Education

- edited by Vida Demarin, Leontino Batisttin and Hrvoje Budincevic, published by Springer 2023. 344 pages, hardcover and e-book, 33 chapters.

Author:
Marko Pećina

After the success of their previous book "Mind and Brain, Bridging the Neurology and Psychiatry" published by Springer two years ago, the editors decided to broaden their focus on the interrelation between brain and mind by introducing even more interdisciplinary approach by inviting neurosurgeons, psychologists, physiatrists and PNEI experts to get a larger platform of opinions and multidisciplinary research. A special attention is paid to education within a separate chapter.

The contents of the book is devided into three main parts, the first is mainly dealing with research and ideas considering the mind, and the second part is devoted to different topics and research of the brain and its importance, as the main subject. These topics are often rather connected and it was not always possible to put strict boundaries among them. All chapters are written by experts in the field, and each of them decided on the topic, thus there is a wide platform of various topics and approaches.

The content of the third part is devoted to education. A special emphasis is given to the role of traditional scientific gathering Mind &Brain in Pula, as a platform for educating young colleagues and widening their perspectives in the field of both disciplines. The authors present their ideas related to the possibilities of providing a kind of educational activities as well as emphasizing its importance in creating knowledgeable, educated and well-informed professionals.

The interrelation between the mind and the brain is fascinating and still rather challenging topic. Researchers are trying to contribute to its better

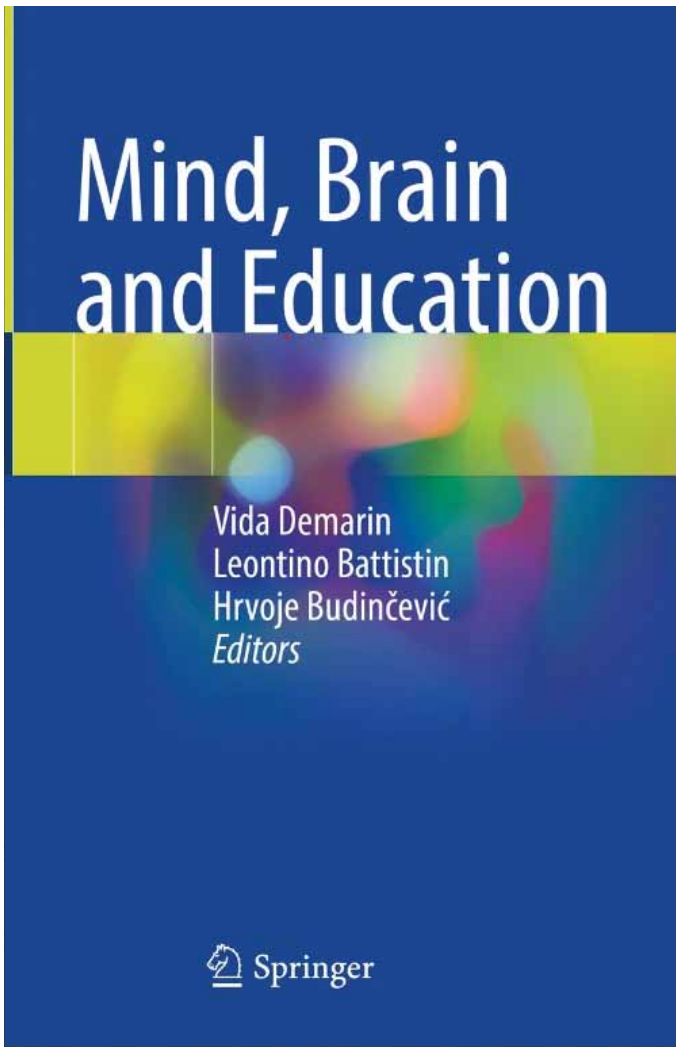
understanding by their original and innovative approaches and this debate is still open and ongoing,

The first part of this book comprises of thoughts on neuroesthetics, arts, migraine, personality disorders, autoimmune psychosis, and many other interesting topics.

The second part is mainly devoted to brain, where one can find the ways of successful maintenance of the brain sharpness, functional neurological disorders, headaches, stroke, multiple sclerosis, neurodegenerative diseases, telemedicine, data on new discipline psychoneuroendocrinoimmunology and many more other interesting and challenging topics.

The third part of the book consists of several topics related to education, like „Psychopathology Summer School" in Pula Congresses, Education and Autism, Co-Creativity in the therapy with children and adolescents and many more.

With great privilege and estimation, the editors express their sincere gratitude to all collaborators, experts in the field for their commitment and excellent contributions. The same words of gratitude go to devoted members of the team of their publisher Springer, for their precision and excellence in finalizing this project.



Nevertheless, we expect from a new book to bring a great depth of information, experience and knowledge. In this book we can find even more – it enrichess our knowledge, open our mind to different and distinct points of view and open us to a larger perspectives of humanic and professional fulfillment.

Book review: Stella Fatovic-Ferencic, editor. *Osijek School of Medicine – 25 Years of Independent Work*

Author:
Martin Kuhar

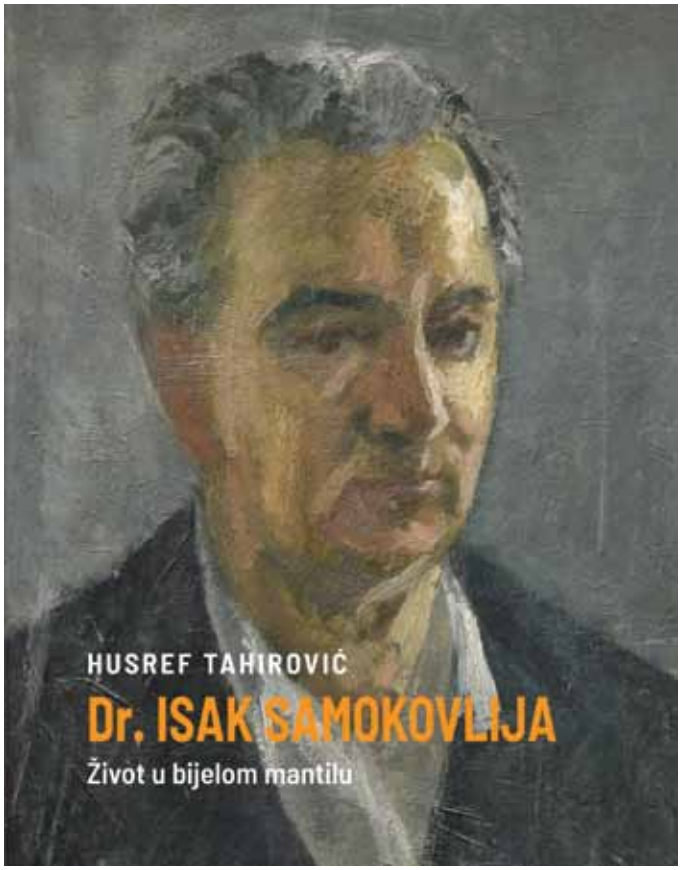
Faculty of Medicine, Josip Juraj Strossmayer University of Osijek issued a monograph on the occasion of the 25th anniversary of its independent work. It consists of ten chapters: *History and Development of the Faculty; Space, Equipment and Infrastructure; Position of the Faculty of Medicine Osijek within the University and Mobility within the European Area of Higher Education; Teaching and Study Programs; Science at the Faculty of Medicine Osijek; Organization; Chairs; Publishing; Students; Appendix.* The monograph records all the efforts in the active and intensive development of the teaching process, the involvement of the Faculty in the international academic processes, the development of scientific and medical practice, the adoption of new educational strategies, the encouragement of lifelong education, the introduction of studies in the German language, etc. This material is given special liveliness by revealing the close connections between students and teachers in various projects, in the community work and in efforts to raise awareness about current medical issues. It also emphasizes the Faculty's involvement in the broader social and cultural context, its interweaving with the life of the city and the people who live in it. The monograph, which has 474 pages with over 400 illustrations and tables, is designed and graphically arranged by the academic painter and designer Ante Rašić.

Book review:
Husref Tahirovic, *Dr. Isak Samokovlija – Life in a White Coat*

Sarajevo: Academy of Sciences and Arts of Bosnia and Herzegovina, 2023)

Author:
Stella Fatović-Ferenčić

In the premises of the Cultural and Information Center of the Embassy of Bosnia and Herzegovina in Zagreb, in cooperation with the Academy of Sciences and Arts of Bosnia and Herzegovina – Center for the Coordination of Medical Research in Sarajevo, the promotion of the book by academician Husref Tahirović, Dr. Isak Samokovlija - Life in a White Coat, was set up on November 9, 2023. The promotion was opened by the ambassador of Bosnia and Herzegovina in Croatia, Elma Kovačević-Bajtal. The book was presented by: academician Lidija Lincender-Cvijetić, Stella Fatović-Ferenčić, the Head of the Division for the History and Philosophy of Science, Croatian Academy of Sciences and Arts, Julija Koš, expert in Jewish studies, and finally its author Husref Tahirović, academician of ANUBiH. Zoran Perković, minister-counselor at the Embassy of Bosnia and Herzegovina in Zagreb, also gave short introductory speech. The moderator was an actor Mirza Pinjić. The promotion aired traditional Sephardic songs from the *Unforgettable Sephardic Melodie*s cycle by singer-songwriter Jagoda Flory.



Isak Samokovlija is primarily known for his literary works such as: *Od proljeća do proljeća* (1929), *Nosač Samuel* (1946), *Tragom* života (1948) and *Priča o radostima* (1953), as well as several dramas such as *Hanka, Plava Jevrejka, On je lud,* and *Fuzij.* Less recognized on the other hand is his medical work in various places throughout Bosnia and Herzegovina. This evidently motivated the author Husref Tahirović to elaborate on that part of Samokovlija's life. The book contains two parts: the first is Samokovlija's biography, represented and illustrated in detail and documented with ninety-eight quotations. The second part contains Samokovlija's articles divided according to their form into four categories: texts with developed characters, short stories, professional articles and poetry. Among the texts with developed characters, the series of texts by *Baba Mara* stands out. All presented texts have educational commitment and are composed in a simple and memorable way that public can understand it properly.

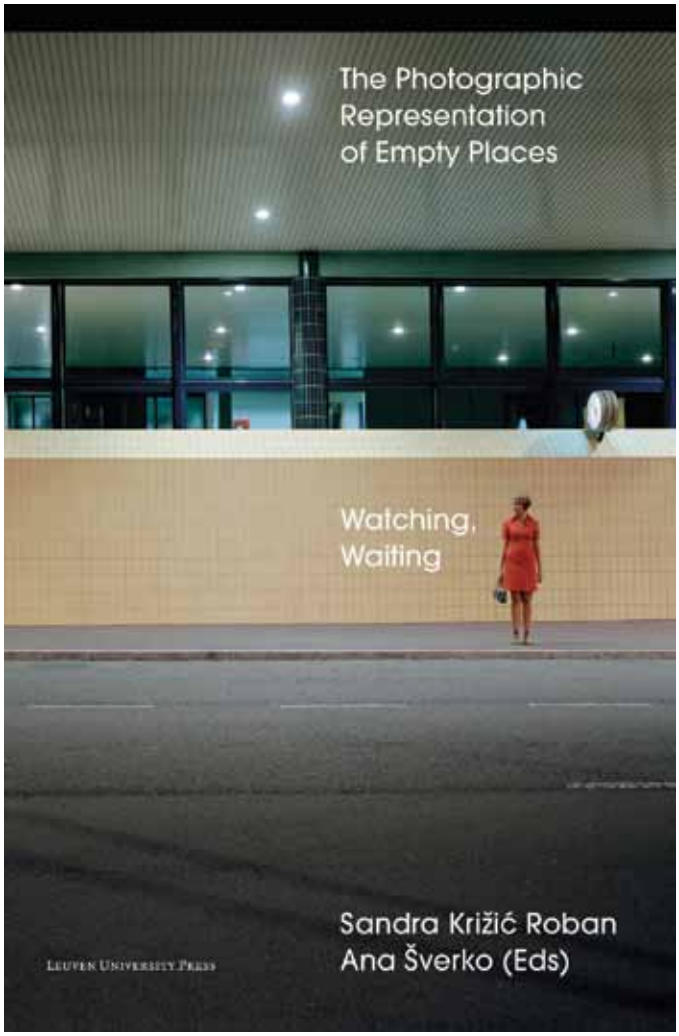
Samokovlija healed people who belonged to different nations or religions, and who, even during periods of peace, lived next to each other bringing support or spiritual upgrading to each other. The book is instructive and almost addictive. I believe, therefore, that its content will take root among readers in the same way that Izak Samokovlija's enlightening texts led the fight against diseases and ignorance and took root among the people of our territories.

Book review: Sandra Krizic Roban and Ana Šverko, editors. Watching, Waiting. The Photographic Representation of Empty Places

Leuven: Leuven University Press, 2023

Author:
Silvija Brkić Midžić

The politics of representing emptiness, returning to the places defined by emptiness, artists' visions and portrayals of emptiness, are some of the topics elaborated in the book *Watching, Waiting. The Photographic Representation of Empty Places*, published in the Fall of 2023 by the renowned European publishing house Leuven University Press. The book has been edited by Sandra Križić Roban and Ana Šverko as part of the project *Exposition. Themes and Aspects of Croatian Photography from the Nineteenth Century until Today*, conducted at the Institute of Art History. In 2020, during times of overwhelming stillness of the world and the sudden emptiness resulting from the spreading of the novel coronavirus, a conference was organized on the topic of emptiness; the contributors, although prevented from meeting in person, reacted to the call for papers with a series of intriguing presentations, part of which have been included in this book.



