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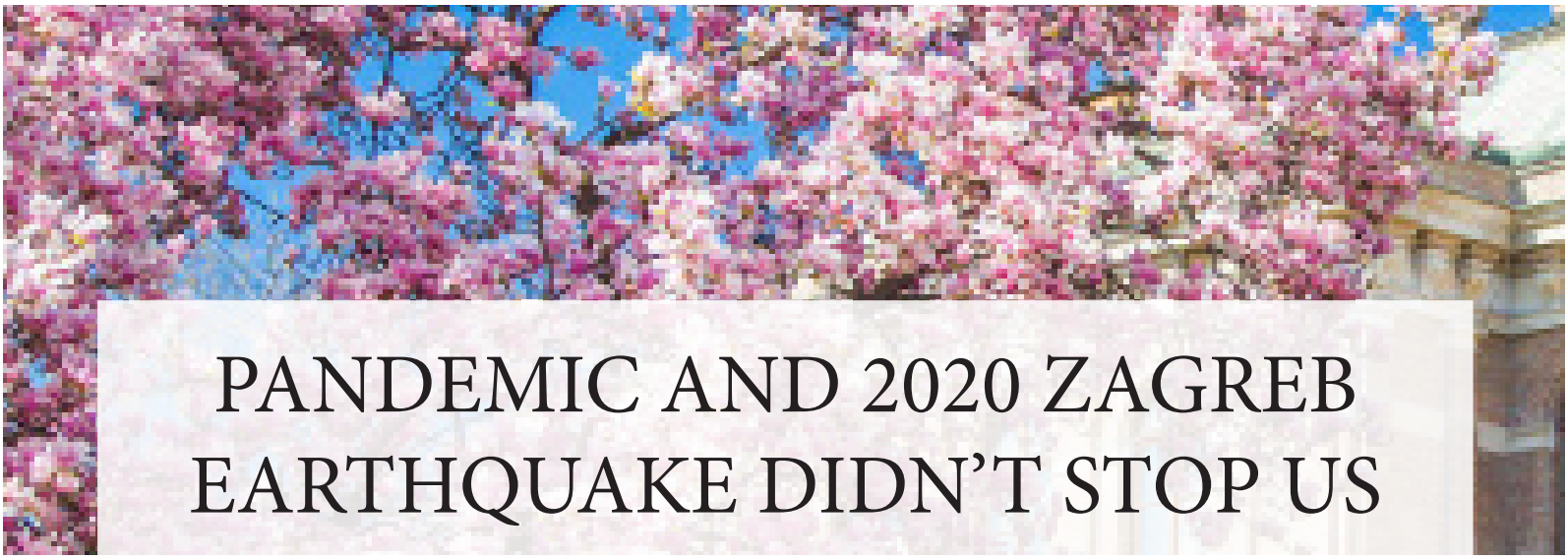
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PANDEMIC AND 2020 ZAGREB EARTHQUAKE DIDN'T STOP US

Vida Demarin, Marko Pećina

In spite of the two recent disasters – COVID-19 pandemic and strong earthaquake in Zagreb, having the enormous impact to everyday life, we prepared for you a new double issue of our RAD medical sciences 50-51.

Activities of everyday life have almost stopped for many persons in our country and all over the world, but resarch and science could not be stopped!

As you know COVID-19 disease has started in December 2019. The new coronavirus, not known until than under the name SARS-Co-19-2 was identified as a cause of the disease. Disease has spread rapidly all over the world, causing immeasurable health and economic challenges.

World Health Organization (WHO) declared the global pandemic on March 11th 2020. The first patient with COVID-19 in Croatia was diagnosed on February 25th.

Even before that, on February 14th Department of Medical Sciences of our Academy together with Croatian Society for Biosafety and Biosecurity and the University Hospital for Infectious Diseases "Dr. Fran Mihaljević" organized the symposium "New Coronavirus from China: Biosecurity Threat and Challenge for Health Care Professionals", catching extreme attention of many colleagues and other health professionals. More data about this symposium could be found in the News and Education part of this issue.

On March 17th members of Croatian Academy of Sciences and Arts published the Statement related to COVID-19 pandemic, which can be found at the Academy's web site, thus contributing to better understading of the whole situation.

A great deal of research has been carried on all over the world in order to get more insights about this new disease. In this issue we publish the review „COVID-19 pandemic – neurological aspects of the disease" which provides a comprehensive summary of the main clinical and neurological manifestations of this new infectious disease. The main clinical manifestations of COVID-19 are related to respiratory system, but neurological symptoms and diseases are also possible due to neuroinvasive potential of the virus. Most COVID-19 cases experience mild clinical symptoms and recover without complications, but 5% of cases need intensive care treatment. The most common neurological symptoms are headache, dizziness, hyposmia and hypogeusia. Neurological diseases which are associated with COVID-19 are stroke, encephalopathy, meningoencephalitis, and Guillain Barre syndrome. Preventive measures are the most effective for containment of COVID-19.

In the context of prevention and seriousliness of pandemic, Croatia have long history which lead the past to 1377 when Dubrovnik's (known in that time as City Ragusa) Great Council passed a ground-breaking law to prevent the spread of the pandemic requiring all incoming ships and trade caravans arriving from infected areas to submit to 30 days of isolation. *The legislation, Veniens de locis pestiferis non intret Ragusium vel districtum* (*engl.* "Those arriving from plague-infected areas shall not enter Ragusa or its district"), stipulated that anyone coming from pernicious places must spend a month in the nearby town of Cavtat or the island of Mrkan for the purpose of disinfection before entering



the medieval walled city. In recent history we have great professor and medical doctor Andrija Štampar, his grandiose hygiene-epidemiology, prevention-prophylaxis and important curation program in organization of health measures and activities in former Yugoslavia countries and even wider in Europe was of high rating and quality. Even today, Štampars ideas and programs are stil actual and highly cited in modern medicine, especially due to the actual pandemic.

We are all aware that strong earthquake, that hit Zagreb in early morning of March 22nd caused enormous damage. Material damage is huge, many buildings are destroyed, among them the Palace of our Academy, as well as its Library and the Glyphotheca, leaving us in fear and disbelief. Many people still don't have the place to live, schools, universities, hospitals, theatres, museums, galleries are severely destroyed. This material damage would be repaired, sooner or later. As it was done after the big earthquake that happened in 1880. But repairing of our "mental damage" would need much more energy, confidence, trust and beliefs. Doctors, nurses, pharmacists and other health care providers were devotedly working days and nights reducing the devastating consequences of COVID-19 disease. And now, after putting the virus under control, the work is not over! There is a huge need to repairing peoples' mind, to replace the fear with hope and to restore the inner peace.

And during all that time of torments and worries scientists are intensively engaged in trying the find the answer how to proceed for better and deal with the virus.



Figure 1. Lobby of the Palace of the Croatian Academy of Sciences and Arts

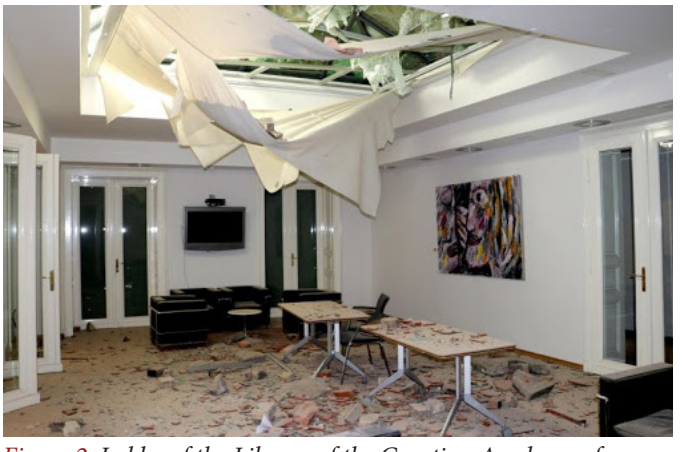


Figure 2. Lobby of the Library of the Croatian Academy of Sciences and Arts

COVID-19 Pandemic – Neurological Aspects of the Disease

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Abstract:

With severe acute respiratory syndrome corona virus-2 disease the World is faced with a new pandemic. It has become a global public health concern similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks. The aim of this review is to provide a comprehensive summary of the main clinical and neurological manifestations of this new infectious disease, named Coronavirus disease 2019 (COVID-19). The main clinical manifestations of COVID-19 are related to respiratory system, but neurological symptoms and diseases are also possible due to neuroinvasive potential of the virus. Most COVID-19 cases experience mild clinical symptoms and recover without complications, but 5% of cases need intensive care treatment. The most common neurological symptoms are headache, dizziness, hyposmia and hypogeusia. Neurological diseases which are associated with COVID-19 are stroke, encephalopathy, meningoencephalitis, and Guillain Barre syndrome. Preventive measures are the most effective for containment of COVID-19. These measures include isolation modalities with physical distancing, cover coughs or sneezes, and frequent handwashing with soap and water or using hand sanitizers, and avoiding public gatherings. Unfortunately, no specific antiviral medication or vaccine is currently available. The new virus enters the cell through a cellular receptor angiotensin-converting enzyme-2, the questions regarding use of the renin-angiotensin-aldosterone system inhibitors. According to the recent data most professional societies recommended the use of these medications.

Keywords: Coronaviruses, COVID-19, neurological, nervous system.

Sažetak:

COVID-19 pandemija – neurološki aspekti bolesti

Bolest uzrokovana virusom teškog akutnog respiratornog sindroma 2 dovela je do pandemije. Ova globalna javno-zdravstvena prijetnja slična je prethodnim epidemijama sindroma teškog respiratornog sindroma (SARS) I bliskoistočnog respiratornog sindroma (MERS). Cilj ovog rada je pružiti pregled vodećih kliničkih i neuroloških manifestacija ove nove zarazne bolesti, nazvane Coronavirusna bolest 2019 (COVID-19). Glavne kliničke manifestacije ove bolesti povezane su s dišnim sustavom, ali mogući su neurološki simptomi i bolesti zbog neuroinvazivnog potencijala virusa. Većina slučajeva COVID-19 ima blage kliničke simptome i oporavlja se bez komplikacija, ali 5% slučajeva zahtijeva intenzivno liječenje. Najčešći neurološki simptomi su glavobolja, vrtoglavica, hiposmija i hipogeuzija. Neurološke bolesti povezane s COVID-19 su moždani udar, encefalopatija, meningoencefalitis i akutni poliradikuloneuritis (Guillain Barre-ov sindrom). Preventivne mjere najučinkovitije su za suzbijanje COVID-19. Te mjere uključuju metode izolacije i tjelesnog distanciranja, metode sprječavanja širenja bolesti kapljičnim putem (pokrivanje lica pri kašljanju i kihanju) te učestalo pranje ruku sapunom i vodom ili korištenje sredstva za dezinfekciju ruku, kao i izbjegavanje javnih skupova. Nažalost, ova

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bolest nema specifičnih antivirusnih lijekova ili cjepivo. Novi virus ulazi u stanicu putem receptora za angiotenzin konvertirajući enzim 2, radi čega je u znanstvenoj zajednici postavljeno pitanja uporabe inhibitora renin-angiotenzin-aldosteronskog sustava. Prema najnovijim podacima većina profesionalnih društava preporučila je nastavak uporabe inhibitora renin-angiotenzin-aldosteronskog sustava.

Ključne riječi: : koronavirusi, COVID-19, neurologija, živčani sustav

Introduction

The World is faced with a new pandemic with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19)[1]. The global public health concern is on high level since last two outbreaks caused by severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012[2]. Due to a great threat for public health safety the World Health Organization (WHO) on March 11, 2020 declared a pandemic for COVID-19. In Wuhan, China, the first patients were discovered on December 1st,2019. The pandemic quickly and widely spread worldwide[3]. On May 19, 2020 there were 4696849 confirmed cases of COVID-19, including 315131 deaths. In the same period, Croatia had 2226 confirmed cases, including 95 deaths[4].
The aim of this review is to provide a comprehensive summary of the main clinical and neurological manifestations of this new infectious disease named Coronavirus disease 2019 (COVID-19).

Coronaviruses

Corona viruses (CoV) family is a class of enveloped, positive sense single stranded RNA viruses having extensive range of natural roots[5]. Genotypically and serologically coronaviruses are divided in four subfamilies: alpha, beta, gamma, and delta[5-7]. Similarly, to SARS-CoV and MERS-CoV, the SARS-CoV-2 belongs to the beta-CoV subfamily[2,5,8]. The virus is a RNA (26 to 32KB genome) type with a recombination rate up to 25% and covered by a crown of glycoproteins that can mutate frequently[9,10].
All human CoVs have zoonotic origins [11]. The natural hosts for all known CoVs are most likely bats[11]. The virus is probably transmitted by another animal host, such as SARS-CoV by civet and MERS-CoV by camel[8]. The probable animal host of SARS-CoV2 is pangolin[12]. Currently, human-to-human transmission is now considered the main form of transmission[13]. SARS-CoV-2 (sized 0.125um) is transmitted predominantly by inhalation via respiratory droplet, direct or indirect contact and potentially by fecal-oral[14]. Symptomatic individuals are the most common source of the infection[14]. However, asymptomatic individual may transmit the virus[14,15] . Basic reproduction number is 2.2 [13], what is more contagious than SARS and MERS[16]. The mean incubation period is 5 days (2 to 14 days)[17-19] . CoVs can cause multiple systemic infections that can lead to respiratory, enteric, hepatic and neurologic diseases[14]. Infection within CoVs (especially SARS-COV, MERS-CoV and SARS-CoV-2) may lead to severe clinical symptoms with high mortality[20] . SARS viruses infect the cells of pulmonary alveolus, causing acute diffuse alveolar damage, edema and inflammation which can evolve to acute respiratory distress syndrome (ARDS) in adults[21]. These viruses can be functionally inactivated with the use of ethanol (60%), ether (75%) and chlorine-containing disinfectants[14].

Neuroinvasive potential of coronaviruses

Despite known respiratory tract infection, coronaviruses may also invade the central nervous system, e.g. human CoV-OC43 has been associated with fatal encephalitis in children[22]. Neuroinvasive character of beta-CoVs are reported in SARS-CoV and MERS-CoV[23]. Due to high similarity showed between SARS-CoV and SARS-CoV-2, it is likely that potential neuroinvasion of SARS-2 plays an important role in the acute respiratory failure of COVID-19 patients as well[23].
The entry of SARS-CoV host cells is mediated by a cellular receptor angiotensin-converting enzyme 2 (ACE2)[23]. The MERS-CoV enters the human cells mainly via dipeptidyl peptidase 4 (DPPS4)[23]. Receptors for ACE2 is expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestine cells[23]. The DPP4 is present in the lower respiratory tract, kidney, small intestine, liver and the cells of immune system[23]. The previous reports showed that the expression level of ACE2 or DDP4 are very low under normal conditions[24]. ACE2 expression is widespread in the brain (on neurons and glial cells), not only in the cardiorespiratory centers in medulla, but also in the striatum[25]. SARS-CoV infection, through binding of viral S protein to ACE2, seems to reduce the receptor expression[26,27]. ACE2, a homologue of ACE, is an integral part of the cell membrane protein with catalytic domain on the extracellular surface exposed to vasoactive peptides[26]. ACE2 converts Ang II to Ang 1-7 – with vasodilatory and antifibrotic action when it activates Mas receptor[26]. ACE2 expression in heart, type II alveolar cells (AT2), capillary endothelium and enterocytes demonstrates an essential role in the cardiovascular and immune system, basically in the development of hypertension and diabetes mellitus complications[26]. SARS-CoV-2 penetrates the cell through ACE2, but necessities type II transmembrane serine protease (TMPRSS2) for effective priming of viral spike (S) protein[26]. The binding of S protein to ACE2 allows proteolytic digestion by TMPRSS2 – which enables viral and cell membrane fusion and later release of viral particles[26,28,29].
Recent two independent studies with patients with heart failure

found that the plasma concentrations of ACE2 were higher in men than in women, but neither an ACE inhibitor nor an ARB was associated with a higher plasma ACE2 concentrations 30. Experimental studies using transgenic mice revealed either SARS-CoV or MERS-CoV could enter the brain via olfactory nerves and then rapidly spread to thalamus and brainstem[31,32]. Detection of high viral load in the brainstem after SARS-CoV infection is indicative of the spreading of the infection from the respiratory tract to the central nervous system via vagal nerve to ambiguous and solitary tract in the brainstem[23]. The involvement may also suggest that the respiratory center contributes to the severe respiratory distress caused by COVID-19[33]. Recently there was a report of a patient with COVID-19 with the loss of involuntary breathing process – probably Ondine's course syndrome[23]. Since the SARS-Co-2 shares similarities with SARS-CoV and as a member of coronaviruses family it is likely to possess similar potential for neuroinvasion, especially medullary neurons causing headache, nausea, and vomiting[23]. The coronavirus RNA can be detected in the cerebrospinal fluid[34,35]. The involvement of CNS is probably caused by focal meningitis/encephalitis affecting rhinal cortex, gustatory cortex or appropriate subcortical ascending /descending tracts[35].

Other potential entry points are peripheral nerve terminals that gain access to the CNS via a synapse connection route – trans-synaptic transfer[23]. The peripheral nerve system is targeted by SARS-Cov-2, in particular nerves I, VII, IX, X 35. Hyposmia which is caused by a direct contact and interaction of the virus with gustatory receptors and olfactory receptor cells[35].

Clinical presentation

Generally, coronaviruses are responsible for 5-10% of acute respiratory infections[36]. The SARS-CoV-2 may present as a mild, moderate and severe disease[14]. The disease is asymptomatic or milder in children and young adults[33]. The symptomatic adult form has increasing severity with age, health care workers are notable exception[33].

COVID-19 can have a clinical presentation similar to influenza, typically with fatigue, fever and non-productive/dry cough[19]. Other symptoms include dyspnea, hemoptysis, sore throat and leg pain[2,37]. Dyspnea and/or hypoxemia occurs in patients with severe course after the first week[38]. Diarrhea has been reported as an initial symptom in fewer cases[33]. Critical cases were rapidly progressive with complications such as ARDS, septic shock, refractory metabolic acidosis and coagulation dysfunction[38]. SARS main clinical manifestations were fever, chills, dry cough and difficulty breathing[39]. Severe cases led to respiratory failure (ARDS 20%) and death[39]. MERS patients were usually presented with pneumonia related symptoms such as fever, myalgia, cough and dyspnea[40]. Severe cases led to ARDS (5%), septic shock and multiorgan failure, acute renal failure and death[40]. Most COVID-19 cases (80%) experience mild clinical symptoms and recover without complications, 5% of cases need intensive care due to pneumonia and respiratory failure developing in up to 14 days 40. The most severe cases require prolonged duration of care (more than 14 days)[33]. Age is the most important risk factor; there is a progressive rise of cases after 50 years of age 41. Registered lethality varies between European countries ranging from 1.5% in Germany to over 10% in Italy 4. Risk factors associated with more severe cases are: arterial hypertension, cardiovascular and cerebrovascular disease, diabetes and immunosuppression[42]. Table 1. shows risk factors for COVID-19.

Chen T et al. evaluated 113 deceased patients with COVID-19 and found predominance of male sex (73%), median age of 68 years, chronic hypertension and cardiovascular comorbidities (48%), with leukocytosis (50%) and lymphopenia (91%) and the most common complication was ARDS (100%)[43]. Du Y et al. have analyzed fatal cases of COVID-19 from Wuhan, China[44]. They showed that the most of 85 cases were males over 50 years of age with noncommunicable chronic diseases (arterial hypertension, diabetes and coronary heart disease), and the majority of patients died of multiple organ failure[44]. Poor prognosis was associated with early onset of shortness of breath and eosinophilopenia[44]. The most common complications included respiratory failure (94.1%), shock (81.2%), ARDS (74.1%), and arrhythmias (60%). The reported case fatality rate is 1.8 to 3.4%[44].

Laboratory findings includes lymphopenia (83%), thrombocytopenia (36%), neutropenia (34%), elevated D-dimer levels (47%) and prothrombine time, lactate dehidrogenase (41%), C-reactive protein (36%)[14,19]. As in SARS and MERS, most COVID-19 patients have a characteristic ground glass appearance on chest CT scans and bilateral patchy shadowing in more than 50% of patients[10].