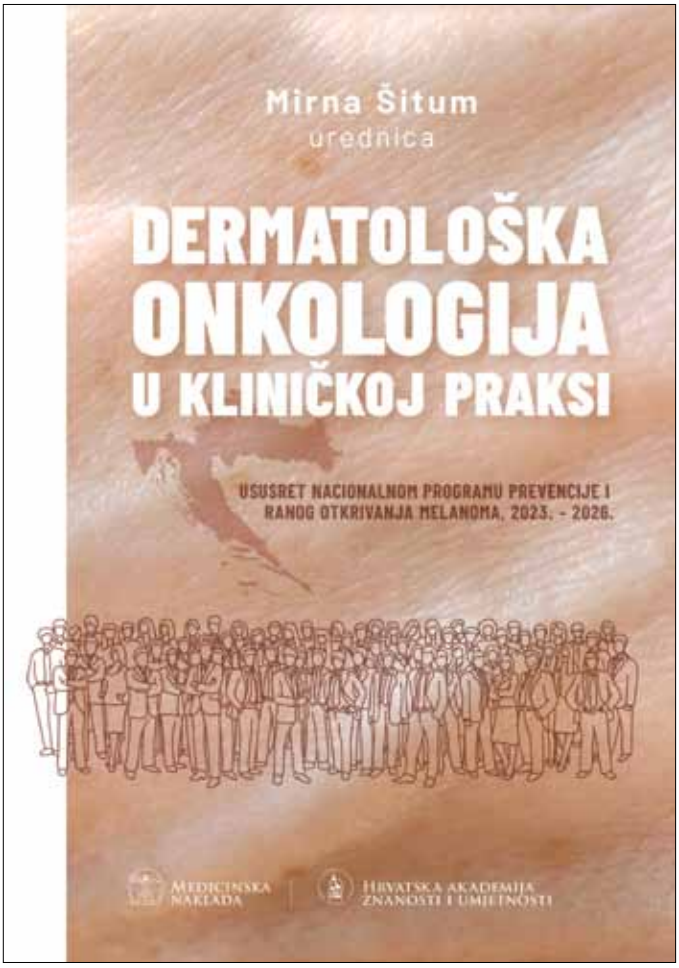
This is a primarily interdisciplinary publication with works by authors from various parts of the world and with different backgrounds – artists, theoreticians and researchers from both science and humanities. They are all united in critical thinking about what photography can communicate in situations like these, in which local differences pointed to the economic, political and cultural issues at a global level. One of the chapters, entitled "Emptiness as a Tool in the Representation of Public Health Monuments in Croatia", is written by Stella Fatović-Ferenčić and Martin Kuhar, researchers at the Division for the History of Medical Sciences of the Academy's Institute for the History and Philosophy of Science. The material presented in this paper is a part of the rather considerable photographic collection kept at the Croatian Museum of Medicine and Pharmacy. These black and white photographs, which were collected by the prominent phthisiologist Vladimir Ćepulić, mounted on cardboard and displayed at the Museum for the History of Healthcare in Croatia in 1944, tell a unique story about the longevity of Croatian public health and its importance in the survival of the Croatian people.

From the invention of photography in the 1830s until today, the relationship between this medium and place is often marked by the phenomenon of emptiness. It is a specific topic explored as much by the contemporary artists as by the historians of photography. Emptiness is a phenomenon that can occur both spontaneously and intentionally; it points to the breaks in urban fabric which are, for example, created to enable certain hygienic standards. Emptiness also speaks about the specificity of the development of photography and its (im)possibility, in its early times, to capture a specific moment, later only made possible by the impressive technological advances. Slow and ancient photographic processes, however, again became relevant in the last several years, while a different sense of time characterized recent pandemic times. Then, it seemed as if the world came to a halt and as if our existence was solely determined by stasis, while the photographs which interpreted the emptiness became a means of communication.

Book review: "Dermatological Oncology in Clinical Practice -Towards the National program for prevention and early detection of melanoma 2023-2026"

editor Academician Mirna Šitum

Author:
Mirna Šitum



"Dermatological Oncology in Clinical Practice -Towards the National program for prevention and early detection of melanoma 2023-2026", editor Academician Mirna Šitum

The scientific monograph, "Dermatological oncology in clinical practice - Towards the National framework for the prevention and early detection of melanoma 2023-2026," edited by Academician Mirna Šitum, published by the Croatian Academy of Sciences and Arts and Medicinska naklada. Monograph was prepared for the occasion of the twentieth traditional scientific dermatovenereological symposium "National program for prevention and early detection of melanoma: twenty years of enthusiasm of Croatian dermatologists," organized by the Croatian Academy of Sciences and Arts, Department for Medical Sciences, Department of Dermatology and Venereology, University Hospital Center Sestre milosrdnice and the University of Zagreb School of Dental Medicine, Croatian Association of Dermatological Oncology of the Croatian Medical Association, and the Croatian Dermatovenereological Society of the Croatian Medical Association. The monograph consists of 97 pages divided into 20 chapters, with a prominent foreword content, and a list of authors. Forty-three authors from various medical fields, engaging in the interdisciplinary field of dermatological oncology, participated in writing this book.

The book provides an overview of a range of interesting entities and case presentations of patients in the field of dermatological oncology diagnosed and treated in dermatovenerological clinics, both in private clinics and general and county hospitals, as well as in major Departments of four Clinical Hospital Centers. The first part of the monograph is dedicated to melanoma, from extremely rare congenital forms to presentations of rare clinical forms of melanoma, the diversity of metastatic melanoma presentation, side effects and complications of targeted and immunological oncological therapies for metastatic melanoma, up to values of digital digital dermoscopy in diagnosing melanoma and the challenges of aligning clinical and dermoscopic findings with the histopathological diagnosis of melanoma. The second part of the monograph illustrates various types of non-melanoma malignant skin tumors that are rarely diagnosed. This includes the presentation of two cases of angiosarcoma of the skin, Kaposi's sarcoma as a sign of HIV infection, coexistence of T- and B-cell lymphoproliferative diseases, metastatic lesions on the skin associated with primary breast carcinoma, squamous cell carcinoma in skin lesions resulting from hidradenitis suppurativa, diagnostically challenging "pink lesions," among which are the diagnoses of non-neural granular cell tumors, earlobe tumors, and finally, nodular tumor lesions of infectious nature. The special and added value of the monograph comes from 75 original clinical, histopathological, and immunohistochemical photographs that support the text and make it clearer. At the end of each chapter, the authors have highlighted an extensive list of literature referring to recent works from domestic and international scientific literature. As emphasized by the editor in the foreword, the choice of topics presented in the monograph demonstrates the complexity of the dermatovenereological and dermatooncological profession and science, especially because many dermatooncological entities in everyday practice remain unrecognized and are diagnosed late by physicians of various specialties.

Throughout the book, the importance of interdisciplinary cooperation and a multidisciplinary approach is clearly expressed, as it is the only correct path to a comprehensive approach to patients with oncological diseases in dermatology.

Finally, the monograph outlines the extensive knowledge and experience of Croatian dermatologists and their excellence, resulting from continuous long-term education in the field of dermatological oncology in all dermatovenerological institutions in the Republic of Croatia.

All the authors are long-standing participants in public health activities for the prevention and early detection of melanoma and other malignant skin tumors across various regions of the Republic of Croatia. Their dedicated work has been translated into a new national program, the National Program for Prevention and Early Detection of Melanoma 2023-2026. Therefore, this monograph also serves as an acknowledgment of enthusiasm, continuous learning, dedication, and commitment toward the significant goal of Croatian dermatovenereologists, whose foundations were laid over twenty years ago.

Ultimately, this work, in all its elements, represents a valuable contribution to the study of the progressive and vital part of medicine: dermatological oncology. It will prove useful in the education of dermatovenereology specialists and subspecialists, dermatological oncologists, oncologists and radiotherapists, internist oncologists and oncologic surgeons, dermatopathologists and specialists in pathology and cytology, radiologists, as well as family medicine specialists.

VII scientific symposium "Josip Matovinović" THYROID IN HEALTH AND DISEASE

April 21, 2023, HAZU Revival Hall, Zagreb

Author:
Tomislav Jukić

On April 21, 2023, the VII Scientific Symposium "Josip Matovinović" with the theme "Thyroid in Health and Disease" was held in the Birth Hall of the Croatian Academy of Sciences and Arts in Zagreb.

The symposium was organized by the Croatian Thyroid Society of HLZ, the Oncology and Nuclear Medicine Clinic of KBC Sestre milosrdnice - Reference Center for Thyroid Diseases of the Ministry of Health of the Republic of Croatia and the Department of Medical Sciences at HAZU. The meeting was attended by more than 100 participants, and due to the influence of the thyroid gland on numerous organs and organ systems, the meeting brought together experts from various specialities involved in the treatment of thyroid diseases. After the welcoming speech of Academician Zvonko Kusić, President of the Organizing Committee of the Symposium and President of the Croatian Thyroid Society of HLZ, the participants were greeted by Academician Josip Madić in front of the Department of Medical Sciences of HAZU. The first part of the Symposium was dedicated to the latest findings in the field of thyroidology, thyroid physiology and its influence on numerous metabolic and developmental processes in the body. The introductory lecture "Thyroid Hormones in Health and Disease" was held by Prof. Ph.D. Tomislav Jukić from KBC Sisters of Mercy. After that, Assoc. Ph.D. Tatjana Bogović Crnčić from KBC Rijeka presented an overview of the latest global guide-

Welcome speech by Academician Zvonko Kusić, president of the Organizing Committee of the Symposium

lines in the diagnosis and treatment of thyroid diseases and changes in classification. Then Assoc. Ph.D. Sanja Kusačić Kuna from KBC Zagreb held a lecture on the topic "Medical treatment of thyroid disease". Prof. Davor Vagić, director of KBC Sestre milosrdnice, presented an overview of surgical treatment of thyroid disease, prof. Ivan Mihaljević from KBC Osijek, dean of the Faculty of Medicine in Osijek, presented the role of iodine-131 in the treatment of thyroid diseases, and doc. Ana Barić from KBC Split presented the influence of drugs on thyroid function. The first part of the Symposium was chaired by Prof. Dražen Huić from KBC Zagreb and Prof. Davorin Đanić from the Faculty of Dental Medicine and Health Osijek. In the second part of the Symposium, specialists from KBC Sisters of Mercy presented the correlation of the thyroid gland with other organs and organ systems. dr. sc. Jelena Marinković Radošević, the specialist in endocrinology, presented the relationship between the thyroid gland and other endocrine glands, prof. Ph.D. Ognjen Zrinščak, a specialist in ophthalmology, the correlation between the thyroid gland and eye diseases, prim. Ph.D. Marija Punda, a specialist in nuclear medicine, the influence of the thyroid gland on the bone system, and Prof. Krunoslav Kuna, a specialist in gynaecology and obstetrics, presented the role of the thyroid gland in pregnancy and reproductive age. After that, Assoc. Ph.D. Gorana Mirošević, the specialist in endocrinology, presented the connection between nutrition and thyroid disease, and Dr. Roko Granić presented several patients who require a multidisciplinary approach to treatment and follow-up. The second part of the Meeting was chaired by Velimir Altabas from KBC Sisters of Mercy and Andrea Mutvar from KB Dubrava.

Prof. Dražen Huić and Prof. Ph.D. Davorin Đanić, chairman of the first part of the Symposium

32th Breast Diseases scientific meeting

September 28th 2023 at the Academy library

Author:
Željko Soldić

The Committee for tumors of the Department of Medical Sciences, Croatian Academy of Sciences and Arts and the Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center organized the 32th Breast Diseases scientific meeting that was held on September 28th 2023 at the Academy library. Welcoming speeches were held by **academician Vida Demarin**, Secretary of the Department of Medical Sciences, **academician Zvonko Kusić**, and Željko Soldić, president of the Organizing committee.

Academicians Vida Demarin and Zvonko Kusić emphasised the importance of improving service quality and treatment outcomes through multidisciplinarity. Our gathering brings together an increasing number of specialties dealing with breast cancer. We are on the threshold of a very interesting era in oncology, gene expression profiling in tumors, treatment guided by comprehensive gene profiling, new effective drugs such as conjugates of antibodies and drugs and targeted therapy. All of the above will improve the treatment outcomes of our patients. We hope that we have justified the trust that Academician Prpić showed us and that we can successfully continue the tradition that has lasted for more than three decades.

In a comprehensive introductory lecture, **Ljiljana Vukota**, representative of the Patient Association *Sve za nju*, spoke about the importance of psycho-oncology and the support that patient associations provide to our patients.

Karolina Bolanča Čulo spoke about algorithm of radiological diagnosis of the breast diseases according to the age of the patient. **Snježana Ramić** talked about the role of testing of hereditary BRCA1 and BRCA2 gene variants in breast cancer patients: who and how to test and the technical issues. **Snježana Tomić** answered a very important question that we encounter in everyday clinical work - HER2 low status in breast cancers - a pathologist's view. **Andrej Roth** talked about the advances in the surgical treatment of local recurrence of the disease. **Katarina Antunac** talked about the role of De-escalation of axillary radiotherapy - has the time come? **Marijana Jazvić** spoke about, rarely disscused but important topic in oncology, breast cancer and fertility preservation. **Tajana Silovski** presented the progress made in the treatment guided by comprehensive gene profiling in patients with advanced breast cancer. **Branka Petrić Miše** presented treatment modalities of Triple negative breast cancer - neoadjuvant/adjuvant treatment. **Martina Bašić Koretić** spoke about new possibilities of endocrine treatment. **Ingrid Belac Lovasić** discussed algorithms in the treatment of HER2 positive advanced breast cancer. **Josipa Flam** presented optimal duration of adjuvant endocrine therapy.

An important part of the meeting were the dynamic panel discussions with leading experts in breast cancer patient care, who tried

to resolve dilemmas and answered key questions that we encounter in our daily work.

All 12 lectures presented at the 32th Breast Diseases scientific meeting was published in a special edition volume of the Croatian Academy of Sciences and Arts, which is important in the continuing education and improvement of the quality of work of health professionals involved in breast cancer prevention, diagnosis and treatment. The Breast Diseases scientific meeting, which traditionally reviews existing paradigms and latest breakthroughs and sets new standards in the prevention, diagnosis and treatment of breast cancer, has once again shown that diligent and continuous work based on scientific findings and a multidisciplinary approach brings great advances in breast cancer treatment, with great impact on patient survival and quality of life.

In the last few decades, great progress has been made in the treatment of breast cancer, which has enabled patients to live longer and with better quality. We are on the cusp of a very interesting era in oncology, multigene tumor profiling, treatment guided by comprehensive gene profiling, new effective drugs such as antibody-drug conjugates and targeted treatment targeting specific mutations. Diagnostics is becoming more and more precise, and the possibilities of radiotherapy and surgery as local forms of breast cancer treatment are increasing.

Twelve lectures and multidisciplinary panel discussions by leading experts and scientists in the field of breast cancer make this meeting traditionally one of the most respected medical meetings in the Republic of Croatia.

The Symposium – Anthrax and African Swine Fever in Croatia

Author:
Josip Madić

The symposium entitled Anthrax and African Swine Fever in Croatia was held on 13th of October 2023 in the Library of Croatian Academy of Sciences and Arts (CASA) in Zagreb. It was organized by the Committee of Animal and Comparative Pathology of the Department of Medical Sciences of CASA. It was aimed to present the epidemiological aspects of the newest outbreaks of anthrax and African swine fever in Croatia.

At the beginning of the Symposium, the participants were welcomed by academician Vida Demarin, the secretary of the Department of Medical Sciences of CASA, and academician Josip Madić, who was the chairman of the Organizing Committee.

Epidemic of anthrax appeared in summer of 2022 in cattle and humans in the Lonjsko Polje Nature Park. Its causative agent, *Bacillus anthracis,* is one of the most likely agents to be used for bioterrorism.

African swine fever (ASF) occurred in June 2023 in Vukovar-Srijem County and is still lasting. Before that, the disease was diagnosed in the neighboring countries of Serbia and Bosnia and Herzegovina. It is obvious that the measures adopted by the veterinary administration to eradicate it, are not effective enough or have not been applied by the pig owners. Because of this, the disease continues to spread in Croatia and in mid-October it also affected pigs in some villages of the Osijek-Baranja County.

The first part of the Symposium was dedicated to the epidemic of anthrax. The first presentation under the title Bioterrorism - Threat and Challenges was presented by Prof. Alemka Markotić, MD, PhD, from The University Hospital for Infectious Diseases „Dr. Fran Mihaljević“, Zagreb. She emphasized that the strength of biological weapons lies in their ability to cause high morbidity among the affected population and a high mortality

rate. Prof. Ljubo Barbić, DVM, PhD, from the Department of Microbiology and Infectious Diseases with Clinic of the Faculty of Veterinary Medicine University of Zagreb referred to the role of the veterinary profession in ensuring food safety and monitoring and controlling zoonoses. In his lecture entitled Veterinary Medicine from Anthrax to African Swine Fever, he stated that the work of the veterinary profession is difficult in conditions of mistrust of animal owners and certain parts of society in scientific truth and institutions, which unfortunately is becoming a feature of modern society.

Epizootiological characteristics of anthrax in the area of the Lonjsko polje Nature Park in 2022 were discussed by Tihana Miškić, DVM, from the Veterinary and Food Safety Directorate, Ministry of Agriculture of the Republic of Croatia. Anthrax was proven in cattle and horses in areas of common pastures Repušnica, Osekovo, Gračenica and Veliko Svinjičko in the area of the Nature park Lonjsko polje in Sisak-Moslavina County.

Details of diagnostic methods and prevention of anthrax in animals were presented by Dr. Gordan Kompes, DVM, PhD, from the Department of Bacteriology and Parasitology, Laboratory for General Bacteriology and Mycology of the Croatian Veterinary Institute.

At the end of the first part of the Symposium, we heard about anthrax epidemics in humans in Croatia with special reference to the last epidemic in the Lonjsko polje Nature Park in 2022. The epidemic in humans began on July 13, and ended on August 19. A total 17 people fell ill with the skin form of anthrax. Sonja Pajtlar, MD, spec. epid., epidemiologist of the Public Health Institute of Sisak-Moslavina County spoke about it.

After the lectures of the first part of the Symposium were presented, an extensive discussion developed, primarily about the way the causative agent was transmitted to humans.

The second part of the Symposium was intended to present the African Swine Fever epizootic in Croatia. Prof. Lorena Jemeršić, DVM, PhD, from the Department of Virology of the Croatian Veterinary Institute, Zagreb, emphasized that ASF remains one of the most damaging ongoing panzootics which is significant threat to pig production worldwide. No vaccine or treatment is available against ASF. Prevention is based on early detection and strict biosecurity measures that can prevent further spread of the disease and minimize contamination of environment and the likelihood of infection in wild boar. Her lecture was followed by the lecture of Prof. Dean Konjević, DVM, PhD, Department of Veterinary Economics and Epidemiology, Faculty of Veterinary Medicine, University of Zagreb. He explained in detail the role of wild boar in the epidemiology of ASF. He showed the trend in wild boar abundance and the influence of population density, environmental factors, hunting activities, poaching and carcasses in hunting grounds on the spread and maintenance of ASF virus.

In the summary of her presentation Ljupka Maltar, DVM, PhD, from the Veterinary and Food Safety Directorate, Ministry of Agriculture of the Republic of Croatia, described the measures for the control and eradication of ASF in Croatia. On June 26, 2023, the disease was confirmed for the first time in the territory of the Republic of Croatia, in the Vukovar-Srijem County, from a sample of domestic pigs taken from two farms on June 23, 2023, in the area of the municipality of Drenovci, Posavski Podgajci settlement, near the border with Bosnia and Herzegovina. From that day until September 28, 2023, a total of 909 outbreaks were confirmed in locations of 19 municipalities of Vukovar-Srijem County and two municipalities in Brod-Posavina County.

In the discussion at the end of the Symposium, many questions were raised regarding the failure to stop the spread and eradication of the ASF in Croatia.

Symposium „Infections of the spine“ on the occasion of the World Spine Day, Zagreb, 12th October 2023

Author:
Frane Grubišić

Croatian Society for Vertebrology of the Croatian Medical Association in cooperation with Department of Rheumatology, Physical Medicine and Rehabilitation,University Hospital Center Sestre Milosrdnice Zagreb and Department of orthopedics and traumatology, University Hospital Dubrava organized symposium entitled „Infections of the spine”. The symposium took place on 12th October 2023 in the Library of the of the Croatian Academy of Arts and Science with Prim. Darko Perović, MD, PhD and Assistant Prof. Frane Grubišić as chairs and moderators. As for many years before, this 20th annual symposium was also held under the high auspices of the Croatian Academy of Arts and Science.

Welcome speech was addressed by academicians Prof. Vida Demarin (on behalf of the Croatian Academy of Arts and Science), followed by Prof. Dinko Vidović (on behalf of the prof. Davor Vagić, principal of the University Hospital Center Sestre Milosrdnice Zagreb) and Prim. Darko Perović (president of the Croatian Society for Vertebrology).

Assist. Prof. Frane Grubišić and Ines Doko Vajdić, MD, PhD (University Hospital Center Sestre Milosrdnice Zagreb) opened symposium with lecture titled „Epidemiology and risk factors of the infections of the spine”.

Nikolina Bušić,MD (University Hospital Dubrava) in-coautorship with Goran Kurdija, MD (University Hospital Center Zagreb) presented lecture on the etiology and etiopathogenesis of the infection of the spine.

Following lecture was focused on the topic when should we think of the infection of the spine and it was delivered by Dražen Kvesić, MD, MSc (Special Hospiral Aritera).

Karolina Dobrović, MD, PhD (University Hospital Dubrava) presented important steps related to microbiology diagnostic of the infections of the spine.

Luka Novosel, MD, PhD (University Hospital Center Sestre Milosrdnice Zagreb) presented an important topic on the invasive procedure of obtaining tissue sample important for diagnostic algorhythm as well as for the potential treatment options – minimally invasive radiologic interventions.

Eugen Divjak,MD, PhD in coauthorship with Associate Prof. Gordana Ivanac, MD, PhD (Univeristy Hospital Dubrava) presented the role of various imaging techniques.

Prof. Ivan Puljiz, MD, PhD (University Hospital for Infectious Disease Dr. Fran Mihaljević) presented data on the extensive pharmacological protocols used in the treatment of the infections of the spine.

Prim. Darko Perović, MD, PhD and Assist. Prof. Vide Bilić, MD, PhD (University Hospital Dubrava) together with Prof. Boris Božić, MD, PhD (Special Hospital Spine) presented surgical treatment options of the hematogenous infections, postoperative spondylodiscitis and perimplant spinal infections.

Prim. Tatjana Nikolić, MD and Dubravka Sajković, MD, PhD (University Hospital Center Sestre Milosrdnice) in co-authorship with Dubravka *Šalić* Herjavec, MD (Department of Rehabilitation and Orthopaedic Devices, University Hospital Center Zagreb) presented lecture entitled "Rehabilitation and orthotics in the treatment of the infections of spine.

There was an interactive discussion followed after lectures. This year symposium gathered around 115 participants maintaining high quality level of presentations and discussion.

The Exhibition a Shift in Time: The Ent Department at the Zagreb School of Medicine from the Analogue to the Digital Age

Božidar Adžija Library, Zagreb, 15 November – 15 December 2023
Organised by: The Croatian Museum of Medicine and Pharmacy,
the Croatian Academy of Sciences and Arts, and the Božidar Adžija Library, Zagreb
Authors of the exhibition: Silvija Brkić Midžić, Prof. Stella Fatović-Ferenčić and Prof. Drago Prgomet
Graphic design by: Studio Rašić, Ante Rašić
The exhibition layout by: Silvija Brkić Midžić

Author:
Silvija Brkić Midžić

With this exhibition, the Croatian Museum of Medicine and Pharmacy has continued its successful cooperation with the Božidar Adžija Library in Zagreb, established with the aim of displaying the museum items and presenting topics from the field of biomedical sciences to the general public during the renovation of the permanent museum building. As part of this collaboration, the Božidar Adžija Library has so far hosted the following exhibitions: *Kaštel at its Peak: Advertising and Packing of Medicines produced by the Zagreb Kaštel Factory in the 1930s and 1940s* (2021) and *Museum Time Machine: the Collection of Folk Medicine as the Core of the Exhibition Display of the first Croatian Museum of Medicine* (2022). Both became very popular among the audience.
The exhibition *A shift in Time: The ENT Department at the Zagreb School of Medicine from the Analogue to the Digital Age* was realised in cooperation with the Croatian Museum of Medicine and Pharmacy and the Division for the History of Medical Sciences of the

Visual identity of the exhibition (author: Ante Rašić)

Croatian Academy of Sciences and Arts with the Department for Ear, Nose and Throat Diseases and Head and Neck Surgery at the Zagreb School of Medicine on the occasion of its 100th anniversary. It was first displayed in the Hugo Botteri Hall at the Zagreb University Hospital from 27 September to 31 December, 2021.

The hundred years of the Department's existence gradually became part of the main idea behind the story of Croatian medicine. It is one of few medical institutions which managed to preserve such an impressive amount of material heritage. This exhibition presents a part of that heritage, a rare collection of photographs portrayed as a time machine, contrasting the past and the present with photographs from the Department's different periods. The starting point of the exhibition were the photographic collection of the Otorhinolaryngology Department at **Šalata**, edited and managed by Ante **Šercer**, which is now preserved at the Croatian Museum of Medicine and Pharmacy, the Croatian Academy of Sciences and Arts, and photographs preserved at the Department for Ear, Nose and Throat Diseases and Head and Neck Surgery of the Zagreb University Hospital at Rebro, courtesy of several prominent names in this profession, such as Dragutin Mašek, Ante **Šercer**, Branimir Gušić, Zvonimir Krajina and the tenth head of the Department, Drago Prgomet. The exhibition shows the locations where the Department was located: Draškovićeva Street, then **Šalata** and finally its current location at the University Hospital Rebro in Kišpatićeva Street. There are photos of doctors, wards, patient rooms, operating rooms, lecture halls, libraries and museums. It is important to note that the valuable heritage of the ENT Department museum in Zagreb is now largely located in the Croatian Museum of Medicine and Pharmacy and will be exhibited in a permanent museum setting.

Part of the exhibition in the Božidar Adžija Library

In addition to the introductory poster with a short text and twenty-one posters with combinations of digital reproductions of old black-and-white photos and new digital colour photographs, the exhibition also includes original museum items from the collection of the Croatian Museum of Medicine and Pharmacy: the representative photo album of the ENT Department from 1941, which was ordered from the photo studio Donegani by its head, Prof. Ante **Šercer**, a more modest photo album of the Department by an unknown author from the period between 1954 and 1971 and a number of separate photographs from the period between the 1920s and the 1970s.

The exhibition features a screening of a documentary about the Department for Diseases of the Ear, Nose, Throat and Head and Neck Surgery, filmed for the Department›s 100th anniversary, and a photo monograph by Stella Fatović-Ferenčić and Drago Prgomet, entitled *A Visual Memory of the Profession – The Otorhinolaringology Department at the Zagreb School of Medicine upon a Century of its Existence (1921 - 2021).* It was a joint publication of the Croatian Academy of Sciences and Arts and the Zagreb School of Medicine, 2021.

For additional information about the exhibition, please visit the Croatian Museum of Medicine and Pharmacy website and Facebook page:
https://hmmf.hazu.hr/u-vremenskom-pomaku/
https://hmmf.hazu.hr/izlozba-u-vremenskom-pomaku-u-knjiznici-bozidara-adzije-u-zagrebu/
https://www.facebook.com/profile.php?id=100063739112448

Conference of the Croatian Hypertension League - "The Silent Killer Hunt - Stress The Omnipresent Demon"

Author:
Marija Domislović

The conference organized by the Croatian Hypertension League "The Silent Killer Hunt - Stress the Omnipresent Demon" was held on November 9 at the Faculty of Medicine in Zagreb, under the wing of the Croatian Academy of Sciences and Arts, and brought together experts from the medical community, health workers, industry, and the curious public.

The central theme of the conference was stress as a serious risk factor for arterial hypertension, and different perspectives on this topic were discussed through panel discussions and lectures. Medical experts, including academic Vida Demarin and academics Bojan Jelaković and Davor Miličić, led panel discussions focused on understanding stress as an omnipresent demon and its impact on arterial health. The panel discussions emphasized the importance of awareness of arterial hypertension as a major public health problem in Croatia. In addition to doctors of various specialties, nurses, and pharmacists, nutritionists and kinesiologists participated as mandatory members of teams for the care of patients with chronic non-communicable diseases, as well as meteorologists, climatologists, and people from public life, pharmaceutical, publishing, food, and digital industries. Since yoga and mindfulness are mentioned in the new guidelines as a new "auxiliary tool" for treating patients with arterial hypertension, these experts were also panelists.