Neurological manifestations

During a pandemic neurologic manifestations might be overlooked[45]. On the other hand, the COVID-19 pandemic caused the reduction of neurology services, especially showed through stroke care where there was a reduction in the number of hospital admissions[46]. Neurological manifestations may be caused by direct or indirect (para-infectious) mechanisms of invasion by CoVs[45]. CoVs infections have been associated with neurological manifestations such as: febrile seizures, convulsions, change in mental status and encephalitis[2]. Neurological symptoms were rarely reported in the previous SARS and MERS outbreak[47]. The high number of patients with COVID-19, which may have the presence of the virus in the CNS, require monitoring for early and late onset neurological symptoms, including neurological and neurodegenerative disorders[48,49]. In SARS outbreak the reported neurological manifestations include axonopathic polyneuropathy, encephalitis, myopathy, rhabdomyolysis and acute ischemic stroke[50]. The reported neurological symptoms within MERS outbreak include disturbance of consciousness, Bicker-

Risk factors for COVID-19
Age (>65 years)
Current smoker
Hypertension
Diabetes
Coronary heart disease
Atrial fibrillation
Chronic obstructive lung disease
Chronic kidney disease
Cancer
Obesity (BMI>30)
Immunosuppression

staff's encephalitis overlapping with Guillain-Barre syndrome, ischemic stroke, vasculopathy, ADEM, infectious neuropathy, intensive care acquired weakness and seizures[51]. A greater concern than direct invasion of the CNS may be para-infectious neurological diseases such as GBS, transverse myelitis and ADEM – such as in the ZIKA virus epidemic in 2015-2016[45]. However, neurological manifestations of COVID-19 have not been studied appropriately yet[2]. CNS involvement and neurological manifestations are probably present particularly in patients with severe illness[2,52]. The most commonly reported preexisting neurological diseases in COVID-19 patients were cerebrovascular diseases, nervous system diseases, prior stroke, dementia and Parkinson's disease[53]. According to the study from Wuhan which showed that 36.4% of patients had neurological symptoms, and these were more frequent with severe disease[52]. The most common reported symptoms identified were headache (8-34%) and dizziness (16,8%), while anosmia occurred in 5.1% and hypoageusia in 5.6% cases[38]. However, the study of Lechien et al. found that olfactory and gustatory dysfunctions were found in more than 85% of patients with mild to moderate COVID-19[54]. In the study female patients were particularly affected by olfactory and gustatory dysfunctions[54]. Therefore, the sudden onset of anosmia or ageusia should be recognized as a symptom of COVID-19[54]. Other reported neurological symptoms were: nausea, fatigue, myalgia, ataxia, deficit in visual field, neuralgia and seizures[38,46,52,55,56]. Intracranial infection related symptoms included headache, seizures, disturbance of consciousness[38,52]. The recent retrospective study by Lu et al. concluded that there is no evidence that suggesting an additional risk of acute symptomatic seizures in people with COVID-19[57]. A French study reported that COVID-19 might be presented as encephalopathy, prominent agitation, confusion or corticospinal tracts signs[58].

The study by Herman et al. found that 8% of hospitalized COVID-19 patients had pre-existing neurological illnesses[53]. Secondary neurological complication rate were between 6 and 36.4%[53]. Cases of encephalopathy, meningoencephalitis, and Guillain Barre syndrome are associated with COVID-19[56]. One of first reported cases was a COVID-19 patient with acute necrotizing encephalopathy[52]. The study of Chen et al. reported up to 20% hypoxic/ischemic encephalopathy[43].

Patients with cerebrovascular diseases are prone to develop COVID-19 with severe respiratory complications or multiple organ failure[43]. The same study from Wuhan which found 36 % (from 216 cases) of neurological manifestation and 2.8 % of patients suffered a stroke (6 cases)[52]. Acute stroke was more common among 88 patients with severe COVID-19 infections (5.7%, 4 ischemic strokes, 1 intracerebral hemorrhage) than in non-severe infections (0.8%, 1 ischemic stroke)[52]. Another retrospective study of data from the COVID-19 outbreak in Wuhan showed the incidence of stroke of 5% (11 cases: 5 had large artery disease, 3 had cardioembolic stroke, and 3 had small artery disease)[59]. Oxley et al. and Beyrouti et al. reported the case series of large vessel occlusion strokes in COVID-19 patients [59-60]. The associated of COVID-19 and development of ischemic stroke is linked to prothrombotic state causing venous and arterial thromboembolism and elevated d-dimer levels[61-63]. Causes of stroke were associated with raised levels of D-dimer, exaggerated systemic inflammation, a "cytokine storm" (a hallmark of severe disease) and cardioembolism (from virus related cardiac injury)[46,62]. The presumed incidence of stroke in patients with COVID-19 is 4.9%, and the possibility that COVID-19 increases the risk of stroke is 7.82 folds within first three days after the onset of respiratory tract infection[61].

Health care providers engaged in acute stroke care are at risk of acquiring COVID-19 from stroke patients with COVID-19[64]. The recent pooled analysis of four studies by Aggarwal et al. showed that cerebrovascular disease to be associated with 2.5 fold increased disease severity in patients with COVID-19[64]. There was no significant association of stroke mortality in patients with COVID-19 infection[64]. Nevertheless, it was found that there was a decrease of 39% in the numbers of patients who received evaluations (neuroimaging) for acute stroke in United States of America during COVID-19 pandemic[65].

Conversely, there could also be associated factors which could have reduced stroke incidence, such as air pollution, many countries reported reduction in air pollution 46. The assumption that air pollution conditions facilitate the spread of a virus was shown during SARS outbreak in 2002 and during COVID-19, but this hypothesis still has to be validated[66,67]. Effect of social distancing measures and anxiety may contribute for disease development[59].

Autopsy reports of COVID-19 patients have revealed brain edema and partial neuronal degeneration in deceased patients[68]. The study of Helms et al. showed unexplained encephalopathic features in patients with COVID-19 who had MRI performed. The perfusion abnormalities were noted in 11 patients: leptomeningeal enhancement in 8 patients, and 3 patients had ischemic stroke on MRI[58].

This review covers mostly short-term effects of COVID-19, but we should be aware of the long-term effects that SARS-COV-2 could produce regarding other or chronic neurological conse-

Potential treatment options for COVID-19	
Mechanism of action	Examples
Viral entry inhibitors	1. Chlorquine and hydroxychloroquine – antimalarials 2. APN01 – recombinant human ACE2 protein 3. Leronimab (PRO 140) – humanized IgG4 monoclonal antibody against CCR5 receptors
Viral replication inhibitors	1. Remdesivir and Favirapir – nucleotide analogs 2. Lopinavir-Ritonavir – protease inhibitors 3. Camostat (FOY-305) and Nafamostat mesilate – serine protease inhibitor 4. Umifenovir – membrane fusion inhibitor of influenza virus (available in China and Russia) 5. 3Clpro (Mpro) – protease of beta coronaviruses
Vaccine	1. S-trimer 2. Nucleic Acid Vaccines 3. mRNA vaccines
Miscellaneous	1. Azithromycin 2. Convalescent plasma 3. Tocilizumab – anti human IL-6 receptor 4. Steroids

quences (e.g. cognitive impairment, ADEM, etc.)[45].

Treatment options

Isolation remains the most effective measure for containment of COVID-19[14]. Preventive measures include isolation modalities with physical distancing, cover coughs or sneezes, and frequent handwashing with soap and water or using hand sanitizers, and avoiding public gathering[14].

No specific antiviral medication or vaccine is currently available[3]. Treatment includes symptomatic care with oxygen therapy 14. Researchers are currently investigating specific treatments for COVID-19. The treatments which are being investigated are shown in the table 2 [3,29,69,70].

The question was raised regarding the safe usage of renin-angiotensin-aldosterone system (RAAS) inhibitors during COVID-19 pandemic[71]. RAAS inhibitors include ACE inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) which increase expression of ACE2[72]. The use of ACE-I and ARB was more frequent among patients with COVID-19 than controls because of their higher prevalence of cardiovascular disease[73]. However, there was no evidence that these medications affect the risk of COVID-19, despite the previous concerns about possibility that these drugs could predispose individuals to severe COVID-19[73,74]. A recent study confirmed that outpatient use of RAAS inhibitors does not increase the risk of COVID-19 requiring admission to hospital, including most severe cases[71]. The study of Khera et al. showed that the use of RAAS inhibitors was not associated with the risk of hospitalization or mortality among patients infected with SARS-COV-2[75]. Interestingly, the same study showed that the risk of hospitalization was nearly 40% lower in patients who used ACE-I[75]. The study of Mehra et al. which included 8900 COVID-19 patients showed that the use of either ACE-I or statins was associated with better survival[76]. Most professional societies recommend the continuation of the use of these medications because their positive effect on the cardiovascular system[26,73].

Summary

In summary, COVID-19 caused higher infection and mortality rates than SARS and MERS, mainly caused by respiratory failure. As in the previous two outbreaks (SARS and MERS), the SARS-CoV-2 shows neuroinvasive potential with various neurological manifestations. We should be aware of the short- and long-term neurological consequences of this pandemic. Unfortunately, the treatment options are still only symptomatic. As far as preventive measures are concerned isolation is the most powerful option for containment of COVID-19. Specific therapies are being evaluating in clinical trials. Additional investigations are warranted in order to evaluate the impact of the development of neurological manifestations of COVID-19.

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Dentin Bond Strength and Reliability of Experimental Bioactive Composites

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Abstract:

Weibull analysis of bond strength

Aim: To compare differences in outcomes of statistical approaches of reliability analysis (Weibull) and conventional statistics for bond strength of experimental remineralizing composites and disclose changes that would not be discernible by using just one statistical approach.

Materials and Methods: Experimental composites were made by blending a Bis-GMA/TEGDMA resin with bioactive glass (BG) and inert fillers (barium glass and silica) in a centrifugal mixer. Inert fillers were admixed to the total filler load of 70 wt%. Control composite incorporated only inert fillers (70 wt%). Two remineralizing composites with 10 or 40 wt% of BG were marked as bioactive-10 and bioactive-40. Dentin substrates were prepared from intact third molars, polished under the water using P600 silicon carbide paper and embedded into an acrylic resin. Composite cylinders (d=3mm, h=2mm) were bonded on dentin substrates using a two-step self-etch bonding agent (Clearfil SE Bond 2, Kuraray). Specimens were stored at 37 °C in distilled water and fractured in shear mode after 1 week and 1 year. Per experimental group 20 samples were prepared in order to obtain the optimal sample size for Weibull analysis (total n=120 for the whole study).

Results: Mean bond strengths measured after 1 week and 1 year were statistically similar for the control composite (21.9 vs. 24.0 MPa) and for bioactive-10 (19.6 vs. 19.1 MPa). Nevertheless, Weibull statistics identified a significant decrease in bond reliability after aging: Weibull moduli were decreased from 13.5 to 3.9 for the control composite and from 12.3 to 3.8 for bioactive-10. For bioactive-40, mean bond strength declined significantly after 1 year (8.1 vs. 6.8 MPa) but its reliability remained unchanged, as identified by statistically similar Weibull moduli.

Conclusions: A decrease in dentin bond strength after 1 year was identified using Weibull analysis in the control and experimental bioactive composite, while conventional statistics were incapable to distinguish changes in mean bond strength.

Keywords: dentin bond strength, Weibull analysis, reliability, bioactive glass 45S5, shear bond strength adhesives, dental materials, composite resins

Sažetak:

Snaga svezivanja na dentin i pouzdanost eksperimentalnih bioaktivnih kompozita

Cilj: Usporediti razlike u rezultatima snage svezivanja eksperimentalnih remineralizacijskih kompozita dobivenih statističkim pristupom analize pouzdanosti (Weibull) i konvencionalne statistike te otkriti promjene koje nisu vidljive korištenjem samo jednog statističkog pristupa.

Materijali i metode: Eksperimentalni kompoziti dobiveni su miješanjem smole Bis-GMA / TEGDMA s bioaktivnim staklom (BG) i inertnim punilima (barijevo staklo i silicijev dioksid) u centrifugalnoj miješalici. Inertna punila dodana su do ukupnog opterećenja punila od 70%. Kontrolni kompozit sadrži samo inertna punila (70%). Dva remineralizirajuća kompozita s masenim udjelom bioaktivnog stakla (BG) 10% ili 40% označena su kao bioaktivni-10 i bioaktivni-40. Dentinski supstrati pripremljeni su od intaktnih trećih kutnjaka, polirani pomoću papira silicijevog karbida P600 i ugrađeni u akrilatnu smolu. Adhezijska veza između kompozitnih cilindara (širina = 3 mm, visina = 2 mm) i dentina stvorena

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je pomoću dvokomponentnog samojetkajućeg adheziva (Clearfil SE Bond 2, Kuraray). Uzorci su skladišteni na 37 ° C u destiliranoj vodi i testirani u uređaju za mjerenje jačine adhezijske sveze (test smicanja) nakon 1 tjedna i 1 godine. Optimalni broj uzoraka za analizu pouzdanosti dobiven je pripremom n=20 po eksperimentalnoj skupini (ukupno n=120 za cijelo istraživanje).
Rezultati: Srednja snaga svezivanja mjerena nakon 1 tjedna i 1 godine bila je statistički slična za kontrolni kompozit (21,9 naspram 24,0 MPa) i za bioaktivni-10 (19,6 naspram 19,1 MPa). Međutim, Weibullova statistika otkrila je značajan pad pouzdanosti veze nakon starenja: Weibullovi moduli smanjili su se sa 13,5 na 3,9 za kontrolni kompozit i sa 12,3 na 3,8 za bioaktivni-10. Za bioaktivni-40, prosječna čvrstoća veze značajno je pala nakon jedne godine (8,1 prema 6,8 MPa), ali njegova pouzdanost je ostala nepromijenjena, što je utvrđeno statistički sličnim Weibullovim modulima.
Zaključak: Pogoršanje snage svezivanja nakon jedne godine utvrđeno je korištenjem analize pouzdanosti kod kontrolnog i eksperimentalnog bioaktivnog kompozita iako konvencionalna statistika nije mogla razlikovati promjene prosječne snage svezivanja.

Ključne riječi: snaga svezivanja na dentin, analiza povezanosti, pouzdanost, bioaktivno staklo 45S5, adhezijska sveza, zubni materijal,

Introduction

Dental composite materials are mixtures of organic resins and inorganic filler particles interconnected by a coupling agent. The inorganic filler particles are coupled with silanes and scattered in a polymer matrix. Silane makes possible chemical bonding of fillers surfaces with the methacrylate network[1]. Compared to conventional, the experimental, bioactive composites contain unsilanized bioactive fillers which are unable to bond to the methacrylate network and thus can deteriorate mechanical properties[2].
Dental composites are bonded to dental hard tissues by using adhesive systems[3]. Bond strength testing can measure the capability of adhesive system which somewhat provides an indication of the permanence of a restoration[4]. The main characteristic of bond strength data is high variability[5]. Many factors can influence test results, for example test specimen properties, preparation of specimens, handling of materials, specimen storage, experimental setup design, and experimental technique. However, the fundamental source of variability is associated with the brittle nature of materials such as dental composites[6]. Maximum stress brittle materials can resist varies unpredictably from specimen to specimen even if a set of seemingly identical specimens are tested under the same conditions[7]. The fracture is hard to predict because there are no early warnings or visible deformation[8]. The strength of brittle materials is determined by pre-existing defects or flaws present in the specimen, rather than by inherent material properties. Therefore, the measured strength of brittle materials depends on the probability of occurrence of a critical defect in their structure[9].
In materials science, when measuring mechanical properties such as strength, it is normal practice to make a series of measurements on a number of apparently identical specimens[6,10]. The most widely used method for reporting the results from such tests is to give the number of tests performed, the mean strength and the standard deviation[11,12,13]. This method assumes that the mean value is the "true value" and that data scattering around this true value is due to variations in test method or specimen preparation. When the fracture process is of brittle nature, the results show considerable variation, representing characteristics of tested specimens and not the material itself (6, 10). Hence, some authors suggest that it is more suitable to characterize brittle materials by means of the probability of failure at a certain stress level, which can be calculated from the Weibull distribution function[9, 10, 14, 15].
Weibull analysis is based on extreme value distributions and an empirically derived statistical distribution function that relate strength to the failure of the largest flaws[16]. Weibull's basic premise was "the weakest link theory" i.e. if the weakest part of the material fails, the entire sample fails. Weibull distribution can evaluate the probability of failure at a certain level of stress and vice versa[8].
The objective of this in vitro study was to test shear bond strength of experimental composite resins and apply the statistical approach of reliability analysis (Weibull) in order to evaluate aging-related changes. Additionally, the conventional statistical approach (analysis of variance, ANOVA) was applied to the same bond strength data to compare its discriminative capability to that of Weibull analysis.

Materials and methods

Preparation of experimental composites

The photo-curable monomer system for experimental composites was prepared by blending a Bis-GMA/TEGDMA (60/40) resin with a photoinitiator system (camphorquinone/ tertiary

Table 1. Composition of experimental composite materials

Material code	Filler composition (wt%)		Total filler ratio (wt%)	Resin composition	Photoinitiator system
	Bioactive glass 45S5	Reinforcing fillers (Ba-glass+silica)			
control composite	0	70	70	Bis-GMA TEGMA	Camphorquinone Ethyl-4 (dimethylamino) benzoate
bioactive-10 composite	10	60	70		
bioactive-40 composite	40	30	70		

amine) in a magnetic stirrer for 48 h. The obtained resin was mixed with variable amounts of reinforcing fillers (barium glass and silica) and bioactive glass 45S5 in an asymmetric centrifugal mixer (Speed Mixer TM DAC 150 FVZ, Hauschild & Co. KG, Hamm, Germany) at 2700 rpm during five minutes (Table 1). Two remineralizing composites with 10 or 40 wt% of BG were denoted as bioactive-10 and bioactive-40. Inert fillers were added up to the total filler load of 70 wt%. Control composite contained only inert fillers (70 wt%). The experimental composite pastes were then kept for 12 h in vacuum to remove air inclusions.

Specimen Preparation and Shear Bond Strength Testing

Intact human third molars with completed root formation were collected after extraction and stored in 1% chloramine solution at room temperature. Dentin substrates for bonding were prepared using a low-speed saw (IsoMet 1000, Buehler; Lake Bluff, IL, USA) 2-4 months after extraction. The dentin slabs were embedded in a cold-curing methacrylate resin (Technovit 4004, Kulzer, Germany) using a 15-hole stainless steel mold (Ultradent Products, Inc., South Jordan, UT, USA), wet-polished using P600 silicon carbide paper and instantly used for the bonding procedure. Prior to application of the adhesive system, dentin surfaces were gently air-dried to remove any visible moisture. Bonding area was restricted using an adhesive tape with an aperture of 3 mm in diameter. On the flat dentin surface, a two-step self-etch bonding agent Clearfil SE Bond 2 (Kuraray Noritake; Tokyo, Japan, LOT:000031, EXP:2019-02) was applied according to the manufacturer's instruction: primer application with an applicator brush for 20 s, mild air drying for 5 s, applying bond and uniformly spreading the bond layer using a gentle air flow, followed by polymerization for 10 s from a distance of 1 mm (Bluphase Style, Ivoclar Vivadent; Schaan, Liechtenstein, Ser. No. 1120006563).

Using a polypropylene mold (Bonding Clamp and Bonding Mold Inserts, Ultradent Products, Inc., South Jordan, UT, USA) composite cylinders were prepared (d=3mm, h=2mm). Specimens were stored at 37 °C in distilled water and fractured in shear mode by loading in bond strength testing machine Ultratester (Ultradent Products) after 1 week and 1 year. Testing was performed at a constant crosshead speed of 1 mm/min until fracture. The optimal sample size for reliability analysis was obtained by preparing n=20 per experimental group (3 materials x 2 aging times x 20 specimens per group; total n=120 for the whole study).

Statistical analysis

The normality of distribution was evaluated using Shapiro-Wilk's test. The homogeneity of variances among experimental groups was verified using Levene's test. Mean values of bond strength were compared among different combinations of material and measurement time using one-way ANOVA. After identifying an overall statistically significant difference among groups, multiple post-hoc comparisons were performed using Tukey's adjustment.

Weibull analysis

Reliability analysis begins by ranking the samples according to calculated bond strength is how. The values which are plotted along the horizontal axis of a Weibull graph are obtained as natural logarithms of bond strength.

The probability of failure (Pf) for each specimen from a group of n specimens is given by the following expression:

$$Pf = (i-0.5)/n$$

where i is the ranking number in ascending order of bond strength data (weakest rank 1, strongest rank N) while n is the total number of specimens within the experimental group. On the vertical axis is plotted double natural logarithm of [1/(1-Pf)]. Linear regression is then used to fit a linear function through the plotted data points. The slope of the obtained linear function represents Weibull modulus[8].

Results

Mean bond strengths measured after 1 week and 1 year were statistically similar for the control composite (21.9 vs. 24.0 MPa) and for bioactive-10 (19.6 vs. 19.1 MPa) according to

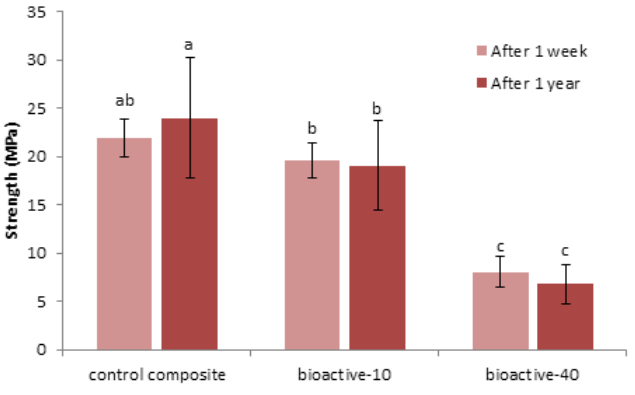


Figure 1. Average bond strength of experimental composites. Error bars represent ± 1 s.d. Same letters denote statistically homogeneous groups.

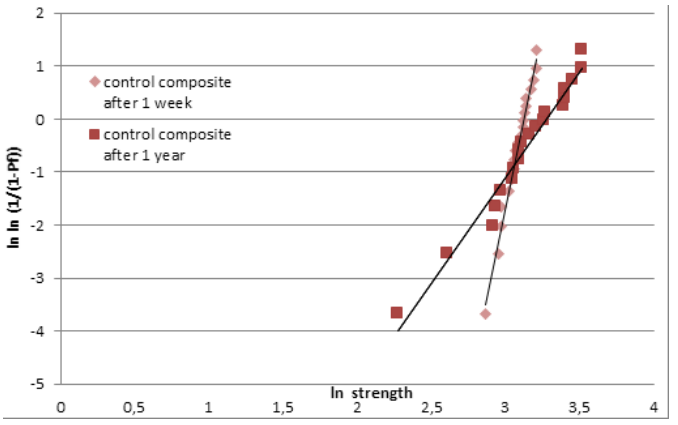


Figure 2. Weibull plots of the control composite

conventional statistics (Figure 1). Concerning the other two tested materials, significantly lower bond strength was observed for the bioactive-40 composite (Figure 1). For bioactive-40, mean bond strength declined significantly after 1 year (8.1 vs. 6.8 MPa).

The shape parameter (Weibull modulus) of the Weibull distribution is represented by the slope of the fit lines: steeper slope indicates higher reliability (Figures 2-4). In comparison to the previously mentioned results of the statistical analysis, Weibull statistics revealed a significant decline in bond reliability after aging: Weibull moduli decreased from 13.5 to 3.9 for the control composite (Figure 2) and from 12.3 to 3.8 for bioactive-10 (Figure 3). For bioactive-40 composite, reliability remained unimpaired, as identified by statistically similar Weibull moduli (Figure 4).

Discussion

This study was conducted based on the analysis of bond strength data by two different statistical methods. The arithmetic mean, which was used to describe the central tendency of bond strength within sample sets showed similar values for the control and bioactive-10 experimental composites after one week and one year. However, Weibull analysis revealed a decline in reliability after 1-year aging.

The Weibull three parameter equation, which links the probability of failure (Pf) to stress (├) is defined as:

Pf=1-exp [- ((├ ┤u)/ ├o)m]

The constant ┤u is the lowest level of stress at which Pf approaches zero and it is customary to assume that ┤u=0. In that case is obtained two-parameter Weibull distribution which is generally used to evaluate material reliability. ├stands for the measured strength. The scale parameter is ├o, defined as the uniform stress at which the probability of failure is 63.2% and intersection with the x-axis gives the logarithm of the characteristic strength. A decline in the scale parameter of Weibull distribution is represented by shifting of the fit lines toward lower values of x-axis i.e. shifts data to the left. Mean bond strength in the conventional analysis is analogous to the characteristic strength in Weibull analysis and both represent the scale parameter of their corresponding distributions[8].

Mean strength marks altogether strength of the material, however, does not describe the relationship of each individual strength value and its corresponding probability of failure[6].

The important practical use has the constant m, which represents the Weibull modulus[8]. In conventional statistics, the spread of data (standard deviation) is represented as an error of measurement, while in reliability analysis scatter of data is not an experimental error but it classified through Weibull modulus. Previously stated parameter provides a measure of material dependability with simple calculations and it is also known as a shape parameter (10). In that sense, Weibull modulus describes the form of the distribution. A high value of Weibull modulus (i.e. flaw sizes within a specimen are similar) indicates a close grouping of fracture stress values while a low value indicates a wide Weibull distribution is typical for a high spread of defects and less predictable bond strength.

Essentially, Weibull modulus is the parameter that makes a difference in interpretation of results compared with a conventional statistical approach using ANOVA. As seen in the results obtained, the mean strength is approximately the same at both measuring times, but the wide range indicates a higher spread of material defects and more unpredictable bond strength after one year.

In bioactive-40 composite the decrease in mean bond strength and reliability was observed. It was expected because unsilanized bioactive fillers behaved as structural flaws[17]. Bioactive fillers cannot be silanized to avoid the interference of the silane layer with ion release. Due to the lack of surface silanization, bioactive fillers cannot participate in the distribution of forces

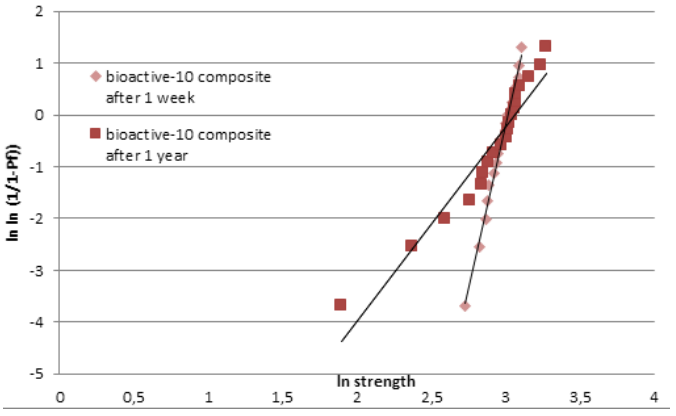


Figure 3. Average bond strength of experimental composites. Error bars represent ± 1 s.d. Same letters denote statistically homogeneous groups.

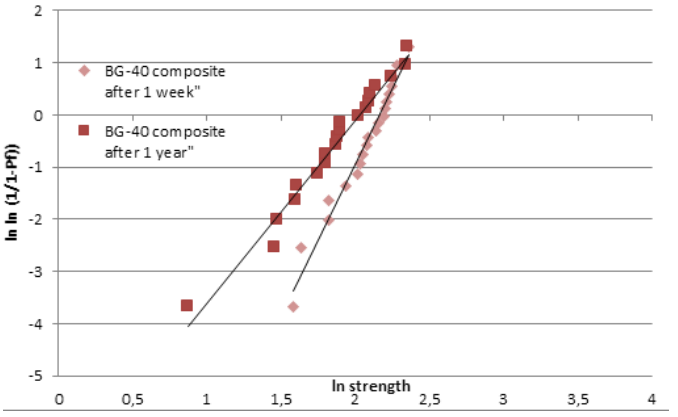


Figure 4. Weibull plots of the control composite

between filler particles and the resin polymer matrix, which ultimately leads to impaired mechanical properties[18]. In order to facilitate water diffusion and the consequent release of ions, resin in bioactive composites is normally more hydrophilic than in conventional composites[19]. High hydrophilicity diminishes mechanical properties because of accelerated degradation of the composite structure[20]. With regards to increase in reliability observed in bioactive-40 composite (6.8 in regards to 3.9 for the control composite apropos 3.8 for bioactive-10) during aging some studies ascribe to the increase of plastic zone ahead of the crack and consequent lowering of material brittleness[21,22]. Bradna et al. compared various adhesive application protocols using reliability analysis. Shear bond strength was determined after 24 h. One of the tested adhesives was Clearfil SE Bond with mean bond strength values (±s.d.) of 22.8 ± 3.6 MPa while Weibull modulus amounted to 6.5. The adhesive was combined with microhybrid composite Opticor New (d=3.5mm, h=2mm)[9]. In our study mean bond strength measured after 1 week for the control composite was 21.9 MPa. The results of this in vitro study are to some extent comparable to those from the study by Par et al. which investigated dentin bond strength during aging for 1 week, 1 month, 3 months, 6 months and 1 year. In that study it was concluded that enhanced BG amount diminished bond strength and reliability. Also, the bond strength reduction was linearly dependent on the amount of BG[17].

Conclussions

With the limitations of this in vitro study, the following conclusions were drawn:

1. Although values of mean bond strength were similar after 1 week and 1 year, decreased Weibull moduli in the control composite and bioactive-10 after one year are indicative of decline in material's reliability and deterioration of bond strength.
2. A decrease in bond strength was observed with an increasing amount of bioactive glass. It is explained by the presence of unsilanized particles which acted as structural flaws.

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Serum Levels of Homocysteine in Young Psoriasis Patients Naïve for Conventional Systemic and Biologic Therapy

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Abstract:

Introduction: Psoriasis is an immune-mediated chronic inflammatory disease, affecting approximately 1-3% of the population worldwide. Psoriasis patients are more likely to be diagnosed with cardiovascular diseases and hyperhomocysteinemia; however, it remains elusive weather serum homocysteine levels correlate to disease activity and duration of disease. The aim of this study was to investigate serum levels of homocysteine in young patients with plaque psoriasis naïve for conventional systemic and biologic therapy. An additional aim was to determine correlation of homocysteine levels with disease severity, inflammation, folic acid and vitamin B12 supplies.

Materials and methods: 26 subjects were enrolled to participate in this case-control study, including 13 adult psoriatic patients naïve for systemic therapy, without comorbidities, malignancies and infectious diseases, and 13 healthy unrelated, age and sex-matched volunteers. The disease severity and life quality were assessed using standardized tools – Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI), respectively. Venous blood was collected and processed for analysis of differential blood count (DBC), erythrocyte sedimentation rate (ESR), C reactive protein (hsCRP), serum levels of homocysteine, vitamin B12 and folic acid in the routine clinical laboratory.

Results Studied cohort consisted of young participants with average age around 35 years. According to the PASI index, disease severity ranged from mild (2.10) to moderate (15.2). There was no significant difference in hsCRP and DBC levels between the groups. Psoriasis patients had significantly higher levels of homocysteine compared to healthy subjects, but there was no evidence of hyperhomocysteinemia related to psoriasis. All subjects had normal serum levels of vitamin B12 and folic acid. A moderate negative correlation was found between plasma homocysteine level and vitamin B12 and folic acid. Furthermore, homocysteine levels did not correlate to hsCRP, total leukocytes, and thrombocytes count, but did significantly positively correlate to ESR.

Conclusions: The risk of cardiovascular diseases should be considered among all psoriasis patients, regardless of age and disease severity, but larger prospective controlled studies are needed to estimate the role of homocysteine in cardiovascular morbidity and mortality in psoriatic patients.

Keywords: psoriasis, homocysteine, folic acid, cardiovascular disease

Sažetak:

Serumska vrijednost homocisteina u mladih bolesnika koji nisu primali sustavnu i biološku terapiju

Uvod: Psorijaza je imunološki posredovana kronična upalna bolest, koja pogađa otprilike 1-3% populacije u svijetu. Pacijenti oboljeli od psorijaze imaju veću vjerojatnost razvoja kardiovaskularnih bolesti i hiperhomocisteinemije, međutim, ostaje nejasna povezanost serumske razine homocisteina s aktivnošću i trajanjem bolesti.

Cilj ove studije bio je ispitati serumske vrijednosti homocisteina u mladih bolesnika s plak psorijazom, koji nisu do sada primali sustavnu, ili biološku terapiju. Dodatni cilj bio je utvrditi povezanost serumske razine homocisteina s težinom bolesti, razinom upale te razinom folne kiseline i vitamina B12.

Materijali i metode U ovo istraživanje bilo je uključeno 26 ispitanika, uključujući 13 odraslih bolesnika s psorijazom naivnih za sustanu terapiju, bez komorbiditeta, malignih oboljenja i zaraznih bolesti te 13 zdravih, nepovezanih, dobno i spolno usklađenih dobrovoljaca. Težina bolesti i kvaliteta života procijenjena je korištenjem standardiziranih testova - Psoriasis Area and Severity Index (PASI) i Dermatološkog indeksa kvalitete života (DLQI). Iz venske krvi ispitanika, u rutinskom kliničkom laboratoriju, određena je diferencijalna krvna slika (DKS), brzina sedimentacije eritrocita (SE), C reaktivni protein (hsCRP) te serumske razine homocisteina, vitamina B12 i folne kiseline.

Rezultati Istraživana skupina sastojala se od mladih sudionika, prosječne dobi oko 35 godina. Prema PASI indeksu, težina bolesti bila je u rasponu od blage (2,10) do umjerene (15,2) psorijaze. Nije bilo značajne razlike u vrijednostima hsCRP-a i DKS-a između ispitivanih skupina. Ispitanici s psorijazom imali su statistički značajno više vrijednosti homocisteina u usporedbi sa zdravim ispitanicima, ali nije bilo dokaza hiperhomocisteinemije povezane s psorijazom. Svi ispitanici imali su normalne vrijednosti vitamina B12 i folne kiseline u serumu. Utvrđena je umjerena negativna povezanost između razine homocisteina u serumu i vitamina B12 te razine homocisteina i folne kiseline. Nadalje, serumska razina homocisteina nije bila povezana s hsCRP-om, ukupnim brojem leukocita i trombocita, ali je uočena značajna pozitivna povezanost serumske razine homocisteina i sedimentacije.

Zaključak: Rizik od kardiovaskularnih bolesti treba razmotriti među svim pacijentima oboljelima od psorijaze, bez obzira na njihovu dob i težinu bolesti. Potrebna su veća prospektivna, kontrolirana ispitivanja kao bi se procijenila uloga homocisteina u razvoju kardiovaskularnih bolesti kod psorijatičnih bolesnika.

Ključne riječi: psorijaza, homocistein, folna kiselina, kardiovaskularna bolest

Introduction

Psoriasis is an immune-mediated chronic inflammatory disease, affecting approximately 1-3% of the population worldwide[1,2].

As opposed to the formerly widespread opinion that psoriasis is a skin limited disease, it is now accepted, due to an increasing number of epidemiological publications and evidence-based research, that significant systemic conditions often accompany this chronic disease [3]. In fact, psoriasis is considered as an independent risk factor for cardiovascular morbidity and mortality[4,5]. Particularly, the risk for the development of myocardial infarction, as well as other cardiovascular events, is noticeably increased in patients with severe psoriasis, especially those between 20 and 50 years old[6].

Even though the association between psoriasis and cardiovascular diseases is lately extensively studied, the exact underlying mechanisms have not yet been uncovered[7].

As suggested in some previously published studies, elevated serum homocysteine levels might contribute to the cardiovascular risk in psoriatic patients[8-10].

Homocysteine is sulfur containing amino acid, displaying atherogenic and prothrombotic features. It is produced in the metabolism of the essential amino acid methionine and can be catabolized by re-methylation to methionine in the presence of co-factors folic acid and vitamin B12 or by trans-sulfuration to cysteine in the presence of cofactor vitamin B6[8,11-15]. Moreover, homocysteine promotes endothelial dysfunction and, consequently, atherosclerosis by reducing the bioavailability of nitric oxide due to inhibition of nitric oxide synthase (eNOS) and oxidative stress, provokes endothelial cell damage, and leads to a state of chronic inflammation of the endothelium [12,16].

A meta-analysis of 24 studies showed that psoriatic patients have higher homocysteine serum levels, a greater prevalence of hyperhomocysteinemia and, conversely, have lower serum folate levels compared to controls. Yet, the two groups did not significantly differ in vitamin B12 serum levels[10].

Rapid keratinocyte proliferation with high mitotic activity of basal cells, along with intestinal malabsorption caused by microscopic inflammatory changes of the intestinal mucosa, might contribute to folate deficiency in patients with psoriasis. Since folic acid is a cofactor in the catabolism of homocysteine, the

decrease in folate serum levels is therefore one of the causes for hyperhomocysteinemia[8,17-20].

However, due to inconsistent results from several studies, it still remains unclear whether a correlation between homocysteine levels, disease activity and disease duration exists or not[8,9,19,21,22]. Another potential link between homocysteine and psoriasis lies in epigenetic changes of human leukocyte antigen (HLA) DRB1, a major histocompatibility complex (MHC) II protein[23,24]. Provided that the expression of HLA-DRB1 on antigen presenting cells (APCs) can be altered by aberrant methylation status of the gene, these methylation changes can affect the APCs capability of antigen presentation to T lymphocytes, the main role of HLA-DRB1[23]. Indeed, hypomethylation of the promoter region of HLA-DRB1 was found in the epidermis of psoriatic lesions when compared to psoriatic non-lesioned skin, whereas the mean methylation rate of HLA-DRB1 in lesioned skin negatively correlated to Psoriasis Area and Severity Index (PASI) score, suggesting that aberrant methylation of this region might play a role in the pathogenesis of psoriasis [23]. Given the fact that homocysteine, as an intermediate, plays an important role in the methylation cycle, the majority of published data supports the claim that high homocysteine serum levels are associated with global DNA hypomethylation in humans. Since the role of homocysteine in the abnormal methylation pattern seen in psoriatic lesions remains unclear, there is a need for further research to elucidate this[15,25].

The aim of this study was to investigate serum levels of homocysteine in patients with vulgar psoriasis naïve for conventional systemic and biologic therapy. An additional aim was to determine correlation of homocysteine levels with disease severity, inflammation, and folic acid and vitamin B12 supplies.

Matherials and methods

Subjects

This was a case-control study, including 13 psoriatic patients with clinically diagnosed plaque psoriasis and 13 healthy unrelated, age- and sex-matched control subjects. Subjects were recruited among the patients admitted at the Department of Dermatology and Venereology of the University Hospital Osijek (Croatia). At the time of enrollment, psoriasis patients had a clinically active and histopathological confirmed disease. The disease severity and life quality were assessed using standardized tools – the Psoriasis Area Severity Index (PASI) and Dermatology Life Quality Index (DLQI), respectively [26,27].

Exclusion criteria for this study were: (1) ongoing systemic therapy for psoriasis (including immunomodulatory therapy, cytostatic, photochemotherapy and phototherapy), (2) concomitant rheumatic and autoimmune diseases (i.e. spondyloarthropathy, rheumatoid arthritis), (3) malignant and infectious diseases, and (4) age (under 18 years). Anthropometric and demographic data, such as body height, body weight, age, gender and parity were assessed using a questionnaire.

The study was reviewed and approved by the Ethical Committee of the University Hospital Osijek (number: R2-9042 / 2018) and the Ethics Committee of the Faculty of Medicine University of Osijek (number: 2158-61-07-18-135). The study was conducted in accordance with Declaration of Helsinki, and all participants signed written informed consent prior inclusion into the study.

Methods

For the purpose of determining differential blood count, C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), serum levels of homocysteine, vitamin B12 and folic acid, venous blood was collected in the morning, after a minimum of 8-hours fasting period. Samples intended for homocysteine level analysis were immediately put on ice. All samples were delivered to the laboratory at the Clinical Department for Laboratory Diagnostics (University Hospital Osijek, Osijek, Croatia) and analyzed within 1 hour. The normal laboratory range for plasma homocysteine was 0–14 μmol/l, and hyperhomocysteinemia was defined as a homocysteine concentration >14 μmol/l[28].

Statistical analysis

All results are reported as the mean ± standard deviation (SD). The Shapiro–Wilk test was used to test the normality of data distribution. Next, data were compared by Student's t-test or the Mann-Whitney rank-sum test for normally distributed data and data that did not follow a normal distribution pattern, respectively. The correlations between serum levels of homocysteine and other assessed parameters were determined by Pearson's correlation tests. $p < 0.05$ was considered statistically significant. SigmaPlot, version 11.2 (Systat Software, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The present study included 26 subjects, of which 13 participants were psoriasis patients with an active disease, and the remaining 13 participants were age- and sex- matched healthy controls. Their demographic and clinical data are shown in Table 1. The average age of enrolled subjects in both groups was around 35. Disease severity in psoriasis patients was assessed using the PASI index and ranged from 2.10 to 15.2. The rate of smokers among psoriasis patients and healthy controls was 46.2% and 23.1%, respectively. C-reactive protein levels and differential blood count did not vary significantly between the groups (Table 1).

Psoriasis patients had significantly higher serum levels of homocysteine compared to healthy subjects (p=0.021; Table 1 and Figure 1), however, there was no evidence of hyperhomocysteinemia related to psoriasis. All included subjects had serum homocysteine levels within the normal reference range except one psoriasis patient who presented with slightly elevated level of homocysteine (15.5 μmol/L), (Table 1).