The specifics that women experience in the context of stress were highlighted at the conference. Associate Professor Valerija Bralić-Lang emphasized the accumulation of stress in women due to family obligations, which is an important aspect of understanding and approach to prevention and treatment. The panels covered various topics, from lifestyle habits and stress at work to digital transformation and stress, and the impact of climate change on arterial hypertension. All these topics have expanded knowledge about the link between stress and health. The topics for the panel discussions were: Silent killer number 1 in Croatia - yesterday, today, tomorrow; Stress as a permanently omnipresent demon; Women and stress; Life habits and stress; Stress at work; Digital transformation and stress; Stress due to climate change and impact on arterial hypertension and total risk; White coat hypertension and masked hypertension as markers of present stress.

The results of the national study EH-UH 2 (Epidemiology of Hypertension in Croatia) and the MMM (May Measurement

Month) project were also highlighted at the conference, which shows an increase in the prevalence of hypertension in Croatia from 37% to 50%! Every second adult in Croatia has elevated blood pressure values, which indicates a serious challenge in public health. The need for primary prevention, a multidisciplinary approach, and the role of different health professionals was emphasized. The Croatian Hypertension League announces a new project to increase health literacy, increasing adherence, but also reducing clinical inertia. In the program called 70/26, the goal is for 70% of treated patients to reach the target blood pressure values by 2026. Symptoms of arterial hypertension usually develop imperceptibly over the years, without any signs or symptoms, and later lead to serious complications such as heart disease, stroke, chronic kidney disease, and other problems. Namely, arterial hypertension is responsible for over 40% of deaths per year in Croatia, and around 30% of Croatian residents suffer from hypertensive diseases, which places us in the unenviable group of countries least aware of the treatment of the "silent killer" and makes this conference even more important for the general health of the population.

The conference "The Silent Killer Hunt - Stress the Omnipresent Demon" represents an important step in raising awareness of the seriousness of arterial hypertension and promoting preventive measures. In addition, the importance of cooperation between different sectors in the community to jointly face this serious public health threat was emphasized.

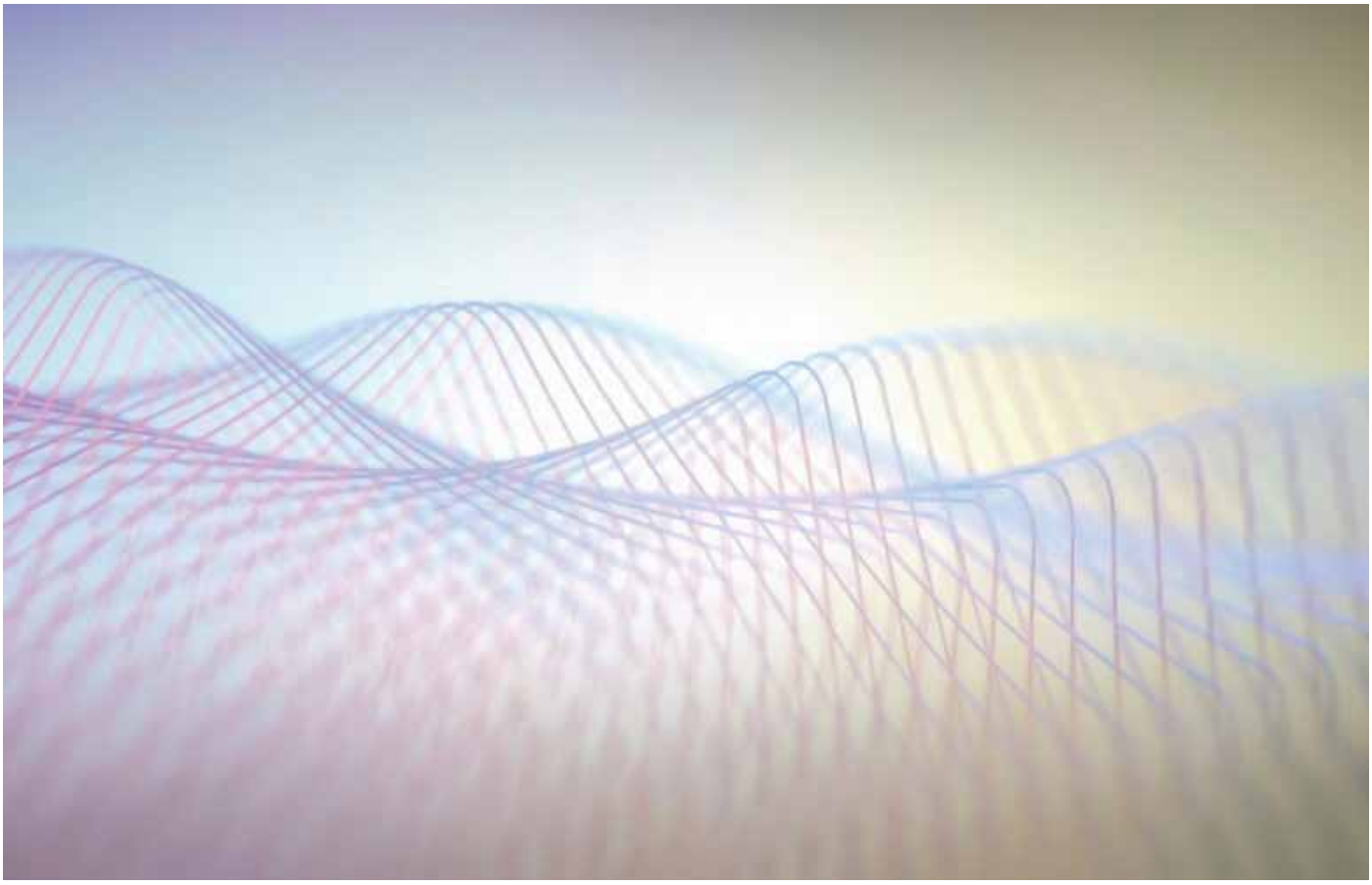
The twentieth "Prosinački" scientific dermatovenereological symposium "National program for the prevention and early detection of melanoma: twenty years of enthusiasm of Croatian dermatologists."

Author:
Mirna Šitum

In organization of the Croatian Academy of Sciences and Arts, Department for Medical Sciences, Department of Dermatology and Venereology, University Hospital Center Sestre milosrdnice and the University of Zagreb School of Dental Medicine, Croatian Association of Dermatological Oncology of the Croatian Medical Association, and the Croatian Dermatovenereological Society of the Croatian Medical Association, a traditional scientific dermatological symposium was held on Friday, December 8, 2023, in the "Vijenac" hall of the Archbishop's Pastoral Institute, located at Kaptol 28A. This year marked the 20th scientific dermatological symposium, with a topic "National program for the prevention and early detection of melanoma: twenty years of enthusiasm of Croatian dermatologists."

The symposium was attended by 160 Croatian dermatovenereologists, including 21 speakers from various dermatovenereological institutions in Croatia, coming from the major Departments of four Clinical Hospital Centers, dermatological practices in general and county hospitals, as well as private dermatological practices. The selection of topics presented at the Symposium highlighted the complexity of the dermatovenereological and dermatooncological profession and science, especially since many dermatooncological entities often go unrecognized and are diagnosed late in daily medical practice by physicians of various specialties.

The special value of this year's symposium topic was the exchange of experiences from clinical practice through the presentation of exceptionally complex differential-diagnostic issues and thera-



peutic challenges in dermatooncological practice. This seemingly clinical topic of the symposium, in each of its examples, particularly emphasized the need for a multidisciplinary approach to patients and for continuous monitoring of scientific insights that serve as a source of knowledge necessary in everyday patient care. The first part of the symposium was dedicated to malignant melanoma, ranging from the presentation of an extremely rare case of congenital melanoma to lectures on atypical clinical forms of melanoma, diverse clinical presentations of metastatic melanoma, and side effects of oncological therapies for metastatic melanoma on the skin. In this part of the symposium, individual clinical experiences confirmed the exceptional value of the adjunct clinical diagnostic method - digital dermoscopy in melanoma diagnosis, and an important presentation affirmed the not uncommon challenges in aligning clinical and dermoscopic findings with the final histopathological diagnosis of melanoma. The second part of the symposium featured presentations on patients with various types of non-melanoma malignant skin tumors that are rarely diagnosed. The presented cases included patients with angiosarcoma of the skin, Kaposi's sarcoma as a sign of HIV infection, and a case of a patient with the coexistence of T and B lymphoproliferative disease. Among the selected topics were entities of metastatic skin lesions associated with primary breast cancer, squamous cell carcinoma in skin lesions resulting from hidradenitis suppurativa, differentially diagnostically challenging "pink lesions," including the diagnoses of non-neural granular cell tumors, skin tumors of the ears and nodular skin lesions of infectious nature. All presentations were supported by an extensive collection of original photographic documentation. The importance of interdisciplinary cooperation and a multidisciplinary approach was clearly expressed in all topics, as it is the only correct way to a comprehensive approach to patients with oncological diseases in dermatology.

During the course of the symposium, a scientific monograph was presented "Dermatological Oncology in Clinical Practice - Towards the National framework for the prevention and early detection of melanoma 2023-2026," edited by Academician Mirna Šitum, published by the Croatian Academy of Sciences and Arts and Medicinska naklada. Additionally, new Guidelines of the Reference center of the Ministry of Health for melanoma for monitoring patients with melanoma were introduced.

The recent commemorative twentieth «Prosinački» scientific dermatovenereological symposium served as a congratulation and expression of gratitude to all enthusiastic dermatovenereologists who, for over 20 years, guided by the visionary idea of Academician Štampar that healthcare professionals must primarily act among health-risk groups and conduct health education, work on public health activities for the prevention and early detection of melanoma and other malignant skin tumors in many regions of the Republic of Croatia. All the speakers at the symposium were actively involved in these public health activities, and the outcomes of their work unequivocally affirmed the necessity for instituting a new national program. This recognition was recently formalized through the decision of the Minister of Health of the Republic of Croatia for the new National melanoma prevention and early detection program 2023-2026.

The symposium, on behalf of the Croatian Academy of Sciences and Arts, Department for Medical Sciences, was inaugurated by the respected Academician Vida Demarin, secretary of the Department for Medical Sciences, who, as a reviewer alongside Prof. Branka Marinović, also presented the scientific monograph.

The 9th International Conference on Prehypertension, Hypertension and the Cardio Metabolic Syndrome in Zagreb

Author:
Armin Atić

The 9th International Conference on Prehypertension, Hypertension & the Cardio Metabolic Syndrome held in Zagreb, Croatia, October 18-22, 2023, patronized by the Croatian Academy of Sciences and Arts, emerged as an excellent platform that brought together leading researchers, clinicians, and practitioners from different medical specialties dealing with these leading morbidities of our time. Colleagues from 39 countries all over the world took part (300 on-site and more than 3000 on-zoom attendees). Participants have had the opportunity to listen to state-of-the-art lectures, engage in discussion with prominent experts from the field of cardiovascular, metabolic and kideny diseases, and partake in workshops regarding prevention, diagnosis, and management of prehypertension, hypertension, and metabolic disorders using novel and innovative techniques. Younger healthcare professionals have shown particular interest in a number of hands-on sessions, such as ultrasound, blood pressure measurement, arterial stiffness, lifestyle, and many others, held by renowned clinicians and distignuished international professors.

One of the hallmarks of this conference was the diversity of topics covered, catering to the varied interests of the attendees, particularly considering the involvement of associated healthcare professionals including pharmacists, nutritionists, nurses, psychologists, and social workers in all aspects of the conference. From the underlying mechanisms of prehypertension to holistic therapeutic interventions for hypertension and the intricate relationship between cardio-metabolic syndrome and other systemic diseases, the scientific program was both comprehensive and dynamic. Special sessions were devoted to obstacles related to the prevention and management of cardiovascular and metabolic diseases, including adherence, the use of „alternative“ medicine, and patient-related factors including individual, socio-economic, and cultural differences within populations, highlighting the need for a holistic approach to healthcare which considers the broad determinants of cardiovascular health. Vibrant meet-the-expert sessions allowed participants to deepen their understanding of specific subfields, creating a collaborative atmosphere and providing multidisciplinary insight into various topics.

Particular attention was given to the new European Society of Hypertension guidelines on the management of hypertension. Roundtables with guideline authors have given a valuable overview of the new recommendations, as well as constructive debates regarding controversial issues, problems, and issues not addressed or fully covered by the guidelines.

Presenters, including seasoned researchers to young scholars, have had an opportunity to display their work in oral presentation sessions, giving an opportunity to the attendees to review the latest research and to engage in one-on-one interactions with the investigators.

The diverse and extensive program has illuminated the current state of prehypertension, hypertension, and cardio-metabolic diseases and has also shown the ongoing progress, current obstacles, and future directions. Chairmen of the Conference, Professors Reven Zimlichmann and Bojan Jelaković concluded this well-organized and diverse conference with messages reinforcing the need for a holistic and multidisciplinary commitment to the management of cardiovascular health.

Symposium 45 Years of Continuous Neurotransmitter Research in Croatia (1978 - 2023)

under the auspices of the Croatian Academy of Sciences and Arts

Author:
Lidija Bach-Rojecky

Under the auspices of the Croatian Academy of Sciences and Arts (HAZU) and supported by the Croatian Pharmacological Society, the scientific symposium **on 45 years of continuous neurotransmitter research in Croatia (1978-2023)** was held in the HAZU Library in Zagreb with the presence of about 75 participants. This meeting celebrated the 45th anniversary of the establishment of the Laboratory for Molecular Neuropharmacology at the University of Zagreb School of Medicine and the 20th anniversary of the collaboration with colleagues from the Department of Pharmacology, University of Zagreb Faculty of Pharmacy and Biochemistry. Two weeks before the meeting, it was announced that the founder of this Laboratory, Professor Zdravko Lacković received the State Award for Science for lifetime achievement, which contributed to the atmosphere of celebration.

Academician Professor Vida Demarin opened the meeting by emphasizing the importance of basic research, especially for the continuous development of neurology.

Professor Lacković described the path from the establishment of a small laboratory in the attic of the faculty building at Šalata 11 to world-renowned achievements. Professor Lidija Bach-Rojecky and Ivica Matak, Ph.D., briefly presented the discovery that botulinum toxin, a powerful poison, drug, and cosmetic product, reaches the CNS by axonal transport after peripheral application. Then Professor Melita Šalković-Petrišić described the discovery that experimental diabetes caused by streptozotocin can be studied as a model of sporadic Alzheimer's disease. This model was additionally discussed by Associate Professor Jelena Osmanović Barilar and Jan Homolak, Ph.D.