All subjects had normal serum levels of vitamin B12 and

		Psoriasis patients	Healthy controls	t test (p value)
Number of participants (N)		13	13	-
Sex	Male (N)	7	10	-
	Female (N)	6	3	-
Age (years)		34.3±7.71 (25.0, 50.0)	35.9±8.38 (24.0, 55.0)	0.630
PASI		9.16±3.91 (2.10, 15.2)	N/A	-
DLQI		5.00±5.85 (0.00, 20.0)	N/A	-
BMI		24.9±4.72 (19.1, 34.9)	25.0±4.28 (19.5, 35.8)	0.936
Smoking	Yes (N)	6	3	-
	No (N)	7	10	-
Parameter (unit; laboratory referent values)				
CRP (mg/l; <5.0)		1.86±2.03 (0.30, 7.80)	1.41±1.09 (0.12, 3.20)	0.488
Leukocytes (x10e9 /L ; 3.40-9.70)		6.77±1.67 (3.7, 9.0)	6.18±1.83 (4.50, 10.4)	0.402
Erythrocytes (x10e12/L; 3.86-5.08)		4.84±0.43 (4.08, 5.34)	5.00±0.36 (4.47, 5.73)	0.342
Thrombocytes (x10e9/L; 158.0-424.0)		271.4±58.8 (214.0, 416.0)	254.1±58.1(145.0, 391.0)	0.458
Sedimentation rate (mm/3.6 KS; 4.00-24.0)		5.45±1.69 (3.00, 8.00)	5.58±4.83 (1.00, 15.0)	0.511
Homocysteine (umol/l)		9.99±2.30 (7.10, 15.5)	8.03±1.36 (6.10, 10.5)	0.021*
Folic acid (nmol/L; 7.0-64.0)		13.7±4.72 (7.0, 19.7)	15.6±5.96 (8.00, 21.8)	0.370
Vitamin B12 (pmol/L; 138.0-652.0)		318.2±103.2 (216.0, 602.0)	291.0±141.6 (136.0, 479.0)	0.550

Data are presented as mean±SD (min, max). The differences were tested by Student's t-test or Mann-Whitney rank-sum test, where appropriate. **p<0.05 was considered significant

folic acid (Table 1). The mean plasma levels of either vitamin B12 (318.2±103.2 pmol/L in psoriasis patients versus 291.0±141.6 pmol/Lin healthy subjects, p=0.370), or folic acid (13.7±4.72 nmol/L in psoriasis patients versus 15.6±5.96 nmol/L in healthy subjects, p=0.550) were not statistically significantly different between two groups. A moderate negative correlation was found between plasma homocysteine level and vitamin B12 (r=-0.603, p=0.004) and folic acid (r=-0.638, p=0.002). Furthermore, homocysteine levels did not correlate to hsCRP (p=0.638), total leukocytes (p=0.203) and thrombocytes count (p=0.291), but did significantly positively correlate to sedimentation rate (r=0.410, p=0.0159)

Psoriasis patients included in this study had mild to moderate disease severity. Mean PASI score was 9.16±3.91, ranging from 2.10 to 15.2. There is no evidence of direct correlation between current disease severity and serum homocysteine levels

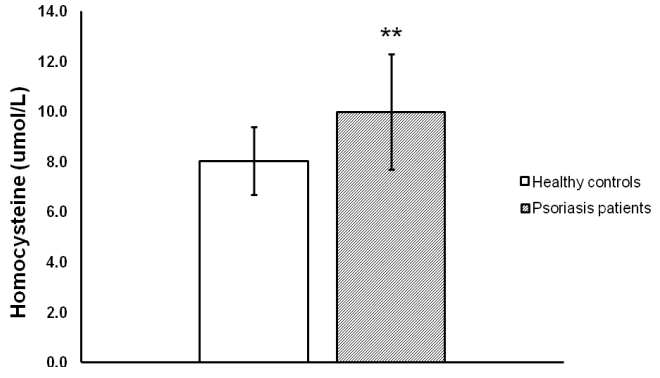


Figure 1. Psoriasis Patients Present with Higher Serum Levels of Homocysteine Compared to Healthy Controls

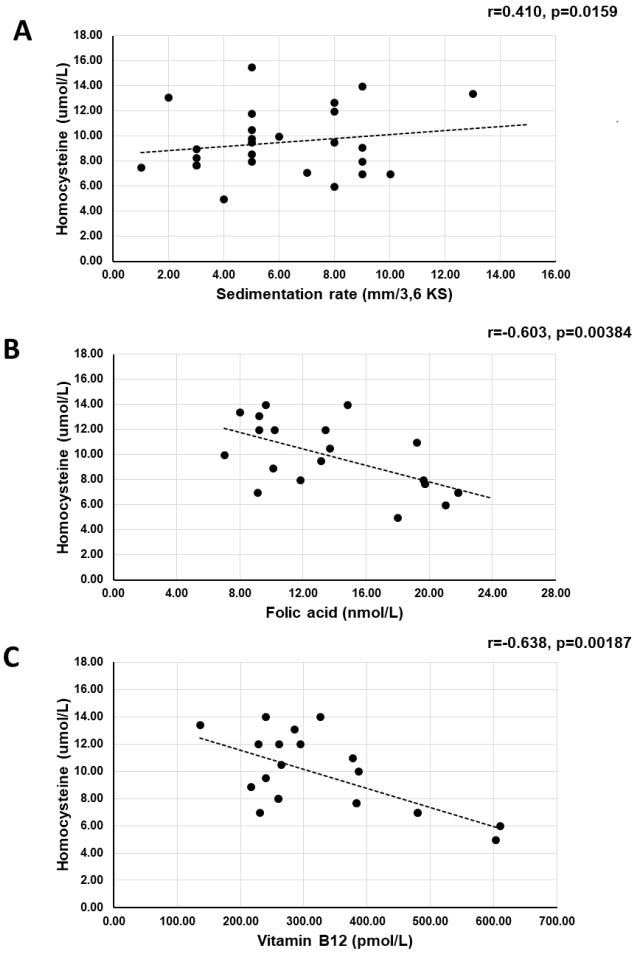


Figure 2. Homocysteine Levels Correlate to Inflammation and Body Supply of Folic Acid and Vitamin B12

(p=0.228), nor the life quality of psoriasis patients and serum homocysteine levels (p=0.392).

Discussion

Psoriasis is considered to be an independent risk factor for cardiovascular morbidity and mortality, but the exact underlying mechanisms have not yet been uncovered [3-5]. Some recent studies suggested that elevated serum homocysteine levels in psoriatic patients might contribute to the cardiovascular risk in psoriatic patients, due to their atherogenic and prothrombotic effect [11-15]. In the present study young psoriasis patients naïve for systemic and biologic therapy presented with significantly higher serum levels of homocysteine compared to the healthy subjects, but still their serum homocysteine levels were within normal reference range. In addition, all participants had normal serum levels of B12 vitamin and folic acid. These results partly correspond to previous studies that are included in the meta-analysis performed by Tsai TY et al[10]. The authors reported significantly higher serum homocysteine level in 18 out of 24 studies, a higher prevalence of hyperhomocysteinaemia in seven studies, a lower serum folate level in 14 studies, and no difference in serum vitamin B12 levels between psoriasis patients and the healthy controls[10]. Although serum levels of folic acid between two groups in our research showed no significant difference, we found a moderate negative correlation between the serum homocysteine level and vitamin B12, as well as between plasma homocysteine level and folic acid level. Similar results were found in previous research concerning negative correlation between serum homocysteine levels and folic acid levels, but none of the previous studies showed significant correlation between the serum levels of homocysteine and B12 vitamin[10]. Negative correlation between homocysteine and folic acid as well as homocysteine and B12 vitamin could be related to the fast epidermal overgrowth and higher mitotic basal cell activity of the psoriasis patients[20]. An additional reason for the higher homocysteine levels among psoriasis patients could be the reduced absorption of folic acid and B12 vitamin in the intestine due to micro damage of the intestinal villi that is caused by long term chronic inflammation in psoriatic patients[29,30]. Furthermore, normal folate levels observed in our study, which is contrast to previous reports, might be explained by younger age (35 years old) of subjects and shorter exposure to systemic inflammation[10]. Additionally, homocysteine levels did not correlate to hsCRP and total leukocytes count, but did significantly positively correlate to sedimentation rate. Consistent to previous reports, we failed to find direct correlation between current disease severity and serum homocysteine levels[10]. These results suggest that hyperhomocysteinemia and cardiovascular comorbidity rise as a result of prolonged exposure to systemic inflammation.

Conclussion

Based on the results of the present study, homocysteine has

the potential as a biomarker of cardiovascular risk in psoriasis patients, primarily during long term follow-up. Single measurements of serum homocysteine levels in population of young psoriasis patients are likely to fall within the normal reference range, and thus could not be used for prediction of cardiovascular risk. In addition, etiology of cardiovascular diseases is complex, including genetic, environmental and other factors thus large prospective controlled studies are needed to overcome immense heterogeneity among them. Here we would like to emphasize

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The effectiveness of diode laser in reduction of inferior turbinate

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Abstract:

Introduction: Inferior turbinate hypertrophy that is refractory to conservative therapy is one of the most common problems in rhinology. Reduction of the inferior turbinate with a diode laser is a minimally invasive and safe method that can be performed under local anesthesia.
The aim of this study is to show the efficiency of diode laser in reduction of inferior turbinate based on symptoms of nasal obstruction, nasal secretion, headache, hyposmia, and rhinomanometry findings before and after surgery.
Materials and Methods: A total of 62 patients were included in this study, who underwent diode laser turbinate reduction between November 2017 and December 2019. Patients were followed up after seven days and one month after surgery. Rhinomanometry was performed before and after surgery.
Results: Nasal obstruction was present in all patients before surgery, nasal secretion in 50% of patients, headache in 22.5%, and hyposmia in 16.1% of patients before surgery. One month after surgery, 88% of patients no longer complained of nasal obstruction and 83.8% of nasal secretion. In 6.5% of patients the symptom of headache persisted and 4.8% of patients continued to complain of decreased sense of smell. Total nasal resistance was significantly lower after surgery ($p < 0.001$). Synechiae were observed in one patient as a postoperative complication.
Conclusions: Reduction of inferior turbinate with diode laser is a safe, effective method with minimal complications and a short patient recovery period, and can be performed under local anesthesia.

Keywords: diode laser; inferior nasal turbinate; rhinomanometry

Abstract:

Efikasnost redukcije donjih nosnih školjki diodnim laserom
Uvod: Hipertrofija donjih nosnih školjki koja je refraktorna na konzervativnu terapiju je jedan od najčešćih problematika u rinologiji. Redukcija donjih nosnih školjki s diodnim laserom je minimalno invazivna i sigurna metoda koja se može provesti u lokalnoj anesteziji.
Cilj rada je prikazati efikasnost redukcije donjih nosnih školjki diodnim laserom na temelju subjektivnih simptoma nazalne opstrukcije, nazalne sekrecije, glavobolje i smanjenog osjeta mirisa, te nalaza rinomanometrije.
Materijali i metode: U studiju je uključeno 62 pacijenta kojima je učinjena redukcija donjih nosnih školjki diodnim laserom u razdoblju od studenog 2017. godine do prosinca 2019. godine. Postoperativno kontrole su provedene sedmi dan i mjesec dana nakon operacije.
Svim pacijentima je učinjena rinomanometrija na kompjuteriziranom rinomanometru prije i nakon operacije.
Rezultati: Kod svih pacijenata je bila prisutna nazalna opstrukcija prijeoperativno. Kod 50 % pacijenata je bila prisutna nazalna sekrecija prijeoperativno, kod 22,5 % glavobolja, te u 16,1% slučajeva pacijenti su slabije osjetili mirise. Mjesec dana postoperativno 88% pacijenata se više nije žalio na nazalnu opstrukciju, a 83,8% na nazalnu sekreciju. Kod 6,5% pacijenata je i dalje perzistirao simptom glavobolje, te 4,8% pacijenata se i dalje žalio na smanjen osjet mirisa.

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Značajno su manje vrijednosti ukupnog otpora zraka na rinomanometrijskom nalazu postoperativno (p<0,001).
Kod jednog pacijenta su uočene sinehije kao postoperativna komplikacija.
Zaključak: Upotreba diodnog lasera u redukciji donjih nosnih školjki je sigurna, efektivna metoda s minimalno komplikacija i kratkim periodom oporavka pacijenata, te se može provesti u lokalnoj anesteziji.

Ključne riječi: diodni laser; donje nosne školjke; rinomanometrija

Hypertrophy of the inferior turbinate is a common occurrence in patients with allergic rhinitis, vasomotor rhinitis, chronic rhinosinusitis, deviated nasal septum, and rhinitis medicamentosa. Inferior turbinate hypertrophy (ITH) is the second most common cause of nasal obstruction, after septal deviation[1].
The inferior turbinate is composed of the bony turbinate, the submucosal tissue and the overlying nasal mucosa[2]. The most important functions of inferior turbinates are warming and humidification of inhaled air. Many factors can cause pathologic enlargement of inferior turbinate[3].
Inferior turbinate hypertrophy is caused by the deposition of collagen in submucosal tissue, which remodels the turbinate bone. This pathophysiological mechanism occurs in chronic inflammation of the nasal mucosa, which is present in allergic and vasomotor rhinitis. The primary conservative therapy for ITH includes topical decongestants, antihistamines and corticosteroids. The most common symptoms in patients with inferior turbinate hypertrophy are nasal obstruction, sneezing, rhinorrhea and headache[4].
Surgical treatment includes resection, ablation or crushing part, or all of the turbinate to increase the size of the nasal airway. The best choice of procedure may depend on a patient's anatomy and other concurrent procedures performed (such as septoplasty) as well as the presence or absence of other comorbidities such as allergic rhinitis[2].
If conservative medical treatment does not produce results, then surgical reduction of the inferior turbinate is usually performed. The optimal surgical technique should be a compromise between effective turbinate volume reduction, but also preserving the nasal function, and avoiding complications. The diode laser coagulation effect is comparable to that of the argon laser. Its tissue-cutting effect is comparable to that of the CO2 laser. Laser turbinate reduction can be performed under local or general anesthesia. Surgery often takes a short time. It has minimal intraoperative and postoperative complications and is usually well tolerated by the patients[4].
The objective of this prospective study was to show the efficiency of diode laser in the treatment of ITH, based on symptoms of nasal obstruction, nasal secretion, headache, hyposmia, and rhinomanometry findings before and after surgery.

Materials and methods:

This prospective clinical study included 62 patients who underwent inferior turbinate reduction with a diode laser (LEONARDO® DUAL by biolitec®, Germany), between November 2017 and December 2019. The inclusion criteria were: inferior turbinate hypertrophy, which is refractory to conservative therapy with corticosteroids. The exclusion criteria were: presence of acute infectious diseases, nasal septum deviation, nasal polyposis, age less than 18 years, patients who did not want to sign an informed consent, and who did not attend to postoperative follow-up visits.
At the first visit, all patients underwent complete ENT examination, including nasal endoscopy and anterior rhinomanometry. Nasal endoscopy was performed to evaluate nasal septum, meautuses, turbinates, and nasal valve. History of nasal obstruction, nasal secretion, headache and hyposmia were noted. Patients were followed up after seven days and one month after surgery. One month after surgery, anterior rhinomanometry was repeated and patients symptoms were noted.
The measurements were done by using anterior rhinomanometry (Rhino 31 computer rhinomanometer, Atmos, Germany) in accordance with the guidelines[5]. The rhinomanometry was carried out in the sitting position, with one nostril of the patient being completely blocked with a nose olive filled with sponge, and the patient was asked to breathe through an unblocked nose olive with the mouth closed. The measurement data were displayed in real time as a rhinogram. The parameter that was recorded and statistically processed was total nose resistance. Although, the nose resistance was calculated at a pressure of 75, 150, and 300 Pa/cm3/s, only the data for the pressure of 150 Pa/cm3/s will be discussed.
This study was approved by the Ethical committee of our institution. All the patients involved were adequately informed about the methods and objectives of this study. They have voluntarily accepted to participate in the survey, and informed consent was obtained from all participants involved in the study.

Statistical analysis:

All the data were analysed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The normality of the distribution of numerical variables was tested by the Kolmogorov-Smirnov test. Differences between the two independent groups were tested with the Mann-Whitney U test. Differences between the two dependent groups were tested with the Wilcoxon test. The McNemar test was used to analyze the presence od nasal obstruction, nasal secretion, headache and hyposmia before and after laser turbinate

Table 1. Number of patients with respect to presence of symptoms before and one month after laser turbinate reduction

	Symptoms after surgery			P*
	YES	NO	Total	
Nasal obstruction before surgery				
YES	14	48	62	<0.001
NO	0	0	0	
Total	14	48	62	
Nasal secretion before surgery				
YES	10	21	31	<0.001
NO	0	31	31	
Total	10	52	62	
Headache before surgery				
YES	4	10	14	0.002
NO	0	48	48	
Total	4	58	62	
Hyposmia before surgery				
YES	4	6	10	0.03
NO	0	52	52	
Total	4	58	62	

reduction. All P values are two sided. The significance level was set at alpha = 0.05.

Results

Out of 62 patients (median age 32.5 years, interqurtile range 23.8-42 years), 34 were males with a median age of 30 years (intequartile range 22.8-35.5 years) and 28 were women with median age of 36.5 years (interquartile range 27- 44.5 years). There was no significant difference in age with respect to gender (p = 0.11, Mann-Whitney U test).

Significantly fewer patients had symptoms of nasal obstruction, nasal secretions, headaches, and hyposmia after laser turbinate reduction compared with before surgery (Table 1).

There was significantly lower value of total nasal resistance after laser turbinate reduction (Table 2).

Synechiae were observed in only one patient after surgery. At first follow-up visit, seven days after surgery, all patients had nasal crusting.

Discussion

Nasal obstruction caused by inferior turbinate hypertrophy is a comorbidity that affects the quality of patients' life[6]. The primary treatment of nasal obstruction caused by inferior turbinate hypertrophy is conservative. Inferior turbinate hypertrophy that is refractory to conservative therapy is one of the most common problems in rhinology. The surgical approach is considered if conservative therapy is not satisfying enough. There are many surgical techniques of inferior turbinate reduction, which confirms the lack of good outcome so far[7]. The diode laser inferior turbinate reduction technique is a method that is minimally invasive and safe, and which was confirmed by several other studies[8-11]. The most frequent symptoms affecting the quality of life in patients with inferior turbinate hypertrophy are nasal obstruction, nasal secretion, sneezing, headache, hyposmia and snoring.

In this study, we have focused on four symptoms: nasal obstruction, nasal secretion, headache and hyposmia.

The results show that there were more males than females with inferior turbinate hypertrophy, which is in line with findings of previous studies[12].

Before surgery, nasal obstruction was present in all of the patients in this study. In the preoperative period, nasal secretion was present in 31/62 (50%), headache was present in 14/62 (22,5%) and hyposmia in 10/62 (16.1%) of the patients. All patients felt subjective improvement postoperatively, and there were a significantly smaller number of patients complaining of nasal obstruction, nasal secretions, headaches, and hyposmia after laser turbinate reduction. This result is consistent with previous research[13]. In the most of the patients there was a significant improvement regarding nasal obstruction and only 14/62 (22.5%) patients complained of nasal obstruction after surgery. The remaining symptoms of nasal obstruction that were present in 14 patients after surgery can be explained with postoperative oedema and crusts. When comparing our results to those of older studies[4,12,13] it must be pointed out that we used anterior rhinomanometry as an objective evaulation method for nasal obstruction, and that there was significantly lower value of total nasal resistance after diode laser inferior turbinate reduction. However, similar to our findings, Min et al. reported that patients in diode laser turbinate reduction group had significant improvement in nasal obstruction and significant decrease in nasal airway resistance 6 months following the surgery[14]. Janda et al.[15], showed that patients in diode laser turbinate reduction group did not have much improvement in the symptom of nasal obstruction during the first

Table 2. Total nasal resistance before and one month after laser turbinate reduction

	Median (interquratile range)		P*
	Before surgery	After surgery	
Total nasal resistance (all patients)	0.83 (0.77-0.93)	0.59 (0.57-0.60)	<0.001

2–4 weeks owing to the postoperative edema and crusting, but they had statistically significant improvement of the nasal airflow and nasal cavity volume 6 months and 1 year after laser surgery respectively. A subjective improvement of nasal airflow was described in 76% of patients after 6 months and 1 year of laser treatment respectively in their study 15. Volk et al. 16, reported that diode laser turbinoplasty led to improvement of nasal airflow of 37.1%, eight weeks after the surgery, and total of 73.2% of patients reported improvement of nasal obstruction and only 12.2% experienced deterioration. Rhee et al.17 compared radiofrequency volumetric tissue reduction and diode laser turbinate reduction, demonstrating improvement of 87.5% patients in laser turbinate reduction group. In both groups the severity and frequency of nasal obstruction and statistically significant improvement was observed at 4 weeks after treatment[17]. In our study majority of patients had significant improvement in nasal obstruction 1 week after surgery and relief of nasal obstruction persisted in 88% of patients one month postoperatively.

One month after the surgery, 52/62 (83,8%) did not complain about nasal secretion. This result is in line with research by Supiyaphun et al.18, who showed that KTP laser turbinate reduction produces significant reduction in rhinorrhea post operatively. The relief in rhinorrhea can be explained with the destruction of vascular submucosa, seromucinous glands and branches of posterior nasal nerve, which plays an important role in hypersecretion. Out of 14 patients who complained of headache before surgery, at the end of the one month follow up period, 10 (71.4%) patients showed an improvement in regards to headache. This may be because of improved nasal patency. Hyposmia was present in 10 (16,1%) patients in our study, before surgery. Out of 10 patients with hyposmia, 7 (70%) of them were not complaining about the symptom one month postoperatively. The improvement may be attributed to the improvement in nasal patency following surgery.

Crusting was the main complaint in the immediate postoperative period, and synechiae were observed only in one patient. In a study by Papon et al.[19], crusting occurred in 41.6% of the patients who underwent Nd: YAG laser turbinate reduction. There was no incidence of septal perforation, epiphora or osteonecrosis of the turbinate bone in our study.

In conclusion, this prospective clinical study dealt with one of the commonest conditions in rhinology; that of inferior turbinate hypertrophy unresponsive to conservative therapy. The diode laser turbinate reduction is minimally invasive, safe, effective in improving the symptoms associated with ITH, and can be performed under local anesthesia. There are no serious intraoperative and postoperative complications.

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Sport and Leisure-time Physical Activity at Patients with Cardiomyopathy

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Abstract:

Cardiomyopathy (hypertrophic, dilated, left ventricular non-compaction and arrhythmogenic cardiomyopathy) is primarily a genetic disease associated with an increased risk of potentially fatal cardiac arrhythmias and sudden death/cardiac arrest during exercise.

The diagnosis of cardiomyopathy is based on complete cardiac evaluation with detailed personal and family history, 12-lead ECG, echocardiogram, cardiac magnetic resonance imaging (CMRI), stress-testing, genetic testing and counseling. The differentiation between the physiological adaptation to exercise and cardiomyopathy is of the mutual importance.

In this review, we outline the latest recommendations published by the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC) on sport and leisure-time physical activity in patients with cardiomyopathy. It offers recommendations for practicing cardiologists and sport physicians managing athletes with cardiomyopathies and provides advice for safe participation in competitive sport at professional and amateur level, as well as in a leisure-time physical activity.

Keywords:

cardiomyopathy, athletes, competitive sport, leisure-time physical activity.

Sažetak:

Sport i slobodno vrijeme u bolesnika s kardiomiopatijom

Kardiomiopatija (hipertrofijska, dilatacijska, hipertrabekulirana lijeva klijetka, aritmogena kardiomiopatija) je primarno genetska bolest povezana s povećanim rizikom potencijalno fatalnih kardijalnih aritmija i iznenadnom smrću/kardijalnim arestom tijekom vježbanja.

Dijagnoza kardiomiopatije bazirana je na kompletnoj kardiološkoj obradi s detaljnom osobnom i obiteljskom anamnezom, učinjenim elektrokardiogramom, ultrazvukom srca, magnetskom rezonancijom srca, stres testiranjem, genetskim testiranjem i savjetovanjem. Razlikovanje fiziološke prilagodbe srca na vježbanje od kardiomiopatije je od neobične važnosti.

U ovom pregledu donosimo najnovije preporuke Sekcije za sportsku kardiologiju pri Europskom društvu za preventivnu kardiologiju (engl. EAPC) o sportskoj i rekreativnoj fizičkoj aktivnosti u bolesnika s kardiomiopatijom. Ona sadrži preporuke za kardiologe i sportske liječnike koji se bave sportašima s kardiomiopatijama i donosi savjete o sigurnom participiranju u kompetitivnom sportu na profesionalnoj i amaterskoj razini, kao i kod rekreativne fizičke aktivnosti.

Ključne riječi:

kardiomiopatija, sportaši, kompetitivni sport, rekreativna fizička aktivnost.

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Introduction

In this review article, we outline the latest recommendations published by the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC) on sport and leisure-time physical activity in patients with cardiomyopathy.[1] Cardiomyopathy is primarily a genetic disease recognized as a cause of exercise-related sudden cardiac death/cardiac arrest (SCD/CA) in athletes. The diagnosis of cardiomyopathy is based on complete cardiac evaluation with detailed personal and family history, 12-lead ECG, echocardiogram, cardiac magnetic resonance imaging (CMRI), stress-testing as well as genetic testing and counseling at some patients. The differentiation between the physiological adaptation to exercise and cardiomyopathy is of the mutual importance. The presence of cardiac symptoms and family history of cardiomyopathy are important red flags for pathology. The current document outlines the pertinent electrical, structural and functional features, which facilitate the differentiation between physiological cardiac adaptation and cardiomyopathy in athletes.[2]

Sports activities are classified according to the cardiovascular changes associated with the exercise training and the long-term impact on cardiac morphology, as follows:

- Skill sport (golf, sailing, car/motor racing, table tennis, shooting, equestrian, archery, curling, scuba diving) includes athlete's neuromuscular coordination and skill (i.e. low dynamic, low static). It increases heart rate, which may be substantial, and only modest blood pressure and cardiac output. The long-term cardiac adaptation is minimal or no morphologic cardiac remodelling;
- Power sport (weightlifting, wrestling, shot-putting, bobsleigh, alpine skiing, snowboarding, sprinting, water skiing, rock climbing) includes explosive muscle power (i.e. high-static exercise). It increases blood pressure and heart rate for several, short repetitive bursts. The long-term cardiac adaptation is increase in LV wall thickness and modest change in LV cavity size;
- Mixed sport (soccer, basketball, volleyball, football, rugby, waterpolo, handball, hockey, tennis, fencing, cricket) is based on the alternate phases of work (either dynamic and/or static) and recovery periods. It increases heart rate and blood pressure, while the long-term cardiac adaptation is an increase in LV cavity size and modest change in LV wall thickness; and
- Endurance sports (cycling, rowing, canoeing, triathlon, pentathlon, cross-country skiing, mid-long swimming, running and skaring) is based on prolonged and intensive dynamic exercise (i.e. high-dynamic, often associated with high-static exercise), with very high cardiac output, through persistent increase in heart rate and blood pressure. The long-term cardiac adaptation is increased LV cavity size and wall thickness.

Hypertrophyc cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is primarily a genetic disease caused by mutations within genes encoding sarcomeric contractile proteins and one of the most common causes of exercise-related sudden cardiac death/cardiac arrest (SCD/CA) in athletes.[3-5] It is characterized by a hypertrophied left ventricle (LV) not related to cardiac or systemic disease (ie. aortic stenosis, arterial hypertension) capable of inducing the same magnitude of LV hypertrophy.[6,7]

Diagnostic evaluation

The most of subjects are asymtpomatic with an abnormal 12-lead ECG (large QRS voltages, T-wave inversions, ST-segment depression, pathological Q-waves), while the other may have a normal ECG and present with angina, syncope, or palpitation.[8-10]

Echocardiographic changes may include unexplained LV hypertrophy with maximum end-diastolic wall thickness ≥16 mm in any segment.6,7 Other individuals with LV wall thickness of 13–16 mm, another family member with HCM, positive genetic testing, or repolarization anomalies, may also have HCM.[2,6,7] The most frequent is an asymmetric pattern of LV hypertrophy, with normal or reduced LV end-diastolic cavity size, while one-third of athletics had the apical variant. [2,6,7,8,9] Normal athletes with physiological LV hypertrophy show a more homogeneous and symmetric distribution of wall thickness and an enlarged cavity (i.e. LV end-diastolic diameter >54mm).[11,12] Tissue Doppler Imaging (TDI) abnormalities may be present in the early stage of the disease, with the septal E'<12 cm/s and lateral E'<12 cm/s as the best diastolic markers for HCM.2,9,12,13 Strain assesment may be used for the detection of mycocardial contraction disturbances.[2] Serial echocardiographic studies demonstrating regression of LV hypertrophy after a 3-month period of complete deconditioning in an athlete without family history of HCM are consistent with diagnosis of physiological LV hypertrophy.[14]

CMRI is recommended in all athletes with equivocal findings (LV wall thickness of 13–16 mm, electrical abnormalities, or symptoms suggestive of cardiac disease in the context of a family history of HCM) and in excluding localized hypertrophy of segments that cannot be visualized adequately with echocardiography (apex, antero-lateral segments). The presence of late gadolinium enhancement (LGE) is suggestive of myocardial fibrosis, and consistent with the diagnosis of HCM.[15,16]

Stress-testing with the presence of symptoms, non-sustained ventricular tachycardia (nsVT), ST-segment depression/T wave inversion, flat systolic blood pressure response (increase <20 mmHg), and a low peak oxygen consumption (<84% predicted) suggest pathological LV hypertrophy.[17]

24-hour holter ECG with the occurrence of nsVT, or any complex ventricular arrhythmias in an athletic individual with a LV wall thickness 13-16 mm also favours the diagnosis of HCM.

Genetic testing is currently recommended only in patients clearly fulfilling the diagnostic criteria for HCM, to enable cascade genetic screening of their relatives. [6,18]

Recommendations

Participation in high-intensity and highly dinamic competitive sports (ie. basketball, football, and swimming) has been considered as an independent risk factor for SCD/CA, due to accompanying alterations in hydration, electrolyte, and acid base status and surges in catecholamine levels.[19] Participation should be considered on an individual basis, after full evaluation of the disease characteristics and risk determinants.

The major clinical features (parameters) which increases the risk of SCD/CA are age, family history of SCD/CA, unexplained syncope, LV outflow tract gradient (LVOT), maximum LV wall thickness, left atrial diameter, nsVT and abnormal blood pressure response to exercise. According to these parameters, patients are classified to low (<4%), medium (4-6%) and high (>6%) 5-year risk.[6]

• Sports participiation is absolutely contraindicated after aborted SCD/CA, symptoms (unheralded syncope), exercise-induced VT, high ESC 5-year risk score, significant increase in LVOT gradient (>50 mmHg), and abnormal blood pressure response to exercise (Class IIb/Level C).

• Adult athletes with mild clinical expressions of HCM and low ESC risk score may selectively be allowed to participate in all competitive sports, with exception of those where occurrence of syncope may be associated with harm or death (Class IIb/Level C). Such athletes should be reviewed annually to assess symptoms and changes in risk profile.

• Genotype positive and phenotype negative (G+P-) individuals may be allowed to engage in all competitive sports (Class IIa/Level C).

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a myocardial disease characterized by a dilated and hypokinetic LV or both ventricles.20 It may be primary (genetic) or secondary (infection, inflammation, toxic, ischaemic, idiopathic).

3.1. Diagnostic evaluation

The 12-lead ECG may be normal, similar to athletic training (atrial enlargement, axis deviation, large QRS voltages in the lateral leads), or may include T-wave inversions, intraventricular conduction defects (including LBBB), and 1st degree atrioventricular (AV) block or pathological Q waves in the inferior and/or lateral leads (lamin A/C or dystrophin mutations). Occurrence of ventricular arrhythmias, particularly during exercise, may be common.[20]

Echocardiography may reveal the LV cavity enlargement, with more spherical shape, and consequent mitral annulus dilatation, distortion of leaflets and resultant valvular regurgitation. Also, LV systolic function is reduced, the ejection fraction (LVEF) is usually below 50%, and regional wall motion abnormalities are occasionally present.21,22 Elite athletes frequently demonstrate an enlarged LV cavity size.23 It should be interpreted in the context of the sporting discipline and body size (it is advised to relate LV cavity to body surface area) and is usually associated with increased wall thickness.[2,23,24] The presence of concomitant RV remodelling, with normal RV function is consistent with a physiological LV remodelling.2 At athletes with an enlarged LV and mildly reduced LV ejection fraction (45-55%) regional wall motion abnormalities and abnormal diastolic function may support DCM.[25] Also, an increase in LV ejection fraction (>10–15%) during exercise echocardiography or CMR supports the diagnosis of physiological LV dilatation. [26,27]

CMR is the gold standard for the assessment of biventricular dimensions and function in equivocal cases. Late gadolinium enhancement (LGE) identifies areas of replacement fibrosis and the presence of mid-wall LGE and its extent has emerged as an important tool in risk stratification of DCM.[28-30]

Stress-testing may be inconclusive in the early stages of the disease, but the presence of a low peak oxygen consumption in an athlete with an enlarged LV and borderline/low LV ejection fraction supports DCM.

24-hour holter ECG may detect arrhythmias in approximately 30% of DCM patients, even in the presence of only mildly dilated LV cavity, which is important in risk stratification. [30,31]

3.2. Recommendations

Participation in intensive exercise programmes and competitive sport should be considered on an individual basis, after evaluation of the disease characteristics and risk determinants.

• The presence of LV cavity dilatation with preserved LV function, in the absence of a family history of DCM, abnormal ECG patterns, and atrial/ventricular tachyarrhythmias should be considered to represent expression of physiological cardiac remodelling rather than DCM. No restriction to competitive sports is applicable to this cohort of athletes (Class IIa, Level B).

• Sports participation is absolutely contraindicated at athletes with a diagnosis of DCM who are symptomatic, or have LV ejection fraction <40%, or extensive LGE (i.e. >20%) on CMR and/or frequent/complex ventricular tachyarrhythmias on 24-holter ECG and stress-testing, or history of unexplained syncope. These patients should be advised to limit their exercise programmes to leisure-time activities and undergo regular clinical surveillance, consistent with current recommendations for the management of DCM (Class III, Level C).

• Athletes with an unequivocal diagnosis of DCM, but mildly reduced LV systolic function (EF ≥40%) may selectively engage in all competitive sport (with the exception of those where occurrence of syncope may be associated with serious harm or death), if they are asymptomatic, without prior history of unexplained syncope, and without frequent/complex ventricular tachyarrhythmias on 24-hour holter ECG and stress-testing (Class IIb, Level C).

• Irrespective of the severity of LV dysfunction and dilatation, patients with a family history of SCD/CA and/or those

previously identified during cascade screening for familial DCM, with mutations that are associated with an increased risk of life-threatening arrhythmias (such as Lamin A/C or Filamin C mutation), should not participate in competitive sports (Class IIb, Level C).

• In the absence of evidence for DCM, the G+P- individuals may be allowed to engage in all competitive sports, with the recommendation to undergo a periodical evaluation, at least annually, in order to early detect the phenotypic expression of the disease (Class IIa, Level C).

Left ventricular non-compaction cardiomyopathy

Left ventricular non-compaction (LVNC) is a genetic disease characterized by prominent trabeculations within the LV myocardium, separated by deep recesses, and usually associated with LV dysfunction and ventricular tachyarrhythmias.32 At athletes, it is diagnosed by the identification of a prominent trabecular pattern by cardiac imaging.[2]

4.1. Daignostic evaluation

At 12-lead ECG abnormalities include T-wave inversion, ST-segment depression and intraventricular conduction delay (ie. LBBB).[33]

Echocardiography and CMR reveal the presence of a two-layered structure of the myocardial LV wall, with increased non-compacted to compacted LV layer ratio (>2 and >2.3 for echocardiography and CMR, respectively).[2,3,4,5,34,35] Additionaly, we can find LV systolic dysfunction (with LVEF< 50%) and abnormal myocardial relaxation (e ├<9 cm/s at TDI).36

Increased cardiac preload may simply unmask pre-existing trabeculations and make them more prominent. Thus, athletes frequently show increased trabeculations in the LV cavity, and up to 8% may fulfil the morphological criteria for LVNC.36 But, only minority of them (0.9%) exhibit other clinical abnormalities supportive for diagnosis of a cardiomyopathy (abnomal 12-lead ECG, mildly reduced LVEF, family anamnesis); these athletes need to be thoroughly investigated through CMR, exercise echocardiography and 24-hour holter ECG.[2,36-38]

4.2. Recommendations

The clinical outcome of LVNC is variable, related to the magnitude of LV dysfunction and ventricular arrhythmiass. Adverse consequences are largely associated with the severity of hypertrabeculations, LV systolic dysfunction or major ventricular tachyarrhythmias.36,38-41

• Athletes with incidental discovery of LV hypertrabeculation should not be diagnosed as LVNC in the absence of symptoms, positive family history, abnormal ECG patterns and, most importantly, impaired LV function. In such cases, no restriction for all competitive sports apply (Class IIa/Level B).

• Athletes with unequivocal/reasonable diagnosis of LVNC but near-normal LV systolic function may participate in all competitive sports (with the exception of those where occurrence of syncope may cause serious harm or death), if they are asymptomatic, without frequent and/or complex ventricular arrhythmias, or nsVT on 24-hour ECG and exercise stress-testing, and no prior history of unexplained syncope (Class IIb, Level C).

• Athletes with an unequivocal diagnosis of LVNC and impaired LV systolic function and/or frequent and/or complex ventricular arrhythmias, or nsVT on ambulatory monitoring or exercise stress-testing should not participate in competitive sports (Class III, Level C). These patients should be advised to limit their exercise programmes to leisure-time physical activities and remain under regular clinical surveillance.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is caused predominantly by mutations in genes encoding desmosomal proteins. It is characterized by fibro-fatty replacement of the right ventricle and/or LV myocardium, and clinically by life-threatening ventricular tachyarrhythmias triggered by exercise.[42-44]

Diagnostic evaluation

The 12-lead ECG is mostly abnormal.45 In the right-dominant variant, the most common abnormalities (leads V1-V3) are inverted T-waves, prolonged QRS duration >110 ms with right bundle branch block (RBBB) pattern and a delayed upstroke (>55 ms) of the S wave, an epsilon wave, and premature ventricular beats (PVBs) with LBBB pattern (vertical/horizontal axis). In the left-dominant variant, the most common abnormalities are low voltages of R/S wave in the limb leads, the presence of diffuse T-wave inversion in the antero-lateral and inferior leads, and PVBs with RBBB pattern (superior axis).[42,45]

Echocardiography and CMR may show an enlarged RV and/or LV cavity and wall motion abnormalities, which are evident only in advanced stage of the disease.[2,46] It is important to emphasize that CMR has superior diagnostic value in identifying segmental morphological abnormalities, consistent with fibro-fatty replacement, including regional wall motion anomalies.[2,42,47]

As we already mentioned, endurance athletes develop an enlarged RV and LV cavities, both with preserved shape and the absence of segmental thinning or wall motion abnormalities, as consequence of the physiological adaptation to chronic exercise training.[2,48,49] So, pathological RV remodelling needs to be associated with wall motion abnormalities to suggest ARVC.50

Exercise echocardiography/CMR may be useful for discriminating between physiological RV enlargement from pathological RV myocardial remodelling, ie. an increase in LV ejection fraction (>10–15%) during exercise echocardiography or CMR

supports the diagnosis of physiological LV dilatation.[26,27] During stress-testing and 24-hour holter ECG, exercise performance may be preserved. However, ventricular arrhythmias are usually present at an early stage of the disease, and are usually triggered by exercise.

Recommendations

The dilation of the right ventricle associated with regular exercise training may lead to myocardial damage and subsequent fibro-fatty replacement, thereby triggering the morphological features of the disease. Ventricular tachyarrhythmias and sudden death in ARVC commonly occur in association with exertion and ARVC accounts for a substantial proportion of deaths in young athletes.[42,51] These considerations are clinically relevant and support a restrictive advice regarding the participation in intensive exercise programmes and competitive sports in affected ARVC patients. Conversely, recreational exercise programme conveys a reduced risk, such as that of patients physically inactive.

- Athletes with unequivocal or probable diagnosis of ARVC should not participate in competitive sports. These patients should be advised to limit their exercise programmes to leisure-time activities, and remain under clinical surveillance (Class IIa/Level C).
- Athletes who are genetic carriers of pathogenic ARVC -associated desmosomal mutations (even in the absence of phenotypic expression of the disease) should not participate in competitive sports. These athletes should be advised to limit their exercise programmes to leisure-time activities and remain under clinical surveillance (Class IIa/Level C).

Athletes with cardiomyopathy and implanted ICD

The indications for an ICD in competitive athletes should not differ from the general population with a diagnosis of cardiomyopathy. Specifically, the desire of the athlete with cardiomyopathy to compete should not constitute a primary (or unique) indication for ICD implantation (Class IIa/Level C).
Recommendation for sports participations in an individual with an ICD should be based on the fact that the arrhythmogenic substrate of the cardiomyopathy remains unaltered and the ICD does not prevent insurgence of a malignant arrhythmia, especially during intensive exercise, although it will prevent SCD/CA (Class IIa/Level C).
Participation in competitive sports may be considered in the individual patient with cardiomyopathy and ICD, after careful consideration of the type of underlying cardiomyopathy (for instance, ARVC represents reason for contraindication). The decision to participate in competitive sport should be made after full disclosure of the risks of sport participation with ICD, including the likelihood of appropriate/inappropriate shocks, leads failure, and the device-related trauma (Class IIb/Level C). With regard to type of sport, selected patients with cardiomyopathy and ICD may participate in all sport, with exception of sports with bodily contact, such as rugby, American football and martial arts in order to avoid damage to the generator box and the cardiac leads.[52] Patients with cardiomyopathy and ICD should avoid sports where transient syncope from an arrhythmia or the jolt of a shock may cause serious injury or death, such as mountain climbing, surfing, motor racing, or deep-sea diving.[52,53]

Leisure-time physical activity in patients with cardiomyopathy

Exercise prescription in all individuals with cardiomyopathy is appropriate, except some exceptions (some patients with ICD, see section 6).[53-55] It should be individualized, balancing the clinical status of the patient with the type, intensity and frequency of the physical and/or sport activity being considered. Exercise prescription should be based on performed exercise testing and complete cardiac evaluation, aiming for a submaximal, well-tolerated level of exercise intensity.
Patients should be fully informed about disease, its clinical presentation and variety of symptoms that may occur in association with exercise. Exercise should be started with a warm-up period and a cool-down period at the end of the session. Exercise programmes with progressive increase in intensity should be closely monitored by the physician (ideally in contact with the coach). Exercising should be avoided in adverse environmental conditions without prior acclimatization. Patients with cardiomyopathies should be encouraged to exercise in environments equipped with an automatic defibrillator and personnel trained in its use.[53-55]

Conclusion

The diagnosis of cardiomyopathy is based on complete cardiac evaluation with detailed personal and family history, 12-lead ECG, echocardiogram, CMRI, stress-testing as well as genetic testing and counseling at some subjects. The differentiation between the physiological adaptation to exercise and cardiomyopathy is of the mutual importance. Participation in intensive exercise programmes and competitive sport should be considered on an individual basis, after evaluation of the disease characteristics and risk determinants. Exercise prescription in all individuals with cardiomyopathy is appropriate, except some exceptions (ie. after implanted ICD).

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Virtual Reality in Medicine

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Abstract:

For the last few years, we have been witnessing a surge of commercially available virtual reality systems that are on a high grade of usability for both professional and home-based application. Early examples of virtual reality systems used in the medical field were highly sophisticated, expensive and hard to use devices. Now we have reached a point where both prices and ease of use are at a level that it can be easily applied even as a home therapy system. The aim of this paper is to give an overview of the use of virtual reality in selected practical medical fields: psychotherapy, rehabilitation therapy, medical training, and pain management. This review demonstrates different fields of medicine where virtual reality is already an established tool and medical fields where it has just started to become an indispensable tool for a modern-day medical practitioner. We find virtual reality systems to be powerful immersive tools that allow both practitioners to improve their skills and experiences without any damage to the patients and patients to receive better and more personalised care and treatment.

Keywords: virtual reality; phobia therapy; rehabilitation therapy; medical training; pain management.

Sažetak:

Virtualna stvarnost u medicini

Posljednjih nekoliko godina svjedočimo porastu komercijalno dostupnih sustava virtualne stvarnosti koji su na visokoj razini iskoristivosti kako za profesionalnu tako i za kućnu upotrebu. Od ranih primjeraka sustava virtualne stvarnosti u medicini koji su korišteni kao izuzetno sofisticirani, skupi i zahtjevni za upotrebu, došli smo do trenutka u kojemu su i cijena i jednostavnost upotrebe na tako visokoj razini da se koriste čak i kao terapija u domu. Cilj ovog rada bio je istražiti dosadašnja istraživanja koja su se bavila upotrebom virtualne stvarnosti u nekoliko izabranih medicinskih područja: psihijatriji, rehabilitacijskoj terapiji, medicinskoj izobrazbi i kontroli boli. Ovaj rad prikazuje različita područja medicine gdje je virtualna stvarnost već afirmirani alat te ona područja gdje je tek na početku profiliranja kao neizostavni alat u medicini. Smatramo kako sustavi virtualne stvarnosti imaju visoku razinu uvjerljivosti što omogućava medicinskom osoblju poboljšavanje vlastitih vještina i iskustava bez štete po bolesnika, dok bolesniku omogućuje prilagođenu i bolju njegu i liječenje.