Guests from collaborating laboratories in Italy, Professor Marco Pirazzini (Padua) and Professor Eugenio Barone (Rome), spoke about the effect of tetanus toxin and insulin on the brain, respectively. The lecture on the role of cell organelles in brain diseases was held online by Professor Dimitri Krainc from Northwestern University, a member of the American Academy of Medicine and president of the American Society of Neurologists. Academician Professor Peter Riederer (Wuerzburg) spoke about the oxidative stress in neurodegenerative diseases.

The scientific part of the program was followed by a short informal gathering.

IMPRESSIONS
(translation LBR)

***Academician Prof. Peter Riederer, PhD**, German National Academy of Sciences Leopoldina, and Hungarian Academy of Sciences (Wuerzburg)*

It was indeed traveling through the times of neurochemistry and neuropharmacology with all its facets. The development of research into botulinum toxin and the basis of Alzheimer's pathology have been characteristic highlights of the institution that you have founded. Congratulations!!!
I was very much impressed to see the development of your teams … excellent teams of young scientists with a great future ahead. You can be proud! It is hoped that the University recognizes that these teams are a treasure, which lead to an increase in the University's international reputation.

***Academician Prof. Dimitri Krainc, MD, PhD,** National Academy of Medicine (part of the National Academies of Sciences, Engineering, and Medicine) and President of American Neurological Association (Chicago)*

And once again, let me say that I'm sorry I wasn't there in person... I wasn't with you in Lab. for a long time, but the memories are wonderful. Without your initial inspiration and support, who knows where I would have ended up.

***Karlo Toljan, MD**, Neurologist and Neuroimmunology fellow, Cleveland Clinic Foundation (Cleveland)*

Congratulations! 45 years! One epoch! That number will be impossible for many labs in the global world, where so much is produced quickly. This is a testimony that with effort, a lot is possible, no matter how many people mention the phrase "in our conditions" as an excuse.

***Prof. Tonči Matulić, PhD**, University of Zagreb Catholic Faculty of Theology (Zagreb)*

It was an honor and a pleasure for me to take a short part in the celebration of the anniversary and witness the top achievements and excellence of which you are the originator, mentor, and soul... I wish you a lot of happiness and health and God's blessing in everything.

10. SCIENTIFIC MEETING with international participation TUMORS OF THE PROSTATE

Croatian Academy of Sciences and Arts, Department of Medical Sciences – Committee on Tumors
KBC SESTRE MILOSRDNICE, KBC ZAGREB
19 December 2023

Author:
Ana Fröbe

On November 30, 2023 in the library of the Croatian Academy of Sciences and Arts, the jubilee 10th scientific meeting with international participation Tumors of the prostate was held. This scientific meeting was jointly organized by the Croatian Academy of Sciences and Arts, its Department of Medical Sciences - Committee on Tumors, UHC Sisters of Mercy and UHC Zagreb.
The president of the organizing committee of the meeting was prof. Ana Fröbe, head of the Clinic for Oncology and Nuclear Medicine UHC Sisters of Mercy.
The meeting was successful and brought together about 100 medical professionals dealing with prostate cancer. The meeting was attended by leading Croatian experts dealing with the diagnosis and treatment of prostate cancer, with the participation, both live and virtually, of established international experts who are active in researching new possibilities for the diagnosis and treatment of prostate cancer.
The professions represented at the meeting were urology, oncology, pathology, radiology, nuclear medicine and others, emphasizing the multidisciplinary nature of care for patients with prostate cancer.
The group was divided into 4 thematic units: epidemiology and diagnostics, surgery, radiotherapy and systemic treatment. At the meeting, through lectures and discussion, the following current topics of particular interest came to the fore: the place of advanced robotic surgery in modern prostate cancer surgery and the role of laparoscopic surgical techniques (both techniques are available within the Croatian public health system and each has its place). ; following the EU directive Beat Cancer Plan, a national project for early detection of prostate cancer was announced, in which the key diagnostic modality will be multiparametric magnetic resonance of the prostate; international authorities presented experience from a multicenter consortium of localized prostate cancer on the prognostic importance of PSA dynamics during treatment and the role of magnetic resonance imaging in radiotherapy imaging; the role of genomic analyzes in the precise treatment of prostate cancer is emphasized, as well as discoveries in the molecular biology of prostate cancer that may indicate the development of resistance to available therapy in advanced disease. The importance of personalized treatment when many different options are available is more important than ever, and for the therapy to be clinically precise, a prerequisite is molecular and functional biologically precise imaging of prostate cancer with modern PET/CT techniques based on PSMA as an attractive radiopharmaceutical. The meeting also discussed rational pharmacotherapy and interactions of new generation drugs for prostate cancer with other drugs in the context of patients with comorbidities. Clear recommendations for practice were given, and international guidelines were commented on and how best to implement them in Croatian conditions of limited material and human resources.
The special value of the meeting was the live discussions of experts, because the diagnosis and treatment of prostate cancer requires close interdisciplinary cooperation of several medical professions (each of which has a specific view of certain clinical scenarios) in conditions of rapid progress in medical science.
The meeting showed the involvement of the Clinic for Oncology and Nuclear Medicine UHC Sisters of Mercy. in contemporary trends in the treatment of prostate cancer as well as active international participation.
Next year, this scientific symposium is organized by the UHC Zagreb Urology Clinic and its head, academician Željko Kaštelan, who also announced the tentative date of the symposium in November 2024.

The 14th Croatian Congress on Atherosclerosis with international participation in Zagreb

Author:
Dražen Perica

The 14th Croatian Congress on Atherosclerosis with international participation in Zagreb was an exceptional success, creating a dynamic platform for the exchange of cutting-edge research and knowledge on atherosclerosis. The event, which was held from November 3 to 5, 2023, aimed to talk about the hot topics related to atherosclerosis, its consequences in Croatia and global progress in this area. The congress is already traditionally under auspices of the Croatian Academy of Sciences and Arts, the European Atherosclerosis Society and the International Atherosclerosis Society.

The congress began with an inspiring opening ceremony in which the president of the congress and president of the Croatian Society for Atherosclerosis, academician Željko Reiner, and academician Vida Demarin in front of the medical class of the Croatian Academy of Sciences and Arts addressed the auditorium. In their speech, both emphasized the importance of the mission of fighting atherosclerosis, the leading cause of death in Croatia, and expressed their wishes for a successful congress.

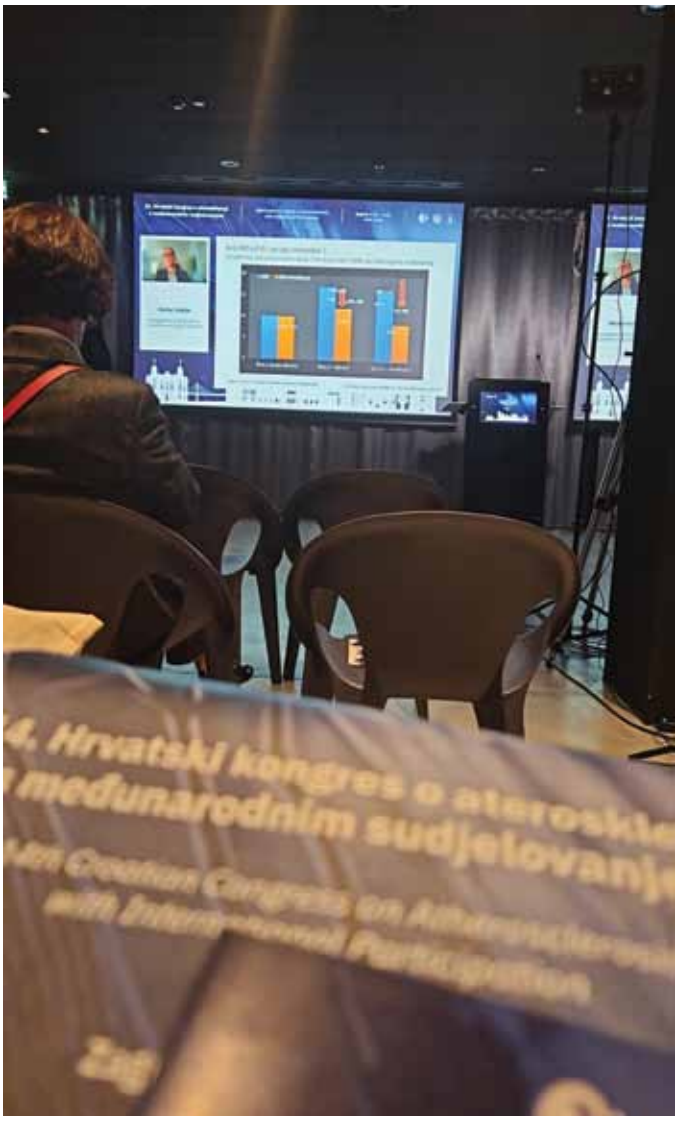
The first day of lectures was opened by academician Davor Miličić from Atherosclerotic cardiovascular disease and equivalent cardiovascular risks. Academician Miličić gave a comprehensive overview of atherosclerotic cardiovascular disease and its cardiovascular equivalents. Next, Gani Bajraktari (Kosovo) gave a lecture "Women and atherosclerotic cardiovascular diseases". The lecture dealt with gender-specific aspects of atherosclerotic cardiovascular diseases, shedding light on unique challenges and considerations for women. After that, Urh Grošelj (Slovenia) gave a lecture "Genetic causes of dyslipidemia in children" The lecture was focused on the genetic basis of dyslipidemia in children. A positive trend of interesting lectures was held by congress friend Michal Vrablik (Czech Republic) - "Treatment of dyslipidemia in patients with type 2 diabetes" In his lecture, he spoke about the important connection between dyslipidemia and type 2 diabetes. Academician Željko Reiner held a lecture "Experience with almost a decade of PCSK9 inhibitors" where he shared a wealth of knowledge based on almost a decade of experience with PCSK9 inhibitors. The lecture presented a retrospective view of the evolution of this therapeutic approach, providing valuable clinical perspectives on its effectiveness and challenges. After an interesting lecture, Dimitri Mikhailidis (United Kingdom) addressed the topic: "Non-alcoholic fatty liver disease and vascular risk. The last lecture of the first day was given by Niki Katsiki (Greece) - "Hepatic steatosis and cardiovascular risk: A continuous journey towards a better definition and treatment" In the lecture, she discussed the challenges and progress in addressing this multifaceted health problem. The session concluded with a lively discussion, allowing participants to engage with the speakers, exchange perspectives, and delve deeper into the complexities of atherosclerotic cardiovascular disease and related topics. The interactive discussion fostered an atmosphere of collaboration, enhancing the overall learning experience.

The morning session on the second day of the congress delivered an insightful session that highlighted key aspects of familial hypercholesterolemia and the intricate role of lipoprotein(s) in cardiovascular health.

Lectures were started by prof. Ivan Pećin, vice-president of the Croatian Society for Atherosclerosis with a lecture on familial hypercholesterolemia in Croatia" Lecture focused on the analysis of familial hypercholesterolemia in Croatia with an emphasis on challenges in diagnosis and treatment in the Croatian population. Still on the trail of the topic of familial hypercholesterolemia Gustavs Latkovskis (Latvia) - shared his experiences with his lecture "Experience in the treatment of familial hypercholesterolemia in Latvia"

Olena Mitchenko (Ukraine) in her lecture entitled "Diagnosis and treatment of true familial and pseudo-familial hypercholesterolemia in Ukraine" provided a comprehensive overview of the diagnosis and treatment of these conditions. After that, Danijela Petković-Ramadža (Croatia) held a lecture entitled "Screening for familial hypercholesterolemia in Croatia" where she presented the preliminary results of the National Screening for Familial Hypercholesterolemia and again highlighted the importance of early detection and screening strategies for identifying at-risk individuals within the Croatian population. After an interesting discussion and a short break, the afternoon session was started by one of the giants of preventive cardiology, David Wood (Canada), where in his lecture "Preventive cardiology – theory and practice" he gave a broad overview of preventive cardiology, including theoretical foundations, practical applications and new ideas. Academician Željko Reiner held a lecture "Lp(a) as a risk factor for cardiovascular diseases" and after him Zlatko Fras (Slovenia) - "On the role of Lp(a) in increasing total and cardiovascular risk in patients with diabetes" and Ioanna Gouni-Berthold (Germany) - "Treatment of Lp(a) - today and tomorrow" In their lectures, everyone emphasized the importance of Lp(a) in cardiovascular risk and the importance of treatment.

Next, Kornelia Kotseva (Ireland) held a lecture "EUROASPIRE and INTERASPIRE". The comprehensive review highlighted the importance of these studies in advancing our understanding of cardiovascular risk factors and treatment strategies. Academi-



cian Bojan Jelaković held a lecture "EHUH 2 study - preliminary data on the prevalence of arterial hypertension, dyslipidemia and metabolic syndrome" The lecture emphasized the ongoing effort to understand the epidemiology of cardiovascular risk factors in the Croatian population. The biggest expert in the field of statins and a frequent guest of the congress Peter Lansberg (Netherlands) held a very important and inspiring lecture "Are statins obsolete?" Optimal strategies for the treatment of dyslipidemia"

Professor Iveta Merćep held a lecture on the pharmacological view of "Statin intolerance". Lale Tokgözoğlu (Turkey) - "New therapies for lowering LDL: Which therapy to choose for which patients? The lecture provided valuable insight into personalized approaches to optimize the effectiveness of these new therapies. Professor Fran Borovečki with the lecture "Genetics of Atherosclerosis" presented genetics research atherosclerosis, revealing the intricate role of genetic factors in the development and progression of this cardiovascular condition. Livija Šimičević held the lecture "The role of pharmacogenetics in the treatment of dyslipidemia and its implementation in clinical routine". Marija Rakovac from the kinesiology aspect presented the lecture "Physical activity and atherosclerosis" by Ibadeta Bytyci (Kosovo) Daily movement and mortality: How many steps lead to longevity? Maciej Banach (Poland) Lifestyle changes or optimal hypolipemic therapy to reduce cardiovascular risk? When and how to choose in 2023? Academician Vida Demarin held a lecture "Atherosclerosis, life style and cognitive health" Finally, Ana Godan Hauptman held an inspiring lecture "Lifestyle and atherosclerosis" and emphasized the importance of a healthy diet and reducing the intake of processed food, which resulted in an interesting discussion.