Ključne riječi: virtualna stvarnost; terapija fobija; rehabilitacijska terapija; medicinski trening; kontroliranje boli

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Introduction

Virtual reality (VR) is defined as a simulated experience that is either trying to simulate the real world or create a completely imaginary world. It is usually achieved by using a head mounted display (HMD), earphones and a couple of controllers. Most modern VR systems include an HMD that supports 6 degrees of freedom and controllers that allow the user to interact with the simulation using both of their arms (Figure 1). It means that with most systems users can freely move about and interact with the simulation with a high level of immersion. In the broader sense, VR also encompasses augmented reality (AR) and mixed reality (MR).

VR has been used as a simple show of concept or even in professional applications since the 1960s and has been growing in function and ability to immerse users ever since[1]. With technological advancement came better and more believable systems. While the use of VR in medical field, such as psychotherapy, dates back to 1995 with the fear of heights study, the cost of such a hardware system was around $150,000 and required a graduate student in computer science to operate it[2]. In year 2000 the fear of flying study was conducted with the hardware cost of around $20,000 and the therapists themselves could operate the system[3]. Year 2010 was the rebirth of consumer level VR and in 2016 first commercial room scale VR systems were available to the public. Today the hardware needed costs roughly $1,000 and can be run by virtually anyone[4,,5].

With these relatively recent advancements in VR combined with the lower cost and easier manageability, more options and easier way of VR implementation in different medical applications is possible.

The aim of this review is to give an overview of the use of VR in selected practical medical fields: psychotherapy, rehabilitation therapy, medical training, and pain management. In the search of scientific and review papers the following keywords were searched on the PubMed search engine: virtual reality, therapy, training, pain management, rehabilitation. For the purpose of this review articles published in English between 1995 and 2019 were selected according to relevance for the topic.

Flight phobia therapy

VR is already considered an effective tool for the treatment of many psychological disorders[6]. There are two advantages of VR in the treatment of these afflictions: the allowed control of the environment and the flexibility. Virtual world allows for greater possibilities compared to the real-world exposure therapy with the added protection and safety. The biggest advantages of VR can be seen in the area of phobias while carrying out exposure therapy. Although exposure therapy is the technique of choice for phobias, it is often rejected for being too aversive in the eyes of the patients. This is the problem that VR can alleviate with the provided control, flexibility and safety[7]. Virtual reality exposure therapy (VRET) is not a new form of therapy, but rather a form of technological adjunct[8].

Advantages offered by VR compared to in vivo exposure therapy are efficacy, preservation of patient's privacy, increased control of the exposure and increased comfort for both the therapist and the patient. Disadvantage of this form of therapy is that some patients are unable to immerse themselves into the VR. In addition, there is a lack of data about who makes a good candidate for VR opposed to in vivo exposure[9].

In recent years 10 randomized controlled studies were conducted, seven clinical trials and few case studies being performed comparing VR exposure therapy to different forms of treatment for flight phobias. Results presented in these studies have shown that VRET for flight phobia reduces symptoms of fear, both physiological and cognitive as well as behavioural avoidance in the real world. All of these studies have shown that waitlist control conditions have been outperformed by the VRET and that VRET results are similar to those shown after in vivo exposure, which is the gold-standard treatment for flight phobia[10].

Posttraumatic stress disorder (PTSD) therapy

According to American Psychiatric Association: "PTSD requires exposure to a traumatic event and symptoms from each of the 4 PTSD symptom clusters, including: intrusive symptoms, avoidance symptoms, negative alterations in cognitions and mood, and alterations in arousal and reactivity"[11]. Today, especially in war-affected areas, PTSD represents a significant disease burden[12]. As an example, epidemiological data from the Republic of Croatia indicates that PTSD has a 12-month prevalence rate of 6.67%[13].

In vivo PTSD exposure treatments are difficult, seldomly expensive and sometimes impossible to conduct. On the contrary, a perfect stand-in would be VRET, which can replicate and easily repeat the situations that have led the patients to develop the disorder. Also, the therapist can easily control all the factors within the VRET. One of the benefits of VRET as a treatment option for PTSD is the appeal to the video game generation[10].

The existing literature of VR exposure therapy for PTSD provides support for its efficacy. According to it VRET shows significantly better results than wait list controls and comparable to the standard exposure therapy. Treatment impact on other commonly occurring comorbid symptoms should be incorporated in future research on VRET for PTSD because it might reveal other effects of treatment or reasons for caution due to possible unforeseen side effects[14].

Rehabilitation therapy

It has been shown that important aspects, which propagate positive impact on rehabilitation and functional recovery of the patients with spinal cord injury (SCI), are training variety, motivating training tasks and movement repetition, while the subject's treatment location is of no importance[15]. A study of feasibility of in-home training with 12 patients that have an in-

complete SCI (iSCI) was performed using a home-based, mobile version of a lower limb VR training system. During the 4 weeks of home-based training motivating scenarios and combined action observation and execution were performed with virtual representation of the legs and feet. The study has shown that unsupervised VR training system at home is a beneficial form of functional training for patients with chronic iSCI, which also suggests that it could be used as a neurorehabilitation tool[16].
A study on 8 patients with chronic complete spinal cord injury was performed over 12 months using a multi-stage brain-machine interface system. The system included intense immersive virtual reality training, visual-tactile feedback and walking with two EEG-controlled robotic actuators (lower limb exoskeleton with tactile feedback capability). With the conclusion of the study all 8 patients experienced neurological improvements in somatic sensation in multiple dermatomes and have also regained voluntary motor control in key muscles below the level of the injury resulting in marked improvement in their walking index. The result was that half of the patients were upgraded to an incomplete paraplegic at the end of the experiment[17].

Medical training

Several relate studies that showed better performance in medical practitioners who were trained with augmented reality than the ones trained in traditional ways[18,19]. Jaeger et al. showed that residents which were using computerized training platform that displays an ultrasound image and real-time needle position in a three-dimensional (3D) anatomical model as an example of AR had better performance metrics on ultrasound-guided lumbar puncture models[20]. Yeo et. al. preformed an experiment on 40 volunteers that were divided into two groups. The aim of their study was to determine if learning the correct placement of a needle for percutaneous facet joint injection would be easier using AR image overlay and laser guidance systems. The overlay group that was trained using AR assistance had a statistically significant higher success rate, and less tissue damage potential[18].
Study by Saratzis A. et al. reported that a VR simulation training for endovascular aneurysm repair, that included 16 vascular surgery trainees, led to significantly decreased procedure duration, fewer complications, and improved selection of device size[21].
Another study, this time on communications skills, showed similar results. Forty-five physician trainees were included in a VR simulation training study to address vaccine hesitancy among parents of paediatric patients. The participants were put into a simulated situation faced with a graphical character that represented a vaccine hesitant parent. The study resulted in better performing physicians that helped reduce vaccine anxiety among parents for the VR simulation training group[22].
As shown in a tech demo in late 2018 using mixed reality (VR integrated with the physical surroundings) allowed six people to share a common VR experience, which leads us to believe that an operating room team training for collaborative learning, at least from the technological standpoint, is possible[23].
While most simulators are made for surgical procedure training, some are used to plan the surgery. Patient-specific VR simulation tool allow for a far superior preparation of surgeons without the risk of harming the actual patient[19]. There is an abundance of papers showing VR/AR advantages in preoperative planning compared to currently available systems[24]. The VR systems allow for the operator to examine the actual patient's CT scan reconstructed in full 3D and plan in high definition course of the procedure.
Although limited evidence is available and there is a significant heterogeneity in the methodology in VR simulation based surgical training, in summary all the recent studies showed a positive association between VR based surgical training and increased surgical skill acquisition[25].

Pain management

Several studies suggest that VR-based distraction therapy can reduce the standard pharmacotherapy in acute pain patients, procedural pain patients and the psychological distress induced by the severity of the medical condition. The best results were reported with immersive VR-based gaming applications[26].
Patients following acute traumatic injury, after receiving VR hypnosis therapy, reported reductions in pain intensity and unpleasantness both immediately and 8 hours later[27].
In the management of burn wound care, as an addition to narcotic pharmacotherapy, VR was used as a distraction therapy during wound debridement. All participants reported decreased paint unpleasantness, lower pain intensity, less time thinking about pain and increased enjoyment. In addition, patients reported pain reduction as VR therapy increased[28].
Similar benefits were shown for paediatric patients while undergoing subcutaneous vascular port venous access as an adjuvant to the standard analgesic pharmacotherapy. Patients using VR-based distraction therapy had reduction in pulse rate during the procedures, reduced patient-reported pain and parent-perceived patient pain and anxiety[29, 30].
In two oncology patients studies (women with breast cancer and patients with metastatic cancer), while undergoing their respective therapies, VR distraction therapy was used and showed significant reduction in patient-reported fatigue and anxiety [131, 32].
Compared to the previously mentioned studies concerning acute and procedural pain there have been a rather few studies on using VR in chronic pain management. Thirty participants with various chronic pain conditions were subject to a 5-minute VR application. The pain was reduced to some degree during or after the session for all participants. VR-based therapy showed as a promising non-opioid treatment option for chronic patients [33].

Conclusion

Although virtual reality systems are neither new technologies nor their use in medicine is a novelty, the costs and difficulty of use

restricted it from being commonly used in everyday practice and medical training. With the development of low cost, but high quality and easy to use virtual reality systems, we are at a point in time where physicians can and are devising new and innovative ways of using it.

The studies we reviewed are a good prediction of a bright future virtual reality systems should and will have in everyday medical profession, still new prospective studies that encompass larger samples should be conducted to substantiate the results.

Virtual reality systems have been here for a while and it is only a question of time when they will become an integral part of medicine, from education to improving established methods and introducing completely new ways of tackling our day-to-day professional problems.

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Neonatal Seizures

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Abstract:

Neonatal convulsions may be the first, in some cases, the only clinical sign of neonatal central nervous system disorder. As such, they require prompt evaluation to determine the cause, as the underlying may have influential causes. Furthermore, since they may contribute to further brain injury, they require immediate treatment. Neonatal convulsions have unique clinical features and their presentation differs from convulsions in older children. They may include focal clonic, focal tonic, myoclonic and epileptic spasms. Furthermore, they may present with abnormal eye movements, lip smacking, swimming or pedaling movements, or apnea. Moreover, nonconvulsive paroxysmal movements are also common in the neonatal population and are sometimes difficult to distinguish from convulsions. Continuous electroencephalogram is the gold standard (cEEG) for the detection of neonatal convulsions. In addition to continuous electroencephalogram (cEEG), amplitude EEG (aEEG) is a useful bedside tool. Neonatal convulsions carry a high risk for early mortality, but are also a negative predictive factor for the development of motor and cognitive disorders and epilepsy.

Keywords: seizures, newborn, neonatal seizures, electroencephalography, epilepsy, developmental disability

Sažetak:

Neonatalne konvulzije

Neonatalne konvulzije mogu biti prvi, u nekim slučajevima i jedini klinički znak poremećaja središnjeg živčanog sustava u novorođenčadi. Kao takve zahtjevaju promptnu evaluaciju u svrhu određivanja uzroka jer u podlozi mogu biti uzroci na koje se može utjecati. Nadalje, s obzirom da mogu pridonijeti daljnjoj ozljedi mozga, zahtjevaju neodgodivo liječenje. Neonatalne konvulzije imaju jedinstvene kliničke značajke te se njihova prezentacija razlikuje od konvulzija kod starije djece. Mogu uključivati fokalne kloničke, fokalne toničke, miokloničke i epileptičke spazme. Nadalje, mogu se prezentirati abnormalnim pokretima očiju, pokretima mljackanja, plivajućim ili pedalirajućim pokretima ekstremiteta ili apnejom. Štoviše, nekonvulzivni paroksizmalni pokreti također su česti u neonatološkoj populaciji i ponekad ih je teško razlikovati od konvulzija. Kontinuirani elektroencefalogram je zlatni standard (cEEG) za detekciju neonatalnih konvulzija. Osim kontinuiranog elektroencefalograma (cEEG), amplitudni EEG (aEEG) je koristan i praktičan alat za dijagnozu neonatalnih konvulzija. Neonatalne konvulzije nose visoki rizik za ranu smrtnost, ali su i negativni prediktivni čimbenik za razvoj motoričkih i kognitivnih poremećaja te epilepsije.

Ključne riječi: konvulzije, novorođenče, neonatalne konvulzije, elektroencefalogram, epilepsija, poremećaji razvoja

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Neonatal convulsions are often a manifestation of a significant neurological disease, but also a predictor of adverse neurological outcomes in the newborn. Rapid diagnosis, detection of causes and prompt intervention are necessary to minimize cardiorespiratory instability and correct treatable causes of seizures. Seizures are generally defined as synchronous excess discharge (depolarization of neurons in the brain). This definition may be too restrictive when applied to neonatal convulsions. According to some authors, it would be more appropriate to define neonatal convulsions as paroxysmal changes in neurological function (behavioral, motor, or autonomic). This definition covers both clinical changes that correlate with epileptiform abnormalities on EEG but also stereotypical, paroxysmal activities that are not clearly related to changes in EEG[1]. The incidence of neonatal convulsions is estimated to be 1-5 per 1000 births[2-4]. However, these studies do not take into account the low sensitivity of the clinical diagnosis of convulsions alone, and continuous prolonged electroencephalogram is not widely available. Therefore, the true incidence of neonatal convulsions remains unknown, which is probably even higher than estimated[5-6]. Compared to older children, clinical presentation and EEG findings in infants are significantly different as a consequence of the immature stage of brain development. Furthermore, neonatal convulsions are rarely idiopathic. The differential diagnosis of neonatal convulsions is broad, and includes structural, metabolic and genetic causes. Acute symptomatic causes including hypoxic-ischemic encephalopathy, infections, intracranial hemorrhage, transient metabolic disorders or thrombosis are much more common causes than neonatal onset epilepsies that may be due to malformations or are genetically conditioned. Rare causes include congenital metabolic defects, B6 vitamin deficiency epilepsies, and neonatal epilepsy syndromes, but these must be considered in the case of refractory seizures[7-8]. Neonatal convulsions carry a high risk of early mortality, with motor and cognitive disorders as well as epilepsy often resulting in survivors[9]. 85 percent of neonatal convulsions are thought to be "symptomatic", hence, the consequences of a specific identifying cause. These causes are generally categorized as: neonatal encephalopathy, structural brain injury (including ischemic and hemorrhagic stroke), metabolic disorders (glucose and electrolyte abnormalities), and systemic and central nervous system infections[10-14]. Epilepsy syndromes account for the remaining 15 percent of all neonatal convulsions. Examples of epilepsy syndromes include benign familial neonatal epilepsy, early (neonatal) myoclonic encephalopathy, and early infantile epileptic encephalopathy. Neonatal convulsions have unique clinical features compared to convulsions in older infants and children. An immature brain is more prone to convulsion initiation, convulsion maintenance, and expansion[15]. Neonatal convulsions are focal (unifocal or multifocal), rarely generalized. The clinical manifestations of neonatal convulsions are focal-clonic, focal-tonic, myoclonic and epileptic spasms. Nonconvulsive paroxysmal events are very common in the neonatal population and are sometimes difficult to distinguish from convulsions. Most of neonatal convulsions are subclinical, hence, without clinical manifestation[14, 16-20]. Unless the convulsive discharges originate or migrate in the motor cortices, they will not be clinically visible as abnormal movement. This is especially seen in immature premature infants. Focal-clonic convulsions consist of repetitive, rhythmic contractions of specific muscle groups of the extremities, trunk, or face. They have clinical correction on EEG. Compared to non-convulsive movements such as clonus or tremor, movements in focal-clonic convulsions are more slower and rhythmic. They differ from tremors and clones in that they cannot be stopped when grasping the extremities. Tremor and clonus can be stopped by gripping parts of the body, and tonic-clonic convulsions cannot, so muscle twitching can be felt in the affected limb. If all four extremities are affected, the appearance of generalized convulsions can be obtained, but careful examination reveals that the extremities do not move synchronously. Focal-tonic convulsions are rarer and are characterized by sustained but transient asymmetrical posture of the trunk or extremity and tonic deviation of the eyes. In term newborns, when the eyes are affected, conjugate deviation of the eyes is observed to one side. Focal-tonic convulsions also correlate with EEG. Tonic convulsions are a hallmark of several neonatal epilepsy syndromes (e.g., Ohtahara syndrome, KCNQ2 encephalopathy). Myoclonic convulsions in infants represent a diverse range of movements, some of which are epileptic in origin and others non-epileptic. Movements in myoclonic convulsions are characterized by contraction of muscle groups of well-defined regions: proximal or distal limbs, whole limbs, trunk, diaphragm or face. Myoclonic events differ from clonic convulsions at the correct rate of recurrence. Some forms of myoclonic seizures are correlated with EEG, others do not. This is because some myoclonic convulsions are generated at the cortical level, while others are generated more caudally in the subcortical structures, limbic system, brainstem, spinal cord, or neuromuscular junction. Some myoclonic convulsions can be provoked by stimulation and suppressed by trapping the extremity or repositioning the body. Epileptic spasms are rare in infants and primarily involve the trunk muscles and limbs. Neonatal convulsions may be manifested by symptoms of the autonomic nervous system, such as changes in heart rate, respiration, blood pressure, salivation or dilation of the pupils[21-23]. However, their isolated appearance is rare and usually occurs with other motor manifestations of convulsions[24-25]. Apnea can also be a clinical manifestation of neonatal convulsions. It is sometimes difficult to distinguish neonatal convulsions from nonconvulsive paroxysmal events or normal newborn behavior, and EEG is required to differentiate them. Clinical observation is inadequate for the correct diagnosis of neonatal convulsions. Neonates with subclinical seizures will not receive adequate therapy without EEG findings, while those with paroxysmal events that are not convulsive will be exposed to

unnecessary medication. Examples of non-convulsive events include various motor automatisms and tonic posture. These events are based on the physiology of reflexes[24, 26]. Other paroxysmal events in the newborns that may be confused with convulsions are tremor, tremor or clonus. Nonconvulsive events do not have correlations or changes in EEG, they can sometimes be triggered by stimulation of the newborn, and can typically be suppressed by grasping or repositioning part of the body[24-26]. Normal neonatal behaviors include stretching, non-specific random movements that may be sudden (especially in premature newborns), random sucking movements. The infant may normally have physiological myoclonus during active sleep[27]. In healthy newborns, the myoclonus disappears when the newborn is awake, appearing exclusively in sleep. The use of EEG has shown that not all clinically suspected events are convulsive and that most convulsions are actually subclinical. Therefore, the diagnosis of neonatal convulsions is primarily based on the EEG. Neonatal convulsions are defined as an abnormal EEG pattern involving an amplitude of > 2 microvolts and lasting longer than 10 seconds[28]. "Electro-clinical convulsions" occur when clinical convulsions overlap temporarily with an abnormal EEG record. "Subclinical convulsions" are convulsions that are confirmed on the EEG without any associated clinical signs. Clinical events that have no correlation on the EEG record are not convulsions. The gold standard for the diagnosis of neonatal convulsions is multichannel video EEG monitoring[29]. A routine 60-minute EEG recording is considered insufficient to screen neonatal convulsions. For infants at high risk for convulsions, the American Clinical Neurophysiology Society recommends EEG monitoring for 24 hours[29]. If convulsions are not verified within 24 hours, recording may be interrupted. Exceptions are neonates with hypoxic-ischemic encephalopathy (HIE) who are on therapeutic hypothermia[29,30]. If convulsions are identified, recording will continue until the infant has no convulsions for 24 hours. When video-EEG monitoring is not available, routine EEG recording with simultaneous observation by a clinician or EEG technician may provide important information. The third option is amplitude-integrated EEG (aEEG) with 1 or 2-channel EEG. aEEG is not an adequate replacement for multi-channel EEG video. All electrographic convulsions cannot be detected by this modality due to limited scalp coverage[31], low amplitudes and slow frequencies of typical seizures[32]. Artifacts can also present a problem. The sensitivity and specificity of the examination ranges from 25 to 80 percent[32,33]. However, if continuous EEG or standard EEG is not available, aEEG may be a useful tool[34]. If a diagnosis of neonatal convulsions is made, the etiology needs to be identified. Possible risk factors for axonal injury such as fetal cardiac decelerations, presence of meconium, low Apgar value and placental abnormalities need to be identified. Other risk factors include macrosomal infant, maternal obesity and abnormal fetal presentation. The anamnesis should include information on possible previous maternal miscarriages (congenital anomalies), gestational diabetes (neonatal hypoglycaemia), sexually transmitted diseases or other infections (neonatal transmission of infection), information on maternal diseases during pregnancy (fever and maternal rash may suggest viral infections)), data on taking illicit substances, data on thromboses or coagulopathies (neonatal stroke). The family history must include information about eventual mortality of an unknown cause in the family or relatives, and information on consanguinity (inherited metabolic disorders), the presence of epilepsy in the family, especially neonatal (benign familial neonatal epilepsy). The examination should include evaluation of vital signs, measurement of head circumference, presence of birthmarks, somatic abnormalities, dysmorphia of the face or signs of infection (strained fontanella suggests meningitis, rash in TORCH infection), mental status, state of consciousness, cranial nerve examination, presence of asymmetry in spontaneous movements or abnormal tone (structural brain lesion or neonatal encephalopathy). Typical presentation of inherited metabolic disorders include feeding difficulties, respiratory distress and lethargy that occur several days after the initial symptom-free period. Hypoglycemia and acidosis should also arouse suspicion of inherited metabolic disorders. Some infants present with isolated convulsions. Signs of systemic or central nervous system infection in the newborn may be nonspecific. If infection is suspected, cultures should be taken and antibiotic therapy should be initiated at the dose recommended for the treatment of meningitis, possibly including acyclovir according to clinical judgment. Lumbar puncture is recommended in cases of positive culture and in cases of suspected sepsis, since clinical signs may be absent in cases of central nervous system infection in the newborn, and infection is one of the most common causes of neonatal convulsions. In cases of refractory convulsions, lumbar puncture is also recommended to rule out inherited metabolic disorders. MRI is the recommended imaging examination that should be performed with all neonatal convulsions to evaluate the presence of intracranial hemorrhage, ischemic stroke, brain malformations, or the presence of hypoxic-ischemic damage. If the infant is unstable or unable to adjust for MRI, then transcranial ultrasound should be performed to evaluate the presence of intracranial hemorrhage or hydrocephalus. CT is not recommended in newborns[29, 30]. Genetic testing is recommended for newborns with epilepsy who have not identified an acute symptomatic cause based on history, clinical examination and neuroradiological imaging. The most common genetic cause is KCNQ2 encephalopathy. It is recommended to use genetic panels for epileptic encephalopathies and brain malformations, or to screen the entire genome instead of testing for single mutations.