The last day of the congress was opened by Alberto Zambon (Italy) with a lecture "Why target lipoproteins containing Apo B instead of triglycerides or other particles?" and introduced a revolutionary perspective on the understanding of atherogenic lipid particles. In the sequel, Richard Česka (Czech Republic), a specialist in lipidology, gave a lecture on "Hyperlipidemia as a rare disease". Assistant professor Maja Baretić held a lecture "Stress, hormones and cardiovascular risk". Mislav Vrsalović held a lecture on the often neglected topic "Peripheral arterial disease: epidemiology, risk assessment and new therapeutic options". Master Eva Pavić gave the lecture "Croatian Epigenetic connection between intestinal microbiota and atherosclerosis - the role of nutrition" The last lecture by Dunja Rogić "Laboratory - partner in the diagnosis and treatment of dyslipidemia" and emphasized the cooperation between clinicians and laboratory diagnostics. Prizes were awarded for the best young researchers, and Academician Reiner thanked everyone for the excellent congress and emphasized that the successful fight against atherosclerosis continues.

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ESSAY - INTERVIEWS

MOST ILLUSTRIOUS ALUMNI OF THE SCHOOL OF MEDICINE, UNIVERSITY OF ZAGREB, ZAGREB, CROATIA

Dear Readers,

In the issue 544=52-53 of our periodical, RAD HAZU – Medical Sciences, we introduced a new feature entitled *ESSAY – INTERVIEWS „Corresponding Members of Croatian Academy of Sciences and Arts, Department of Medical Sciences* ". For the issues 54-55,56-57,58-59,60-61,62-63 and the present issues 64-65 of our journal we decided to expand the scope of that series and include interviews with other internationally known alumni of the School of Medicine, University of Zagreb, Zagreb, so that we could profile even those alumni who are not Corresponding Members of the Croatian Academy of Sciences and Arts. This change of venue required us to change also the title of this series of interviews, and rename it in Latin **Illustrissimi alumni Facultatis Medicae Zagrabiensis.** The same interviews, translated into Croatian will be published on the electronic web site of the Medical Faculty **mef.hr**.

Dr. Ivan Damjanov, Emeritus Professor of Pathology, The University of Kansas School of Medicine, Kansas City, USA, who is also a Corresponding Member of the Croatian Academy of Sciences and Arts agreed to continue conducting these interviews. Like the initial interviews those in the present volume are produced under the same Latin title in cooperation with the editors of "mef.hr", the official website of the School of Medicine, University of Zagreb. The preface to the initial series of interviews is reprinted here for historical reasons and to show that the main goals and intentions for this series remain the same despite the changes of the title of the series. In the issues 58-59 there is one exception because Ivan Damjanov-Interview was conducted by Marko Pećina.

Marko Pećina

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The preface in the Issue 544=52-53

The present series was conceived as a set of informally recorded conversations with the best-known and internationally recognized graduates of the School of Medicine, University of Zagreb. The English version of these interviews is now being published by HAZU to make them accessible to a wider readership, including all those who do not understand or read Croatian.

The primary goal of this series of dialogues in RAD HAZU is to present and recognize the outstanding alumni of the School of Medicine University of Zagreb, Zagreb,Croatia. We hope that our readers will enjoy reading about the memorable events in the lives of these physician-scientists, their achievements, and scientific contributions that made them famous worldwide.

The emphasis of these discourses will be on the human side of science and medicine. Our goal was to give the interviewees a chance to reminisce about their trials and tribulations as well the happiness and fun they experienced in their lives. In other words, the objective of the interviews is and will be to give our esteemed interlocutors an opportunity to tell their life story in their own words and show us "how they did it" while still keeping their personal and professional lives in balance.

Finally, it's a good time to remind you, our readers, of the Latin saying "*verba volant scripta manent*", which justifies publishing so many written words that otherwise would have been forgotten. By producing these pieces, our purpose was to preserve the informal records of the lives and work of featured physician-scientists; and by transforming their verbal testimonials into written documents, leave a permanent trace of their activities for future generations in the archives of HAZU.

Marko Pećina
Ivan Damjanov

Ana Barač Interview

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1. Where were you born and where did you grow up?

I was born and grew up Split. It was the time of "staro splitsko rodilište" and Split as an industrial port in 70-ies and 80-ies, so well depicted in the novels of the Split writers. Years later, living and having a family in the U.S., I found myself reading the "Knjiga o jugu", by Jurica Pavičić, a legend of Dalmatian and Mediterranean literature, and reflecting how birthplace shaped who I became and what I long for. And Tisja Kljaković Braić's 2015 novel "U malu je uša Đava" sent me right back to Splitska Riva in the eighties, with a fantastic laugh and a reminder how these memories influenced my perspective of career and life.

2. What were you favorite subjects in high school?

The high school years were the formative ones, in particular when it comes to discovering interest in science, and I remember them fondly. I went to splitski MIOC, the class of 1998-1992, at the time of one of the re-reforms of the high school education in what was then Jugoslavia. That meant that the curriculum emphasis was still on math, physics, and informatics, however, human sciences classes were reintroduced, and we had Latin, philosophy, sociology, and an option for an additional language. Our class took French, and I loved languages including Latin and Italian which I took outside of school. It is hard to pick the favorite subject! MIOC is known for math and physics which were a highlight and thought in an environment of extremely talented students. In retrospect, biology inspired my curiosity the most and ended up guiding my next decision.

Figure 1. Professors and students of my high school 1992 class from MIOC in Split, 30 years after graduation.

3. How did you decide to study medicine?

Leaving high school, I wanted to study molecular biology which meant going to Zagreb. No one in my family was in biology or medicine so I spoke to friends, older students, and professors about the experiences. The entry exam was in the fall of 1992, and included biology, chemistry, and physics, I believe. I applied for Medical School and Molecular biology which was with Faculty of Science (Prirodoslovno-matematički fakultet) and was limited to 30 students making it very competitive. The results of the exams were posted on the doors of the Faculty of Science – in Zvonimirova for Molecular Biology and in Šalata for Medicine- it is funny how vivid these memories before the online test results are! It was also before the cell phones so I was by myself in Zagreb, if front of the posted lists on the door, having to make a decision between the two programs. I remembered the conversations with senior colleagues about the career options, who told me that several successful Croatian scientists doing molecular biology abroad were alumni of the School of Medicine and that molecular tools were very relevant and for medicine. So I decided to go into medicine to pursue biomedical science.

4. How enjoyable were the first three preclinical years of your studies? Who were your favorite professors?

The second year was my absolute favorite with neuroscience, physiology, and pharmacology, opening the new world of mechanisms, why and how the organs functioned. And if I need to choose one favorite subject it would be the pathophysiology class in the third year, linking the mechanisms to the disease processes. It was logical and scientific. More than the individual professors, I remember working with clinical assistants ("demonstratori"), in particular in pathophysiology, who made me want to become an assistant in pathophysiology as well. I was trying to get to my dream of learning molecular science and truly cherished getting the opportunity to work in a laboratory of pharmacology, led by Professor Zdravko Lacković and, at time senior staff members, Professor Vlado Trkulja and Professor Melita Šalković. That was my first true exposure to basic science publications, literature review, laboratory techniques and running experiments. And it was eye opening: so much to do and learn.

Figure 2. This photograph was taken during my Anatomy course in the Fall of 1992. We are standing in front of the Institute of Anatomy of the Medical Faculty, University of Zagreb. Dr. Ksenija Kos, our clinical assistant for anatomy is in the center, I am in the back row, second from the left, and among my colleagues are several close friends till today, including Dr. Sonja Badovinac and Dr. Lana Bijelić.

Figure 3. As a student I received the Rector's award in 1995.

5. Which were your favorite subjects and favorite professors in the clinics?

My memories of clinics are more blurry, but internal medicine was my favorite subject. And among subspecialties, cardiovascular disease and hematology including blood malignancies were the most fascinating. Both disciplines were dynamic in the late nineties, with new tools such as cardiac imaging and echocardiography blooming, and new treatment approaches transforming the prognosis. I remember reading about it and wishing that our clinical training was more connected to these advances and patient care.

6. Did you have any role models during your medical school years?

Maybe because my path was somewhat unconventional, I remember these years as a pursuit for maximum learning, of both basic and clinical science, without having a role-model in either of the worlds. I became interested in wanting to bridge them, translating interest in mechanisms into clinical world, which in the 90ies and early 2000s was difficult in Zagreb.

Figure 4. In 1998 I received my MD degree. Professor Ana Marušić handed me the diploma.

7. Did you have time for any extracurricular activities and what did you do during your free time?

I loved spending time with friends and going to Kinoteka/movies, Zagrebačko kazalište mladih (ZKM), and other theater and art performances. I remember gloomy weather and so many coffee gatherings.

8. I was told that your GPA at graduation was a perfect 5/5.Is that why you received The University Rector's Award?

This must be corrected, my GPA was 4.9, in the top percentiles but not perfect J. I received the University Rector's Award in the third year for the GPA and for the scientific project that I did in the pharmacology laboratory. I was proud of the achievement and grateful to Professor Lackovic for the opportunity.

9. What did you do after graduation?

I stayed on with the Pharmacology (Katedra farmakologije) as a scientific assistant (znanstveni novak) and enrolled in Postgraduate studies in Biomedicine. My clinical interest was internal medicine and cardiovascular disease but the system of applying and entering the residency program (specijalizacije) at that time was plagued with problems. It was sad to see many of the most qualified students with the highest GPAs having to leave to pursue clinical training. And it felt a bit as a slap in the face when my application for internship positions, including volunteer ones, were rejected at Zagreb and Split hospitals. On the positive side, I could still work in the laboratory and be involved with the students and the Medical school.

10. After two years at the Clinical Hospital in Zagreb you found your way to the research laboratory of Dr. Ivan Đikić in Sweden. How did that happen? Was that a valuable experience?

In October of 1998, the fall after my graduation, I attended the First International Conference on Signal Transduction in Dubrovnik, organized by Dr Ivan Đikić. That was the conference that changed my life. Among the star-studded faculty was the Nobel Prize laureate Dr. Edmond Fischer and it felt that the entire world of cell signaling was there, ready to teach and show us the future. I knew that was what I wanted to do next. I approached Dr Đikić about the opportunity of getting experience in his laboratory and he encouraged me to apply for grants that could cover the trip and stay in Uppsala, Sweden. Options for funding were limited because the postwar Croatia was not yet part of many of the scientific conventions, however after a couple of failures in 1999 I got the scholarship from Swedish Institute, followed by the fellowship of the Federation of European Biochemical Societies (FEBS) in 2000. This allowed me to spend a year, from summer of 1999 to summer of 2000 with Dr. Đikić's lab in the Ludwig Institute for Cancer Research in Uppsala, Sweden. It was the most incredible experience with full immersion into modern molecular signaling, focused on G-protein coupled receptors (GPCRs) and their interactions with other kinases. I absolutely loved working in the lab and learning from other post-docs, students, and investigators. It was one of the most memorable years of my life and it culminated with the presentation at 2nd International Conference of Signal Transduction, held in Dubrovnik in May of 2000. I still have the poster that I proudly presented at that meeting together with all the lab colleagues: it was an incredible feeling to be part of the scientific community. One of the people who came to my poster was Dr Silvio Gutkind, a scientist from the National Institutes of Health (NIH) and expert in GPCR signaling, who was invited faculty at the meeting.

11. Thereafter you came to the US through the Fogarty International Fellowship Program. Why did you choose that pathway? How important was that fellowship for you future career?

I wanted to continue the work in molecular signaling and after talking to Dr. Gutkind the conference in Dubrovnik, he invited me to interview for a position in his laboratory at the NIH. I was awarded a Fogarty International Fellowship which funds international fellows for work at the NIH campus in Bethesda, Maryland. Because medical degree in the US is at the level of graduate school, this was a post-doctoral position and advanced molecular biology experience from Sweden was critical. This was a large laboratory including many fellows from around the world, Italy, Spain, Argentina, Mexico, Thailand, Japan, France, and India: we were all together, all studying different aspects of GPCR signaling. I shared the apartment with one of my colleagues from Zagreb Medical School, Dr Ivana Munitić, whose passion was immunology and who today leads an immunology laboratory and teaches biomedicine at University of Rijeka. The NIH is a unique place with many Institutes dedicated to the investigations spanning essentially entire biomedicine, live on the same campus. Our laboratory was focused on basic science, but I also interacted and collaborate with the colleagues working in clinical areas. And it was these collaborations that proved the most important for my next step in career. Entering my 3rd year of the fellowship at the NIH I wanted to move towards clinical models as the next step. This was the time when molecular signaling was coming full force into the clinical care, in particular in oncology, and the same molecules that we were studying in the lab, were becoming druggable targets. I decided to pursue residency in the US, and matched in the Internal Medicine Program of Georgetown University and Washington Hospital Center located in Washington DC, about 10 miles away from the NIH campus.

Figure 5. In 2006 I received the Saul Zukerman, M.D., Humanitarianism in Medicine Award from the Department of Medicine at Washington Hospital Center, in Washington, D.C. It was an honor to be handed this award by the Chair of Medicine, Dr. Leonard Wartofsky (standing on the right of the photograph), who remains my mentor and a role-model.

Figure 6. My dear mentor, Professor Ivan Đikić. We have continued to collaborate even after I moved to clinical world, and I consider him a forever mentor. Professor Đikić received in 2006. an award from the American Association for Cancer Research (ACCR) for outstanding research achievements. This photograph is from the Annual ACCR dinner of held in Washington, DC, where he was honored with the Award. I am sitting between Dr. Đikić (to the left of me) and my husband Dr. Federico Asch. Tanja Rudež, award winning Croatian science writer is standing behind me.

12. During all that time you were also a postgraduate student working on your PhD degree at the University of Split. How did you manage all that? Did you fly to Split to defend your thesis? Who was you thesis advisor?