Neonatal convulsion therapy must be directly targeted at the cause to prevent further brain damage. This is especially important for convulsions associated with inherited metabolic disorders. Neonatal encephalopathy (hypoxic-ischemic encephalopathy) is the most common cause of neonatal convulsions 14. Newborns with convulsions should be presumed to have an infection until proven otherwise. Central nervous system infection is a relatively

common cause of neonatal convulsions, and when convulsions occur, broad-spectrum antibiotics should be included at the dose recommended for the treatment of meningitis. Metabolic disorders are a correctable cause of neonatal convulsions. Hypoglycaemia must be corrected without delay with a 10% glucose solution intravenously at a dose of 2 ml/kg in a bolus and then continued, depending on gestational age, in an infusion up to a maximum dose of 8 mg/kg/min. Hypocalcaemia is corrected with a solution of 10% calcium gluconate at a dose of 100 mg/kg or 1 ml/kg, respectively, intravenously for 10 minutes, monitoring the heart rate and infusion site. The dose may be repeated in 10 minutes if there is no clinical response. Alternatively, calcium chloride at 20 mg/kg or 0.2 ml/kg may be administered. After the initial correction, calcium should be added to the infusion solution. Neonatal hypomagnesemia is most commonly associated with hypocalcaemia. It is corrected with a solution of 50% magnesium sulfate at a dose of 125 mg/kg or 0.25 ml/kg intramuscularly. The dose may be repeated for 12 hours until normomagnesemia is established. Pyridoxine-dependent epilepsy (PDE) is a rare genetic cause of refractory neonatal convulsions. In infants with seizures who do not respond to conventional anticonvulsant therapy, especially if the cause of seizures has not been established, PDE should be considered. It is recommended that pyridoxine be given intravenously at a dose of 100 mg / kg. The dose may be repeated at intervals of 5 to 15 minutes to a total maximum dose of 500 mg. Alternatively, pyridoxine can be administered at a dose of 15 to 30 mg/kg per day orally divided into three doses. Continuous EEG and cardiopulmonary monitoring is required during therapy, given that there is a risk of apnea. After initial care of the airway and cardiovascular support with etiologically-specific treatment, the next decision is the eventual introduction of anticonvulsant drug therapy. There are no scientifically established or widely accepted guidelines for the medical treatment of neonatal convulsions, and the approach is based on a limited number of clinical trials, observational studies and clinical experience[35, 36]. Neonatal convulsions resulting from reversible electrolyte or glucose disorders do not require the immediate introduction of anticonvulsant therapy, while some other causes, especially if the convulsions are prolonged, presumably lead to the introduction of anticonvulsant drug therapy. In the past, there was an attitude to treat clinically evident convulsions. Such an approach is debatable because in this way newborns with paroxysmal events (not convulsions in reality) are often exposed to unnecessary anticonvulsant medications, whereas infants with subclinical convulsions, on the other hand, will not receive adequate anticonvulsant therapy. Experts recommend the treatment of clinical and subclinical convulsions because the only difference between them may be cortical distribution. It should be noted that after initial treatment in infants with convulsions, electroclinical dissociation may occur, therefore clinically noticeable signs of convulsion disappear, but electrographic (EEG) convulsions persist[24, 37]. Ideal treatment would therefore involve resolution of electrographic convulsions. In case the convulsions persist for longer than expected, the possible etiology should be re-evaluated. For example, neonatal convulsions associated with hypoxic-ischemic encephalopathy should be withdrawn after a few days, and if they persist, possible metabolic disorder or neonatal-onset epilepsy should be considered. Phenobarbital has long been used as the first line of therapy for the treatment of neonatal convulsions[14, 38-40]. It is eliminated via the liver and kidney, therefore, in newborns with impaired liver and kidney function, such as in hypoxic-ischemic encephalopathy, it can be toxic at normal doses. Also, the half-life of phenobarbital is higher in preterm newborns compared to term newborns so that standard dosing can result in toxicity. Measurement of serum concentration is useful when conducting phenobarbitone therapy[41, 42]. The initial dose of phenobarbital is 20 to 30 mg/kg intravenously. Unless the convulsions persist after the initial dose, the bolus dose of 10 to 20 mg/kg may be repeated up to a total daily dose of 50 mg/kg. The initial dose is followed by a maintenance dose of 4 to 6 mg/ kg/day divided into two doses. Another commonly used drug for the treatment of neonatal convulsions is phenytoin. Neither of these two medicines is fully effective nor is more effective than the other 43. The most common formulation of phenytoin used is fosphenytoin because of its lower risk of side effects than classical phenytoin. The initial dose of phenytoin is 20 mg/kg. The following is a maintenance dose of 4 to 6 mg/kg divided into two daily doses. Fosphenytoin is dosed in the same way as phenytoin, but doses are expressed in phenytoin equivalents (1 PE = 1 mg phenytoin). Side effects to keep in mind are hypotension and cardiac arrhythmias. Midazolam can also be used in acute treatment. It is initially given in a bolus at a dose of 0.15 mg/kg followed by continuous infusion, initially 1 mcg/kg/min followed by a dose rise until effect is achieved[44]. Neonatal convulsions that are refractory to phenobarbital generally have a weaker response to another line of anticonvulsant drugs. The drugs most commonly used as a second line of treatment are phenytoin / fosphenytoin, levetiracetam, llidocaine and midazolam. Recently, levetiracetam has been frequently used, which according to some studies has a neuroprotective effect[45]. Given the pharmacokinetics of levetiracetam in infants is not fully known, the range of recommended dosage in the literature is very wide (10 - 60 mg/kg/day). However, when used with refractory convulsions, an initial dose of 60 mg/kg intravenously is recommended, followed by a maintenance dose of 40 to 60 mg/kg daily divided into two or three daily doses[46, 47]. Lidocaine is also used as second line drug. The contraindications for the administration of lidocaine are congenital heart defects and pre-treatment with phenytoin[48]. Lidocaine is initially administered at a bolus dose of 2 mg/kg for 10 minutes followed by continuous infusion at 7 mg/kg/h for 4 hours. The dose is then reduced by 50 percent every 12 hours over the next 24 hours. Intravenous lidocaine administration may be arrhythmogenic and requires continuous non-invasive monitoring. To reduce the risk of arrhythmias, the maximum administration time of lidocaine is 48 hours, according to some

publications, it is recommended to use less than 30h[48, 49]. Continued administration of midazolam should be considered in newborns with epilepticus status[44]. There are no clearly defined criteria that would determine the length of administration of anticonvulsant therapy after control of acute symptomatic convulsions has been established. Since acutely symptomatic convulsions usually recede within three days and usually do not occur afterwards, there is a trend of early discontinuation of anticonvulsive therapy, sooner or shortly after discharge of the newborn from hospital [50, 51]. With regard to chronic therapy, the length of treatment allegations vary from one week to 12 months after the onset of recent convulsions [52, 53]. Contrary to acute symptomatic convulsions, neonates with epilepsy are however advised to have continuous anticonvulsant therapy because of the risk of recurrence. For this purpose, phenobarbital at a dose of 3 to 6 mg/kg per day is usually used, with serum concentration measured. There is some research citing the potential benefit of the use of carbamazepine in the treatment of neonatal epilepsy associated with pathological variants of KCNQ2 and KCNQ3[54, 55].

Conclusion

Unlike older children, in neonates the clinical presentation of neonatal convulsions and EEG findings are significantly different as a result of the immature stage of brain development. Neonatal convulsions are usually focal, rarely generalized. Furthermore, in contrast to adult convulsions, neonatal convulsions are symptomatic in 85% of cases, or the result of some identifiable cause. The most common cause of neonatal convulsions is hypoxic-ischemic encephalopathy. Central nervous system infection is also a relatively common cause of neonatal convulsions. In order to rule out intracranial hemorrhage, brain MRI or transcranial ultrasound should be performed. Most neonatal convulsions are subclinical therefore clinical assessment is not sufficient to diagnose neonatal convulsions. Nonconvulsive paroxysmal events can often be mistaken for convulsions. Therefore, the gold standard for the diagnosis of neonatal convulsions is a continuous electroencephalogram (cEEG). If cEEG is not available, amplitude EEG (aEEG) is a useful and practical tool. Neonatal convulsion therapy must be directly directed to the cause. Neonatal convulsions resulting from reversible electrolyte or glucose disorders do not require the immediate introduction of anticonvulsant therapy, while some other causes, especially if the convulsions are prolonged, presume the introduction of anticonvulsant drug therapy.

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An Integrative Review of the Effectiveness of the Tomatis Method in Children with Autism Spectrum Disorder

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Abstract:

Objective: The aim of the study is to conduct an integrative review that will identify effectiveness of Tomatis method as an option for treatment of children with autism spectrum disorder (ASD).
Data Sources: A comprehensive search of meta-analyses and case studies, letters, opinion papers, citations in papers, references, books in English, French and Spanish published during the last 30 years.
Results: A total of 14 articles and 2 books met the inclusion criteria and all were read and analyzed according to an integrative review protocol then categorized. It was observed that there are 6 quantitative studies, 6 with mixed method design and 4 qualitative studies. Almost all of them support Tomatis method (except 1) as an intervention that can help in children with ASD. Even that 1 study that estimated that the positive results were not related to the Tomatis treatment, concluded that the majority of the children in the study demonstrated general improvement in language. A number of studies indicated as a result that children were no longer considered with ASD.
Conclusion: Tomatis method offers interventions that significantly improve the autistic traits in children but more research has to be done, especially randomized control trials that will strengthen the evidence.

Keywords: "Tomatis", "autism", "children", "autistic", "autisme", "autistes" and "enfants", "autismo", "ninos", autistas".

Sažetak:

Integrativni pregled učinkovitosti Tomatis metode kod djece s poremećaja spektra autizma
Cilj: cilj istraživanja je provesti integrativni pregled koji će identificirati učinkovitost Tomatis metode kao opcije za intervenciju kod djece s poremećajem spektra autizma (PAS).
Izvori podataka: sveobuhvatno pretraživanje meta-analiza i studija slučaja, pisma, referati, citati u radovima, reference, knjige na engleskom, francuskom i španjolskom jeziku objavljene u posljednjih 30 godina.
Rezultati: ukupno 14 članaka i 2 knjige ispunjavalo je kriterije za uključivanje i svi su pročitani i analizirani prema protokolu integrativnog pregleda, a zatim kategorizirani. Uočeno je da postoji 6 kvantitativnih studija, 6 s mješovitim istraživačkim pristupom, 4 kvalitativne studije. Gotovo svi podržavaju Tomatis metodu (osim 1) kao intervenciju koja može pomoći djeci s PAS-om. Čak je i ona 1 studija koja je procijenila da pozitivni rezultati nisu povezani s Tomatis metodom, zaključila da većina djece u studiji pokazuje opće poboljšanje jezika. Brojne studije rezultirale su time da djeca više nisu smatrana s PAS-om.
Zaključak: Tomatis metoda nudi intervencije kojima se značajno poboljšavaju simptomi autizma kod djece, ali potrebno je napraviti više istraživanja, posebno randomiziranih kontrolnih pokusa koji će ojačati dokaze.

Ključne riječi: "Tomatis", "autism", "children", "autistiic", "autisme", "autistes" i "enfants", "autismo", "ninos", autistas ".

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Introduction

1.1 Autism

Not every child with autism spectrum disorder looks like others, some are with very mild, some with severe symptoms. To be diagnosed with ASD, a child must present many disturbances, among important ones are: deficits in social communication and interaction, in nonverbal communicative behaviours, restricted patterns of behaviour, stereotyped motor movements, excessive adherence to routine, fixated interests, etc. Parents often do not receive an accurate diagnosis what would represent a first step in treating autism[1], as diagnosis serves as a base for treatment[2].
There are many different approaches used to improve symptoms of ASD. The therapeutic intervention discussed in this paper - the Tomatis method - is one of many possible interventions available to those with ASD[3]. it is not suggested as a cure to ASD, but as a possibly effective therapy that could improve communication skills, physical and motor skills, and social and behavioral skills in children with ASD[4].

1.2 Tomatis Method

One of the greatest discoveries in neuroscience is neuroplasticity of the brain. Music is a powerful stimulus for neuroplasticity and balances the brain's electrical activity[5]. It is shown by brain scan studies that neurons fire in unity to music in perfect synchrony and that is the reason why music can affect the rhythms of the brain[6].
A lot of data speaks in favor of the exposure of pregnant women and newborns to music which promotes brain development and the inner ear of a child[5]. The impact upon children with ASD is no different. The most significant link between music and performance improvement in neuropsychological activity has been demonstrated in Campbell's studies involving Mozart's music[6].
It is undeniable, as Campbell[7] states, that the rhythms, melodies and high frequencies of Mozart's music inspire creative and motivational areas of the brain. Campbell[7] based his discovery on the works of a French doctor Alfred Tomatis, who hypothesized that the lack of sound stimulation or abnormal stimulation in utero and/or early childhood can cause aberrant behaviours and delayed or disabling communication skills[6].
Tomatis Auditory Stimulation is performed by listening to music (Mozart and Gregorian Chants) mother's voice recording and someone's own voice through an active vocal work, processed and filtered through an electronic device[4].

Methods

This integrative review of the literature aims to gather and analyze the available scientific evidence produced on the effectiveness of the Tomatis method in children with ASD that will contribute to the development of knowledge on the issue. The Integrative Review will be presented in six stages: Guiding questions, Search strategy and sampling of data, Data collection and extraction, Critical analysis of the studies included, Discussion of results and Presentation of the integrative review[8].

Guiding questions

The evidence within the literature will be critically reviewed in order to answer the following guiding questions:
- What has been published in the last thirty years on effectiveness of the Tomatis method in children with ASD and
- Is there any evidence that the Tomatis Method is an effective treatment option for ASD.

Search strategy and sampling the data

The first step of the search strategy was to search for primary sources: meta-analyses and case studies and secondary sources. The Keywords used in the search strategy were: "autism" AND/ OR "autistic children" AND "Tomatis".

Inclusion and exclusion criteria

Inclusion:

1. Timefame: from 1987 to 2019
2. The sample: children with the ASD, age group: from 2-21.
3. Intervention researched has to be Tomatis method
4. Data should be presented in English, French or Spanish language
5. The types of research design are: meta-analyses, randomized control trials, cross-over trials, case-control, letters, opinion papers, case reports, books and other grey literature.

Exclusion:
1.Other sound-based interventions, other music therapies or other Mozart music therapies
2. Other medical conditions and psychological disorders
The literature search identified 113 papers and 2 books. Several articles were also obtained by scrutinising the reference lists of key articles or reviews. After the title/abstract screening, 34 publications were obtained for detailed evaluation. 1 article was sent by e-mail by the author upon the request. After detailed evaluation all sources that did not meet the criteria of relating specifically to Tomatis method and autistic children were excluded. From the final 16 papers and 3 books we excluded brief clinical vignettes and anecdotal stories.
The remaining 16 studies form the basis of this review: 6 of them are quantitative, 6 are mixed method designs and 4 of them are qualitative ones.

Data collection and extraction

The selected studies are analyzed and submitted into a table (Table 2.)

Critical analysis of the studies included

Studies are ranked according to the type of evidence[9] (Table 3).

File Index Ref	Data Base used	Search Terms used	Number of articles
1.1	Cochrane	Autism and children and autism and Tomatis	1
1.2.	CINAHL	Autistic children and autism and Tomatis	1
1.3	MEDLINE PubMed	Autistic children and autism and Tomatis	4
1.4	Lilacs	Ninos autistas and autismo and Tomatis	0
1.5	WEB of Science	Autistic children and autism and Tomatis	8
1.6	Scopus	Autistic children and autism and Tomatis	8
1.7	Google Scholar	Autistic children or enfants and autistes and Tomatis	8
1.8	OVID through UCLAN library	Autistic children and Tomatis	34
1.9	Discovery	Autistic children and autism and Tomatis	14
2.0	Willey Online Library	Autistic children and autism and Tomatis	3
2.1	Proquest Medical Library	Autistic children and autism and Tomatis	16
2.2	Reference lists	Autistic children and autism and Tomatis	9
2.3	Tomatis Association website	Autistic children and autism and Tomatis	5
2.4	Other		4
	TOTAL		115

Level 1 Evidence – Quantitative design, Meta-analyses and systematic reviews

1. Gerritsen[10] conducted a meta-analysis and systematically assessed 35 research studies on the impact of Tomatis method on different disorders, among many - ASD. Gerritsen[10] has reviewed 7 small scale research projects on the impact of Tomatis method in children with ASD: Neysmith-Roy[3], Vervoort et al.[11], Corbett et al.[12], Tatum et al. [13] and Nel[14]. The results indicated the improvement of social, linguistic and psychological skills in all studies, except Corbett et al.[12]. Corbet et al.[12] did not show any statistically significant difference between the Tomatis and a placebo group.

Also Gerritsen[10] reinterpreted the results of Corbett et al.[12] and showed that by changing methodology from quantitative to qualitative, results changed in favour of Tomatis method in terms of positive behaviour changes in children with ASD who benefited from Tomatis method to a certain extent.

2. Gerritsen[4] critically reviewed studies that investigated the effects of Tomatis method in children with ASD: Neysmith-Roy[3], Vervoort et al.[11], Corbett et al.[12] . According to Gerritsen[4], Neysmith-Roy[3] and Vervoort et al.[11] showed significant improvements in behavior in children with ASD and objectively reported positive outcomes.

Corbett et al.[12] according to Gerritsen[4] did not show a statistically significant difference in the language skills between Tomatis treatment and placebo because the sample size very small and too heterogeneous to be analyzed as a group. A cross-over design was also inappropriate to measure the impact of an intervention, after the treatment has been completed, because Tomatis first/ Placebo second measured the sum of the Placebo Effect plus the Extended Tomatis Effect and the second phase was no longer a true Placebo.

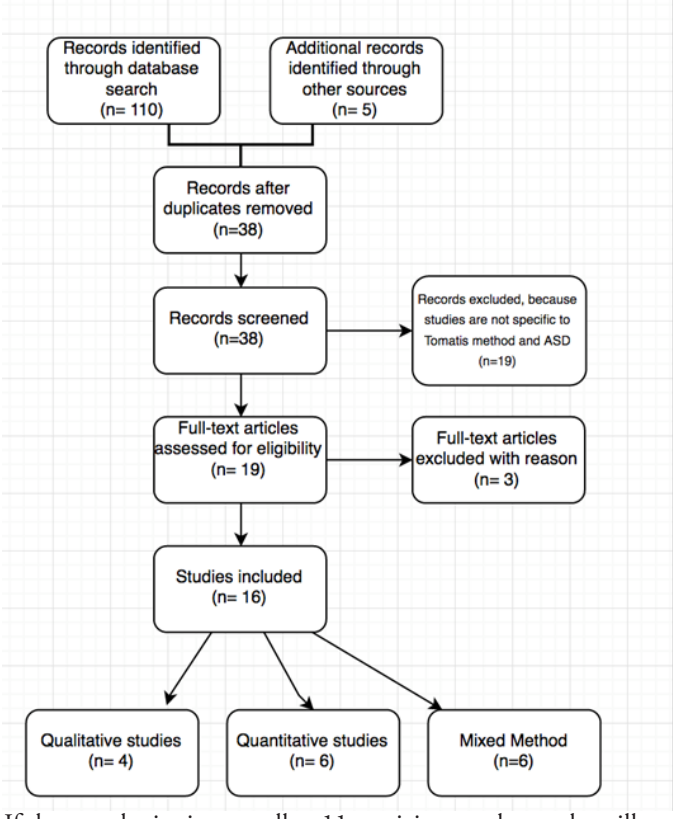
Level 2 Evidence – Quantitative design, Randomized control trials

1. Corbett, et al.[12] aimed to determine the effects of Tomatis method on language skills in children with ASD using randomized, double-blind, placebo-controlled, crossover design. Corbett et al.[12] resumed that the results in the study reflect a lack of improvement in language using the Tomatis Method for children with ASD. Participants in the study were heterogeneous, considering their age, language skills and different IQ levels. While one group had received Mozart music and Gregorian chants with amplified high frequencies with both: air and bone conduction (Tomatis method) first (90 hours) and then placebo treatment (90 hours), the other group - had received an intervention with Mozart's music and Gregorian chants without the modulation of frequencies and without the bone conduction (placebo) and the music was not processed through the Electronic Ear.