The path to PhD started in Sweden, in the laboratory of Professor Đikić where I started the work on the G-protein coupled receptor signaling, and it continued in the laboratory of Dr. Gutkind at the National Institutes of Health, with Dr. Đikić staying on as my PhD thesis advisor. After 4 years in the laboratory, in 2003 I started clinical training which put the thesis writing on hold, but it allowed me to initiate new projects on endothelial dysfunction. It was fortunate that my residency was at Washington Hospital Center in Washington DC, so I could work with my clinical research mentors and colleagues Dr. Julio Panza and Dr Umberto Campia. Most importantly, I am truly grateful to the University of Split that allowed me to become the part of its biomedical postgraduate program and defend the PhD thesis there in the fall of 2008. It was an honor and privilege to have Professor Đikić as advisor and the thesis board (Povjerenstvo) chaired by the Akademik Stjepan Gamulin, and with professor Željko Dujić and professor Mladen Boban participating.

13. With a solid background in science you finished thereafter your clinical training at MedStar Washington Hospital Center and MedStar Georgetown University Hospital, Washington DC. Was that a critical period of your life that made you decide to become a clinician scientist?

You are right, it was during the clinical training when the "aha, that is what my calling is" moment occurred. I was in the cardiac imaging laboratory, looking at the echocardiographic images of the heart and asking why it became dilated, changed, weakened, and what the trigger was. The answer must be at the molecular level, and I felt that we as a medical community were empowered by all the advances in the basic science world. At the same time there were many new layers and questions that opened: how do we study this in the reality of the clinical world? Who are the patients who will develop heart failure and how can be predict and prevent it?

14. Did you ever consider giving up clinical work with patients and devoting yourself to exclusively to basic science research? Or "was it in your stars" to become a hybrid basic research scientist-physician?

Yes, and I have considered it many times. When I started medical school and when I went to Sweden, I thought that basic science research held all the answers and was my life path. And even starting residency I had thought I would go back to the bench full time. What I did not know is how important patient care would become to me: the ability to be there and help one person at time, the relationships with the patient and their families. It was not only a privilege and deeply human experience, to take care of patients, it also became the driver of my research questions. At the same time, this meant that I could not dedicate enough time to pursue having a basic science laboratory, I had to give that up. But I feel fortunate that I can collaborate with basic science researchers and work on bridging the gap between basic science and clinical needs.

15. You are one of pioneers and leaders of a new subspecialty of cardiology, called cardio-oncology. What is that? Could you also describe for us how did you become a cardio-oncologist. For those who want to learn more about your specialty, maybe you could give us a link to one of your on line presentations about cardio-oncology.

Cardio-oncology story is a very personal one. As a cardiology fellow, I became interested in anthracycline-related cardiomyopathy and around that time a basic science paper was published about the deleterious effects of BRCA1/2 mutation on the hearts of mice exposed to doxorubicin. Women carrying the BRCA1/2 mutations very often develop breast cancer and are treated with anthracycline-based chemotherapy, however, it was not known whether they may be at higher risk for anthracycline-related cardiomyopathy due to their mutation. We designed a case-control study to enroll women BRCA1/2 carriers who received doxorubicin as part of the treatment for breast cancer and compare them with similarly treated women with history of breast cancer who were not BRCA1/2 carriers. We invited the study participants for a clinical visit and echocardiogram and the main endpoints were echocardiographic parameters of cardiac function including global longitudinal strain. For this study, I received funding from the Georgetown's Lombardi Comprehensive Cancer Center, however, it was difficult to enroll patients as I was not part of the oncology clinical care. That is where the idea of cardio-oncology clinic came from: it became clear that the cardiovascular needs of oncology patients were broad and that we needed clinical setting to address the needs as well as to be better able to conduct research. Our study was negative, there were no significant differences in the echocardiograms of women with and without BRCA1/2 mutations (https://pubmed.ncbi.nlm.nih.gov/26749359/) , but I felt that it was learning through this project that was critical in training as a specialist in cardio-oncology.

Cardio-oncology spans across the intersections between the cardiovascular disease and cancer; including shared risk factors, growing prevalence of both diseases in aging population, and cardiovascular side effects of cancer therapies. In clinical practice, we define it as cardiovascular care of patients with cancer and survivors and if I need to choose one paper, it would be the Journal of American College publication from 2015 (https://www.jacc.org/doi/10.1016/j.jacc.2015.04.059). There are many fun stories, including the one about the very name of the specialty which was/is also called onco-cardiology, that lie behind this manuscript. It was conceived around 2012 with group of cardiologists in the American College of Cardiology when we formed a working group and performed an environmental survey of cardio-oncology practices in the US. We sent a questionnaire to cardiology division chairs asking about their institutional practices, whether they had specialists, and what they perceived as the gaps in care. The results were interesting: majority identified lack of guidelines in this field as an important barrier, together with the lack of resources and funding for specialized training. Fast forward to 2023, we now have many major society documents, as well as guidelines, addressing different aspects of cardiovascular care in this patient population. We have international conferences as well as two dedicated journals (JACC Cardio-Oncology and Cardio-Oncology Journal) that provide resources and also play an important role in the growth of the field.

Regarding the online presentations, I would love to share one at the ACC.2019 Scientific Sessions (https://www.youtube.com/watch?v=p11sMuqA4t4) where I was interviewed by Dr. Giselle Suero-Abreu, at that time a medicine resident (and a "FIT (fellows in training) Roving reporter") that illustrates the importance of the role of mentorship and professional community building and about the opportunities in training in cardio-oncology.

16. Your current title is D'Aniello Chair and Director of Cardio-Oncology, at Inova Schar Cancer and Inova Schar Heart and Vascular Institute. Why did you accept that position? Could you describe for us what your duties are at this Institute?

Inova is a large health care system located in Northern Virginia and geographically forms part of what is called DMV (District of Columbia-Maryland-Virginia) metropolitan area. The invitation to join Inova came with a task to create a true link between two large service lines, Inova Schar Cancer Institute (ISCI) and Inova Schar Heart and Vascular ISHV). The position of the D'Aniello Chair was created with the philanthropic support of the D'Aniello family which enabled us to create a unique environment that bridges clinical care and research beyond traditional

structures of separate cardiology and oncology departments. For example, I report to the Presidents of the ISHV and to the President of the ISCI, and work closely with cardiologists and oncologists, on both clinical and research projects. That is one of the reasons I accepted this position: I was challenged with developing new models of care needed for the maturing field.

17. Do you still work in a research laboratory and do you see patients?

I see patients for cardiovascular needs throughout the cancer treatment continuum. This means addressing cardiovascular risk factors, identifying need for cardiopreventive strategies prior to cancer treatment, monitoring, and management during treatment as well as visits during cancer survivorship. I also read imaging studies in the echocardiographic laboratory and the cardiac magnetic resonance laboratory. And I participate in clinical research which involves collaboration with the laboratories, in particular for biomarker studies.

18. You have an impressive bibliography. Could you give us some numbers, please.
How many original scientific papers published in refereed journal did you write? How often were they cited? What is your h-index?

This is very kind of you to say but I want to point out that numbers of papers and citations get skewed depending on the field. The National Library of Medicine resources have become my go to place to update bibliography (https://www.ncbi.nlm.nih.gov/myncbi/ana.barac.2/bibliography/public/) Of 162 publications in peer reviewed scientific journals, about 105 are original

Figure 7. Presentation on Global Cardio-Oncology Society Annual meeting in Madrid, October 2023. (Barac at the podium with colleagues from cardiac imaging, including (from right to left) Dr. Charlotte Manisty from Barts College in London, Dr. Dinesh Thavendiranathan from University of Toronto, Dr. Marielle Scherrer-Crosbie from University of Pennsylvania, and Dr. Lauren Baldassare from Yale University, discussing cardiac magnetic resonance (CMR) in cardio-oncology.

research and more than 50 are clinical documents, state of the art reviews, and editorials. For the citations, Research Gate website gives a number of 9843 citations with h-score of 44.

19. What is your most often cited paper? Is it also the paper that you like the most and consider to be your most important contribution to science?

I was part of the Expert consensus document on Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy developed in collaboration between the American Society of Echocardiography and the European Association of Cardiovascular Imaging which was published in 2014 and at more than 1400 citations it is probably the most cited manuscript that that I co-authored. I say probably because papers on clinical guidance often receive high number of citations, however their relevance may significantly decrease when there is rapid growth of the field. Indeed, in 2023 this paper is rather outdated and in need of a major update. A more recent consensus paper that I think is important to the field is the International Society of Cardio-Oncology statement on the definitions of cardiovascular toxicities of cancer therapies (https://pubmed.ncbi.nlm.nih.gov/34904661/) which was published in late 2021 and within less than 2 years has more than 180 citations.

20. In addition to a list of original papers you list 58 scientific reviews and editorials in refereed journals. Most if not all of these you wrote by invitation, or am I wrong? As the saying goes "if an editor is looking for somebody to write a review or an editorial for his/her journal he/she should invite the busiest person he/she knows." You obviously like to write! Isn't that true? How did you find time to write all these papers?

I am not a fast writer although I keep hoping to become one! I remain inspired by the innovation and good science, and I believe that the editorials and scientific reviews are a way to give back to the community. In clinical world, they often convey a message on "where does this research fit in clinical practice" and I think it is important to pause and think about that. So, I prioritize that time.

21. You gave more than 140 invited lectures. What accounts for so many invitations? Which one of these was the most memorable one?

I believe that the reason for the invitations is the rapid growth of cardio-oncology which was driven in part by the explosion of novel cancer treatments, many of which have cardiovascular effects. I cherish the opportunity to present as it gives me a chance to learn from the audiences and learn about different perspectives and ways of asking questions or organizing clinical practice. Most importantly, it allows me to meet new colleagues, clinicians, scientists, investigators, and trainees, which is very special. It is very hard to single out the most memorable presentation, I would love to mention the recent invited presentation to Karolinska University Hospital in Stockholm, Sweden, where I was invited to present on cardiovascular effects of the immune checkpoint inhibitors, which is one form of cancer immunotherapy. I was invited by my dear colleague Professor Marcus Carlsson who leads the Karolinska Institute's cardiac imaging clinical and research laboratory. It was inspiring to meet with cardiology and oncology colleagues as well as discuss research projects with imaging fellows and trainees on how to move the field forward. It was also was very special to visit Sweden, after more than 20 years of leaving Uppsala.

Figure 8. American College of Cardiology Live Course on Advancing Cardiovascular Care of the Oncology Patient Heart House, Washington DC, April 2023. Course Co-Directors Dr. Ana Barač (first from the left) and Dr. Bonnie Ky (fourth from the left), vice-chair Dr Richard Cheng (3rd from the left) and program committee members.

22. How much interest is there for cardio-oncology in the medical community and the lay public world-wide? Equally among the cardiologists and the oncologists?

I believe that there has been an increased awareness of cardiovascular effects of cancer treatments as well as of the importance of cardiovascular disease as a cause of morbidity and mortality in cancer survivors. There are many positive aspects that we need to recognize: first, that we are witnessing much improved cancer survivorship with many people living longer with and/or surviving cancer. Many cancer-targeted and immunotherapies have dramatically improved prognosis and we have discovered that they are also playing a role in cardiovascular homeostasis. An example are vascular endothelial growth factor (VEGF) inhibitors which very often can cause hypertension as an on-target effect, but can rarely cause heart failure and ischemic effects. There has been a growing interest in cardiology community to better understand these phenomena as well as to develop approaches to treat these patients.

23. You also serve on the editorial boards of several medical journals. Maybe you could list some of them.

I have served on the Editorial board of the Journal of the American College of Cardiology (JACC) since 2008, and I also served as an Associate Editor for the inaugural years of the JACC sister-journal, JACC Cardio-Oncology. It was a privilege to be part of a creation of a new journal and work with the great colleague and friend, Dr. Bonnie Ky from University of Pennsylvania, as the Editor in Chief. Journal represents constant work and constant learning.

24. You also serve and as an *ad hoc* reviewer for many leading scientific journals. You list 37 journals for which you have reviewed one or more papers. Is it that you just cannot say "no" when they invite you or do you think that this is expected of you and only a part of your professional duty; a voluntary contribution to the international biomedical community?

Yes, there is a sense of commitment and the need to give back to the community through constructive review. Receiving a well meant and well written critique can be powerful, and when we do good job as reviewers and editors and investigators, we make the field stronger. That said, I do say "no" today quite often as time restraints have grown together with more requests coming in.

25. After the Rector's Award which you received as a medical student in Zagreb, did you receive any other honors and awards?

Several awards were very special in my career. The Swedish Institute Award and the Federation of the European Biochemical Society Award in 1999 provided me with the funds to spend time in Dr. Đikić's laboratory. During my clinical residency I received the Saul Zukerman, M.D. Humanitarianism in Medicine Award, which is given each year to Washington Hospital Center resident who exhibited compassionate and human care. This was the most special award as it was voted by the peers and faculty, and handed to me by our then Chairman of Medicine, Professor Leonard Wartofsky, whom I consider a lifelong mentor and role model.

26. You are on the teaching staff of several Universities. Do you teach medical students or give practice relatedCME lectures to practicing physicians?

I am on teaching staff at Georgetown University where I mentor students in research.

27. How much do you travel for business or pleasure?

I travel for work approximately once a month, for conferences and meetings. This sometimes includes international travel which is fun and it allows me to meet and stay in touch with inspirational colleagues and friends. Most of my personal travel is to see family, in Croatia and in Argentina. My husband's family lives in Buenos Aires and the decision to stay in Washington DC also had to do with the fact that it has an international airport with good connections to Split and Buenos Aires.

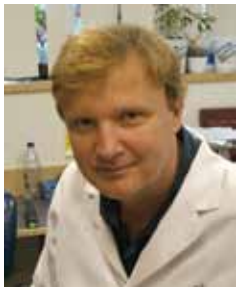
28. Do you have any hobbies, or to say it otherwise, do you have enough time for hobbies and your family?

There is no such thing as enough time: it is a constant balancing act! My husband and I have a 15 year-old daughter Lara who travels each and every summer to Croatia to see her cousins and stay with her "nona" (my mom), and in winter goes to see cousins in Buenos Aires and be with "abuela" (my husband's mom). This means that the time to travel and stay in touch with the family always stays on top of the priorities, and here in Washington DC it is about seeing and being with friends. We have both lived here for more than 20 years now and have been fortunate to be surrounded by great friends.

29. Any messages for the medical students and your junior colleagues in Croatia?

Follow your passion and never give up.

Dimitri Krainc Interview



Dimitri Krainc, MD, PhD,
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1. Where did you grow up?

I grew up in Celje, Slovenia

2. What do you remember from your high school days?

The curriculum was very hard, and the professors were tough! I was a good student, but more interested in sports and girls. But the good news is that I found my wife there, and that I played lots of basketball.

3. How did you decide to study medicine?

The original plan was to be become a professional basketball player, but that did not work out—fortunately. I thought medicine was an opportunity to work with people, something that I liked more than working with "machines", and to learn some interesting biology about human body, and maybe even help cure some bad diseases one day. It was a combination of reasons. The decision to study medicine was also partly done by exclusion of things I did not want to study--and after removing those, very few options were left. I use this approach in general—first decide what I don't want to do (Figure 1).

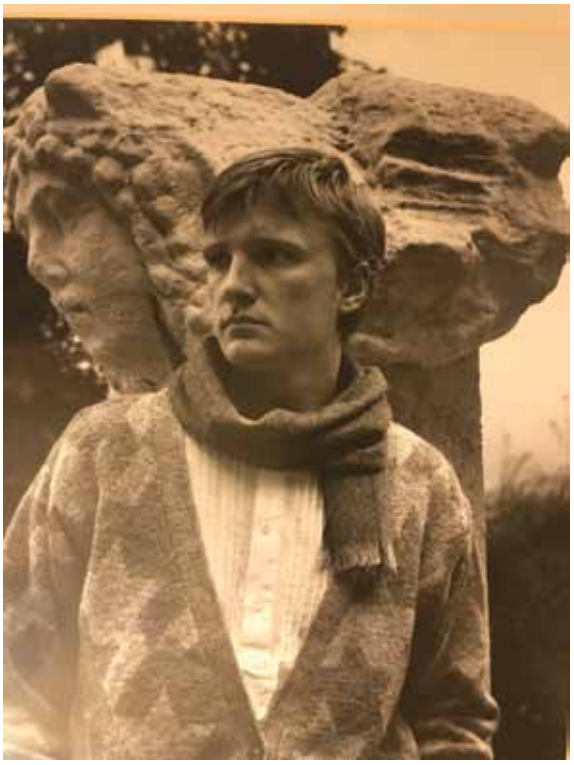

Figure 1. As a youngster who did not care much about medicine

4. How enjoyable were the first three preclinical years of your studies? Who were your favorite professors?

My first year of medicine I completed in Ljubljana, but my mother who was born and raised in Zagreb convinced me to switch to medical school in Zagreb, and so I started my second year at the University of Zagreb School of Medicine. It was the best decision of my life! I would have never reached this point in my career were it not for that move to Zagreb.
I also loved my professors in Zagreb—almost all of them. They were "old school" teachers—kind, helpful,and scholarly. I had many favorites, like Professors Pokrajac, Čulo, Durst-Živković, Lacković.

5. Which were your favorite subjects and favorite professors in the clinics?

I was less happy with the clinical education because it was too theoretical with limited practical teaching.
I remember fondly professor Labar who was very smart and thoughtful as a clinician. He was also very supportive of young people and cared a lot about us students. There were many others who were excellent clinicians, of course.

6. Did you have any role models during your medical school years?

Not really.

7. Did you engage in any extracurricular activities and what did you do during your free time?

I worked in the lab of Professor Lacković. He was great, he truly loved science and cared about helping young people become successful. He created a nice environment in his group with many wonderful colleagues that were encouraging and supportive. I credit him for helping me start my research career. I enjoyed interacting with other scientists in the lab, discussing neuroscience with the them, and attending interesting lectures and meetings (Figure2).

Figure 2. As a medical student attending the First Yugoslav Neurobiology Conference entitled " Neurotransmitters in Health and Disease",Zagreb ,1986.

8. Did you have concrete plans on what to do after graduation?

I went to US during medical school, for a summer project with dr. Norton Neff who used to be a colleague of prof Lacković at NIH and after graduation I returned to his lab.

9. When did you decide to become a neurologist?

During medical school when I saw some terrible neurological disorders and developed a desire to understand them and maybe contribute to finding a cure for them. I also liked the fact that clinical neurology was like building a puzzle during history and exam—like detective work that I enjoyed.

10. Did you try to find a job in Zagreb after graduation and how did you decide to move to Boston?

I completed my internship at KBC Rebro, then went to work with dr. Neff for a short time to complete my project that I started as a medical student, and then went to Harvard where I stayed for 22 years.

11. What do you remember from your training period at the Massachusetts General Hospital in Boston?

It was a wonderful experience. I was surrounded with some of the best clinicians who taught me all the secrets of clinical neurology that still serve me well today. I also had great research mentors and was able to elevate my research work to new heights during that time. The overall culture there was very scholarly, collaborative and pleasant—contrary to common perceptions about Harvard.

12. Was this your first encounter with basic neurosciences?

No! It was with prof Lacković and then Norton Neff

13. Did you ever consider giving up clinical work with patients and devoting yourself to entirely to basic science research?

I did not. I loved both very much and could not give up any of them.

14. Did you have a mentor who influenced you more than all others of your teachers?

Dr. Lacković in Croatia(Figure 3) and Dr.Anne Young in the US. Anne Young was the first woman department chair at MGH/ Harvard and she made major contributions to neuroscience with her studies of basal ganglia in neurology. She was also president of American Neurological Association. I am especially happy to hold the same position now.

Figure 3. Professor Zdravko Lacković my first mentor

15. How did you become interested in molecular biology?

It was at Harvard where I experienced molecular biology first hand in the department of molecular biology where the faculty co-authored the famous "red book" entitled—Protocols in Molecular Biology.

16. What did you do after you completed your training and became a Board certified neurologist?

I started my lab at Harvard, published my first paper as lab PI (in Science) and continued working as clinical neurologist.

17. Could you cite that paper and say what was it all about?

Here is the full citation of that paper:
Dunah AW, Jeong H., Griffin A., Kim MJ, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N. and **Krainc D**. Sp1 and TAF130 transcriptional activity disrupted in early Huntington's Disease**.** ***Science***, 2002.
We found that the glutamine expansion in huntingtin disrupts specific transcriptional programs in neurons. These data suggested that the deregulated gene expression may be an early step in HD pathogenesis as a result of interference by the soluble forms of mutant huntingtin. Our work also indicated that one of the primary and direct effects of mutant huntingtin on transcription is via specific repressor mechanisms, whereas other effects of huntingtin on transcription may be compensatory or secondary.

18. How long did it take you to establish your own laboratory and get your first research grants?

About 2 years after the completion of my neurology residency at MGH.

19. You are now Chair of a University Department. How long did it take you to reach that position?

I was faculty member at MGH/Harvard for 11 years before I became chairman at Northwestern.
I came to Northwestern in 2013 and very soon became an active member of our Medical School and Medical Center. In this photograph I am with my good friend and collaborator Dr. Andrew Parsa (Figure 4), the Chair of the Department of Neurosurgery. He came to Northwestern at the same time like me, but unfortunately he die a few years thereafter from a heart infarct.

20. Coud you list your major duties at Northwestern University School of Medicine in Chicago?

I run my lab, direct a Center for Neurogenetics, and run a very large clinical department with more than 200 faculty and a total of 300 other staff members. I also lead a relatively large research team and run a well funded basic science neurobiology laboratory (Figure 5).

Figure 4. With Dr. Andrew Parsa, Chair of neurosurgery

Figure 5. My research team at the Northwestern University in Chicago

21. How would you define yourself? A neurologist who does basic science research or a basic scientist who also does neurology? In other words, how do you balance your hospital work and patient care with basic science research?

A neurologist who does basic science. At Harvard I got the job primarily because of my clinical performance, coupled with research, of course. Those who are good scientists but lousy clinicians do not get a job there nor at Northwestern. Feinberg School of Medicine at the Northwestern Medical Center is primarily a medical institution and I am first and foremost a physician, who treats patients together with the rest of the medical staff and my physician colleagues (Figure 6).

Figure 6. With two other Chairs at Northwestern University. Dr. Leonidas C. Platanias, Chair of the Cancer Center (left) and Dr. Serdar Bulun, Chair of the Department of Obstetrics and Gynecology.

22. Among the key words on the list of your basic research papers there are many that I would not know how to define. Let's take just two of those: dysfunctional organelles or deregulated gene transcription. Could you give us a brief definition and explain why are these concepts important.

The overarching goal of my laboratory has been to define key molecular pathways in the pathogenesis of neurodegeneration with a goal of identifying targets for therapeutic development. Using genetic causes of disease as a guide, we have focused on pathogenic mechanisms that occur across different neurodegenerative disorders such as accumulation and deficient degradation of aggregation-prone proteins and organelle dysfunction. Importantly, we examined an interesting clinical link between Parkinson's disease and Gaucher disease that is caused by mutations within the GBA1 gene that codes for glucocerebrosidase (GCase). We found that mutations in GBA1 lead to hypoactive lysosomal GCase resulting in accumulation of glucosylceramide that stabilizes a-synuclein oligomers that were shown to be toxic to neurons. We also made a surprising observation that accumulation of a-synuclein can lead to inhibition of normal GCase. Specifically, a-synuclein interferes with ER to Golgi trafficking of GCase which in turn leads to decreased GCase activity, lysosomal dysfunction and more accumulation of a-synuclein. The bidirectional effects of a-synuclein and GCase forms a positive feedback loop that, after a threshold, leads to self-propagating disease (**Mazzulli et al, *Cell*, 2011**). This key study was the first to demonstrate that wild-type GCase was decreased in idiopathic PD, a finding that was later confirmed by several other groups. This work was extended by the analysis of dopaminergic neurons derived from patients with idiopathic and various forms of familial PD, where our group identified a time-dependent pathological cascade that included mitochondrial oxidant stress, accumulation of oxidized dopamine and neuromelanin, deficiency of GCase, lysosomal dysfunction and α-synuclein accumulation. Importantly, this toxic cascade was **observed only in human**, but not in mouse PD neurons, at least in part due to species-specific differences in dopamine metabolism and formation of neuromelanin that is present only in human neurons. Increasing dopamine synthesis or α-synuclein levels in mouse midbrain neurons partially recapitulated pathological phenotypes observed in human neurons (**Burbulla et al, *Science*, 2017**). These findings highlighted the importance of studying human neurons in PD and at least in part explain why animal models of PD do not exhibit degeneration of DA neurons that is observed in PD patients.

In addition to identifying a functional convergence of mitochondrial and lysosomal dysfunction in PD, we recently identified the formation of direct mitochondria-lysosome membrane contacts that mark sites for lysosomal regulation of mitochondrial networks, while conversely, mitochondrial contacts regulate lysosomal dynamics (**Wong et al, *Nature*, 2018**), providing a

new angle to studies of these organelles in neurodegenerative diseases including PD.
Based on the above findings, we developed small molecule activators (**Zheng et al, *J. Med Chem,* 2016 and *JACS*, 2018**) of mutant and wild-type GCase that improved enzyme activity in sporadic PD, as well as multiple genetic forms of PD (e.g. LRRK2, Parkin, DJ-1, GBA1), suggesting that activation of wild-type GCase is sufficient to ameliorate lysosomal dysfunction and accumulation of oxidized dopamine, glucosylceramide and alpha-synuclein in various forms of PD as a therapeutic target (**Burbulla et al, *Science* 2017, *Science Translational Medicine*, 2019**).

23. In 2021 you received a 9 million-8 year research grant (https://news.feinberg.northwestern.edu/2021/05/07/krainc-to-receive-9-million-8-year-nih-grant/). What does your proposal entail and what do you expect to accomplish in your studies.

The goal of our research is to identify modifiers of penetrance in many genetics forms of Parkinson's' disease (since most genes are not fully penetrant). Targeting such modifying pathways may help with more comprehensive therapeutic development of neurodegenerative disease.

24. You have numerous patents to your name. Furthermore you are the principal founding scientist of biotech companies Lysosomal Therapeutics and Vanqua Bio and also serves as Venture Partner at OrbiMed. Why did you establish these companies?

I am listed as the inventor on 31 patents in the field of neurodegenerative disorders, primarily Huntington's and Parkinson's disease, 4 of which have been licensed to companies. I founded a biotech company, LTI, focused on Parkinson's disease that signed a $600M partnership with Allergen before their acquisition by AbbVie. Most notably, we developed allosteric activators of lysosomal glucocerebrosidase (GCase) encoded by the gene GBA1 that is linked to Parkinson's disease (US-10934270—quinazoline compounds for modulating GCase activity). These activators were developed based on our discovery of the role of GCase in synucleinopathies published in *Cell* in 2011 and represent the first example of targeted therapy for neurodegenerative disease. These GCase activators were licensed to Vanqua Bio, which I founded.

25. Outside of your University you are also active in national medical societies. This year you became President of the American Neurological Association. Congratulations! Which aspect of your work or personality prompted your peers to elect you to that position?

I was elected by my peers in recognition of my research discoveries and leadership of the department that my staff and I elevated into one of the top neurology departments in the US..

26. You serve on the Editorial Boards of several journals. Which one of these is the highest ranked journal?

Journal of Clinical Investigation

27. In our interviews we like to include some statistics. What is your h-index? How many citations did your papers receive so far?

My h-index is 94 and my papers received over 48 000 citations so far.
https://scholar.google.com/citations?user=64hgxAUAAAAJ&hl=en

28. What is your favorite paper?

Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, Sidransky E, Grabowski GA, Krainc D. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011;146(1):37-52.
It was cited over 1300 times

29. You are member of several Academies and have also received several other honors and awards. Which one of these do you value the most?

Membership in the US National Academy of Medicine that is part of the national Academies of Science, Medicine and Engineering and is considered the highest honors in our field.

30. Are you still in contact with your Croatian colleagues? Are you planning any joint research projects with them, conferences or publications?

I did a sabbatical in Zagreb about 20 years ago when I served as chair of neurology in KBC Rebro. At that time I developed a Center for genomics at MF Zagreb and trained dr. Fran Borovečki to run it after I retuned back to US. The Center is still active and I consider this my most important contribution to my alma mater.

31. Any messages for the medical students and your junior colleagues in Croatia?

Try to become really skilled in your craft and if you have to leave Croatia to receive additional training, please make sure you return home. Croatia needs you.

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