So called placebo intervention in this study represents an intervention well known and documented the Mozart effect and Corbett et al.[12] should have acknowledged it and should have offered a different form of intervention to the placebo group, in a form of a white noise, which would reduce a possible influence on participants. Because it is unclear if the results reported were caused by the Tomatis method or by Mozart Effect intervention or both, or if they would have occurred anyway. Mozart's effect has also been observed with a positive effect to communication, speech, reading and writing skills[7] .

A cross-over design in this study is the most controversial, because both groups had actually received two different interventions – Tomatis stimulation and Mozart Effect stimulation, and both interventions might have led to significant improvements in majority of children, which might be directly related to interventions themselves rather than, as the author interprets, are unrelated to the interventions received and are independent of them.

Also when interpreting research results it is also important to evaluate the size of the sample. Larger sample sizes would give results with increased precision and better statistical strength.



If the sample size is as small as 11 participants, the results will probably not be statistically significant. Therefore, small sample sizes should not be used to make broad conclusions. This study has substantial weaknesses of a study design and interpretation of results.

2. AbediKoupaeia et al.[15] aimed to investigate the effects of Tomatis method in reducing the autistic symptoms in children using randomized controlled trial. 34 children aged from 4-8 years were randomly assigned and equally divided into experimental and control groups. We cannot confirm, because the authors were not giving the information whether all children in experimental group wore headphones that were equipped with air and bone conduction. It remained equally unclear because it was not explained in the study what sort of music participants had been listening through 30 sessions / 60 hours of the program: were they listening only to Mozart music or both Mozart and Gregorian chants that represent the core of the Tomatis method along with filtered mother voice recording? Also the information was missing if the music was modulated or not in terms of high frequency enhancement which is also specific to Tomatis method. The Listener Profile was made for each participant and served as the basis for choosing the most adequate among different categories of classical music albums. Descriptions concerning Listener Profile test and description of music materials chosen are not included in the description of methods. Comparing the results of the two groups – experimental and control, the research showed that the Tomatis sound therapy could reduce autistic symptoms, increase social interaction, communication, and reduce stereotypical movements according to the Gilliam Autism Rating Scale, G.A.R.S. questionnaire, performed before and after the intervention as a measurement tool in this study. Since the study did not explain whether all the parameters of the Tomatis method were performed: filtering (music modulation), headphones with an attached bone conductor as well as the usual air conduction, it is difficult to say with certainty whether there is an evidence of Tomatis effect or Mozart effect. AbediKoupaeia et al.[15] acknowledge only following limitations of their study: parents' unwillingness to respond to questions during tests and geographical limitation of this study. Since methods are not clearly described the experiment cannot be replicated independently. The study is flawed by weaknesses of reporting therefore conclusions are based on insufficient data.

Level 6 Evidence – Quantitative studies, Case series

1. Davis[16] aimed to investigate changes in 100 children with ASD, after 60 hours of Tomatis method in 12 areas of consideration: Interpersonal growth; Listening and speech; Academic Achievement, Thinking, Learning; Attention; Behaviour; Intrapersonal Growth to know and express Self; Movement, Sports and Rhythms, Musical and Vocal Skills; Relaxation; Creativity; Reading, Writing, Spelling; Well being. The Parents rated each of the area before and after treatment from their point of view. Some of the areas where changes occurred were highly rated (Interpersonal Growth 87%, Listening and Speech 85%, 81% in Academic Achievement, Thinking, Learning, 80% in Attention, 79% in Behavior, 69% in Intrapersonal Growth to Know and Express Self, 66% in Movement, Sports, and Rhythm, etc.) and some of them lower (Well-being 20%). It is significant that in every area of consideration the changes were evident. There is no indication of how long the research has been conducted, it is not indicated if participants were randomly selected and we do not have information if the parents were informed about the research (Informed Consent). It is said that every parents filled the forms before ("Abilities to be Improved" form) and after the 60 hours of intervention ("Abilities improved" form) regardless of whether or not the research has being carried out. It was reported that participants were exposed to 60 hours of a basic Tomatis programme, but it is not described what a basic programme is. The weakness of this study is a lack of transparency in reporting. Also it is possible that the results are biased or that the criteria of improvement differ from parent to parent.

2. Torres de Carella[17], aimed to investigate if Tomatis method could reduce echolalia (immediate or delayed repetition of what has been heard) in children with ASD. Echolalia represents the phase in acquiring and learning language in children with ASD. Research design is quantitative descriptive and the aim is to describe the opinion of the participants on the impact of Tomatis

method on echolalia in children with ASD. The Standardized Questionnaire with 12 questions was prepared for parents of children with ASD who present echolalia. From 51 distributed, only 8 questionnaires were returned are accepted for the research. Tomatis Intervention varied from 62 hours (25% of participants) to 110 hours (50% of participants). 100% children presented echolalia before the treatment. 37% of parents reported improvement in echolalia. Generally, during the Tomatis intervention many other interventions are being undertaken at the same time and the improvement cannot be exclusively attributed to the Tomatis method. 8 questionnaires represent a very small sample to draw any conclusion and results are not statistically significant. The other weakness of this study is unequal duration of the programme that children were exposed to, authors did not report which programmes were included in Tomatis intervention.

Level 7 Evidence

a) - Mixed Method Design, Individual cases study

1. Six boys with severe ASD (aged 4 to 11 years) received the Tomatls Method stimulation with the aim to assist them in behavioural changes[3].

All parents of the children with ASD (diagnosed according to APA criteria[18] were beforehand informed about the possibility that the children might not benefit from the treatment and made an informed decision about their participation signing the Informed Consent Form which described the study in details. The study did not include a control group because of the ethical reasons (withhold of the treatment) and because of the differences of each of the boys.

Twenty-minute video samples were registered for each boy, every time they completed one intensive of the Tomatis programme. After a year, all tapes were randomized and evaluated by educated evaluators who did not know about the treatment program nor about the children. Each participant's videos were rated by the two research assistants and the scores were averaged.

Children's Autism Rating Scale is measured at the beginning and end of treatment. Participants were followed and treated individually.

At the end of each intensive a progress interview was conducted with the parents. Three (50%) boys showed positive changes in behavior after the treatment. From a developmental point of view the changes occurred in pre-linguistic areas for 5 out of 6 boys that are considered as prerequisites for verbal communication.

One boy was no longer considered autistic, two boys showed mild symptoms of ASD and three boys remained within the severely autistic range. These research results suggest that it would be useful to evaluate the effects of the Tomatis Method on children with ASD in a research environment where experimental conditions can be more rigorous.

2. Vervoort et al.[11] aimed to study whether Tomatis Method can reduce neurological dysfunctions in children with ASD in a form of the Qualitative Case Study, using measurement tools: Auditory Evoked Potential technique, EEG Brain Mapping and Tomatis Listening Test System. During the intervention period none other interventions was applied. The observed time of intervention with the Tomatis method differed from case to case (in a range from 6 months to 5 years). The comparison of each of the four cases was with itself (before and after the treatment). All four children exhibited great changes and improvements. Such a small sample, 4, may compromise the conclusions of the study and can prevent extrapolation of the results. On the other hand this study took a lot of time with extensive and intensive treatments because of the severity of the cases. Certainly a bigger sample would impose some practical and technical obstacles but larger samples sizes can lead to statistically significant differences that can contribute to evidence-based practice.

b) - Mixed Method Design, Single case studies,

1. Tatum et al.[13] aimed to investigate whether synergistic benefits exists from the simultaneous combination of Tomatis method with a speech therapy.

Tatum et al.[13] presented the case of a 14-year-old girl diagnosed with ASD, not verbal. In spite of 10 years of speech therapy, she pronounced only few syllables Ba, Da, Ma. The girl was evaluated prior to the start with Tomatis Method (Pre-test "Abilities to be Improved" Form), during the intervention (Daily Observation Form) and after each intensive (Post-test "Abilities Improved" Form).

After the first intensive of Tomatis method without any additional speech therapy, parents reported increasing awareness of listening, independence, motivation, and desire to communicate. She was no longer too sensitive to the sounds and she verbalized more.

From nonverbal, she has had a significant improvement in communication, attention, understanding, socialization and learning in general. The speech therapy alone for 10 years has not made great progress as the Tomatis method contributed through 150 hours of passive and active work program.

This case demonstrate the usual situation In a real word where we cannot observe positive changes of Tomatis Method isolated from other social influences or educational interventions. Further investigation should be done to more precisely determine the effect of combining more interventions for children with ASD.

2. Nel[14] aimed to identify the effect of Tomatis Method on psychological well-being and communication skills in a 14-years old boy with Asperger's syndrome, one of levels of symptom severity of ASD according to DSM-5[18]. Mixed method design is used in a single case study. Qualitative data were obtained through semi-structured interview before and after intervention, quantitative data through Projective drawing and Profile of Mood States (POMS). Tomatis programme consisted of 75 hours of filtered

music, mother's voice recording and active vocal work over 6 months in three intensives. Results indicated improvement in Interpersonal Communication and psychological well-being. A scientific contribution of this case study (Nel, 2005) is in its holistic approach and empirical value.

3. Pralong, Espinosa, & Trigo[19] in their single case study aimed to investigate if the Tomatis Method could reduce autistic traits and improve reading and writing skills in 8 years old boy with ASD. Mixed method design is used. Qualitative data were obtained through observation and analysis of reactions of the boy and quantitative data from measuring anxiety with SCAS (Spence Children's Anxiety Scale) and hyperactivity level (Vanderbilt Assessment Scale, NIOCHQ, 2010). A focus group was also carried out with relatives of the child, with the theme: "Strategies that parents use to confront the crises of their children with ASD". After 4 intensives (9 months and 120 hours) and the use of the Tooballo® (active voice work) 5-10 minutes every day during those 9 months, the child achieved a remarkable level of maturation, a decrease in anxiety levels, but no significant changes in attention and hyperactivity. In the academic part there were advances in the process of literacy. There were significant behavioral improvements.

4. Davies & Smith[20] aimed to investigate whether Tomatis Method could help 18-year-old boy with Asperger disorder (ASD) who suffered from behaviour problems (outbursts of anger and violence, obsessive-compulsive disorder, anxiety), sleeping problems, eyesight problems, motor problems and diarrhea. Before and after each of 4 intensives, the boy was assessed through mixed method design. Qualitative data were obtained through interviews and observations and quantitative through Tomatis Listening Tests (TLTS). TLTS is a measuring instrument used to determine the listening curve and listening distortion and it enables monitoring of changes and planning for the next programme. The programmes were made from filtered Mozart's music and Gregorian chants. Recordings of filtered mother voice and active vocal work has not been introduced into programmes. There were improvements in his behaviour, his sleep and a bowel movement were better, improvements were noted in a posture and motor skills as well. Davies & Smith[20] considered that the Tomatis therapy was more effective because it was used in combination with other interventions. This single case study has not been found searching through electronic database and it has not been published in peer-review journals. It has been identified on Tomatis professional organisation website therefore it is of a lower-level of evidence than previous single case studies.

c) – Qualitative design, Biography

Ruben[21] presented personal experience story, a real autism success story of her daughter who was diagnosed with ASD and completely recovered from it. In a book (Ruben, 2010) we follow a life experience from the time her daughter was diagnosed until she got well and completely out of ASD. When diagnosed with ASD, she was 22 months old. Tomatis method together with sensory integration were applied during about 1,5 year in 6 intensives. Already after the first intensive, a girl started to talk more spontaneously. During the second intensive, mother voice recording and active vocal work were introduced, echolalia appeared as well as her coordination and motor planning improved. After her third intensive, a girl started to talk, sing and express herself. After the fourth intensive she had more balance and coordination, spoke spontaneously, hugged and showed her affection, only year and half beforehand she was still nonverbal. After her 5th intensive, a girl was retested and the results showed a normal child's development. 6th intensive brought further improvement in her body – not only promoted her speech, it liberated her from typical repetitive mannerisms.

Level 8 Evidence – Qualitative design, Opinions of Specialists

1) Madaule[22] observed that many of children with ASD had normal development and then started to present at about the same age (around 18 months) symptoms of ASD. The Tomatis programme of neuro-auditory stimulation for children with ASD usually takes from 150 to 200 hours over 6 to 12 months. Madaule has confirmed that results vary from a child to child, but the overall progress has been observed in 80% of cases, and even more, 80-90% is observed regarding development of pre-linguistic skills. Filtering out the lower frequencies from mother voice recording simulate the hearing sounds in the womb (intrauterine hearing, also called a sonic birth).

2) Gilmor & Madaule[23] observed that children with ASD react more emotionally expressive, especially towards their mothers after they have been stimulated with filtered mother voice recording. Nonverbal children with ASD start to produce sounds, eye contact and attention span improve, repetitive body movement and aggressive behavior decrease. Intensity and duration of periods of autistic social withdrawal diminish and children with ASD start to establish contacts with other children.

3) Madaule[22,23] presented his long professional experience in form of a personal letter, an article and a book which are of lower evidence comparing to previous studies from the higher level of evidence but his opinion gave us possibility of better understanding of the method itself, a procedure of implementing Tomatis programme and possible outcomes. He is the most experienced living expert in this field and he learned about Tomatis method from dr. Tomatis 50 years ago. and was treated from dyslexia by dr. Tomatis himself when he was a young boy in France[6,22]. In this integrative review he has been represented by 3 studies, experts' opinions (lowest level of evidence) because of valuable number of cases of ASD that he has treated, he is indispensable

source of evidence for Tomatis method.

Discussion of results

Date of publication:

16 researched studies were predominantly published during 2000 except two oldest, published in 1989[23] and 1998[22]. The most recent was published in 2016[20].

Authors:
2 authors Gerritsen and Madaule[4,10,22,23] published more than 1 study.
Country of origin:
Studies were conducted in 9 countries: Belgium, Canada, Ecuador, Iran, Mexico, Puerto Rico, South Africa, United Kingdom, United States of America. USA, 4 and Canada, 4 being leading countries.
Designs:
Quantitative design 6: Meta-analyses and systematic reviews 2; Randomized control trials 2; Case series 2;
Mixed Method Design 6: Individual cases studies 2; Single Case Studies 4;
Qualitative 4: Biography 1; Experience of Specialists 3
Measurement instruments:
Choice of measurement instruments depended of design and purposes of particular study.
In Quantitative research various measuring tools were used, ranging from scales relative to autism degree to different psychological evaluation, semi-structured interviews etc.
1 study - The Gilliam Autism Rating Scale (GARS), pre- and post- questionnaire
1 study - Children's Autism Rating Scale (CARS)
1 study - The Autism Diagnostic Observation Schedule-Generic (ADOS-G) The Stanford-Binet Intelligence Scale-Fourth Edition (SB4), IQ, The Peabody Picture Vocabulary Test-Third Edition (PPVT-III), The Expressive One Word Vocabulary Test (EOWVT).
1 study - The Profile of Mood States (POMS), The Draw-a-Person (DAP), The Draw-a-Tree (DAT),
1 study -The Spence Children's Anxiety Scale (SCAS), Vanderbilt test for hyperactivity;
2 studies - Pre- and Post- assessment ("Abilities-to-be Improved" form, "Abilities Improved" form).
1 study - Electroencephalogram (EEG) and Auditory Evoked potentials (AEP).
Only 4 studies used the Tomatis Listening Test[3,11,16,20] which belongs exclusively to the Tomatis method and helps to identify listening potential providing information on voice quality, language acquisition, learning ability and many more. 2 systematic reviews and 3 experiences of specialists are excluded from analysis.

Intervention:

More than a half of studies, 9, specifically mentioned usage of both interventions, passive and active phase, 4 used Mozart music and Gregorian chants with bone and air conduction and 1[15] did not specify what kind of classical music was applied in the research, 2 systematic reviews[10] were excluded from this evaluation because they are not specifically assigned to the music programme. It was observed that all 4 quantitative and 2 mixed method studies used only Mozart music and Gregorian chant, without filtered Mother Voice Recording and active vocal work. 1 of them used additional program which is not part of Tomatis method[15].

Intervention duration:
5 studies are excluded: 2 systematic reviews[10] and 3 experiences of specialists[22,23]. Intervention duration varied from study to study, in a range from 2 intensives - 60 hours to 37 intensives[11]. An intensive usually corresponds to 30 hours - 15 days, 2 hours but it is not always a case.

Aims and purposes:
3 studies aimed to investigate if Tomatis method can reduce ASD symptoms, 1 if it can reduce echolalia in children with ASD, 1 study investigated the effects of the Tomatis Method on language skills in children with ASD, 1 study aimed to investigate the effect of Tomatis method in the area of change in academic achievement thinking, learning, attention, behavior, creativity, interpersonal growth, intrapersonal growth to know and express self, well-being, listening and speech, reading, writing, and spelling, movement, sports, and rhythm, musical and vocal skills, and relaxation. 1 investigated the effect of Tomatis Method on the psychological wellbeing and communication. 1 investigated synergistic benefits from the simultaneous combination of Tomatis method with a speech therapy. 1 investigated if Tomatis Method can reduce neurological dysfunctions.

Participants sample:
The number and age of participants vary from study to study, 5 studies have 1 participant and the biggest sample is 100 participants in 1 study. The majority of studies had small group designs. The youngest participants were 2 years old and the oldest 21. Majority of participants were boys.
Outcomes:
All studies reported similar results: reducing symptoms and stereotypical movements, increasing social interaction and communication, improvements in speech, emotional and attention enhancement. Even a study (12), that estimated that the positive results were not related to the Tomatis treatment, concluded that the majority of the children in the study demonstrated general improvement in language. A number of studies indicated as a result that children were no longer considered with ASD.

Presentation of integrative review

2.6.1 Limitation:

This integrative review has identified 16 studies that reviewed and evaluated the effectiveness of Tomatis method in children with ASD.

The methodological quality of studies in general was adequate although some deficiencies were detected, particularly in aspects related to a cross-over design and a interpretation of results[12], related to poor and insufficient data[15] and generally a very small sample in majority of studies which made results not statistically significant. Only 1 study obtained informed consent thus maintaining ethical standards.

All studies showed that Tomatis method can contribute in reducing symptoms of ASD.

Recommendation:

Most of studies were focused on communication skills because a lack of communication skills is the main feature of ASD. Research outcomes in this integrated review show that the Tomatis method can play a very important role and fill the hole in the current situation where we find ourselves helpless with outdated and inefective measures and protocols in front of growing numbers of children with ASD. Neuroscience gives us new evidences and shows us that auditive neurostimulation, in this case the Tomatis method, can significantly improve the general condition of children with ASD if not completely resolve it.

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The Impact of Allogeneic Hematopoietic Cells Transplantation on Female Reproductive Health: A Short Review

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Abstract:

Hematopoietic Stem Cell Transplantation (HSCT) has been widely used fore decades as the most effective treatment of several malignant and non-malignant hematological diseases. Among many complications with occurrence after HSCT procedure, reproductive issues are often neglected although these can adversely affect the patient quality of life. The most common gynecological complications after HSCT include: ovarian insufficiency, increased risk of cervical atypia and carcinoma, thrombocytopenia-associated menorrhagia, genital involvement of graft versus host disease, osteoporosis, fertility and pregnancy issues etc. Due to their relevance to the patients and constant growing of life expectance of women after HSCT it is of huge importance to diagnose and treat reproductive complications after the transplantation procedure by multidisciplinary approach.

Keywords: Allogeneic hematopoietic cells transplantation, reproductive complications, ovarian insufficiency

Sažetak:

Utjecaj alogene transplantacije hematopoetskih stanica na reproduktivno zdravlje žena: kratki osvrt

Transplantacija krvotvornih matičnih stanica (*engl.* HSCT) široko se koristi desetljećima kao najučinkovitiji tretman nekoliko zloćudnih i nemalignih hematoloških bolesti. Među mnogim komplikacijama koje se javljaju nakon HSCT postupka, reproduktivna su pitanja često zanemarena, iako ona mogu negativno utjecati na kvalitetu života pacijenta. Najčešće ginekološke komplikacije nakon HSCT-a uključuju: insuficijenciju jajnika, povećani rizik od atipije i karcinoma cerviksa, menoragije povezane s trombocitopenijom, zahvaćenost transplantata u odnosu na domaćina, osteoporozu, plodnost i trudnoću itd. Zbog njihove važnosti za pacijente i konstantne rast očekivanog života žena nakon HSCT-a od velike je važnosti dijagnosticirati i liječiti reproduktivne komplikacije nakon postupka transplantacije multidisciplinarnim pristupom.

Ključne riječi: Alogena transplantacija krvotvornih stanica, reproduktivne komplikacije, insuficijencija jajnika

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a widely used medical procedure for treatment of a different hematologic diseases. Around 85% of HCT is performed for curing malignant diseases, such as acute and chronic leukemias and lymphomas, while the rest of the procedures is used for diverse non-malignant states like aplastic anemia or immunodeficiency[1]. Progress in this medical field regarding patient and donor selection, stem cell isolations, supportive care, prevention of different complications and decreased-toxicity of preparative procedures resulted in expansions of the indications for HCT and number of patients treated by this method. On the other hand, the numbers of long-term survivors following hematopoietic stem cell transplantation have been notably increasing in last decade. In modern medicine it became mandatory to consider not only the survival rate, but also the quality of life of patients after HCT. Approximately 40% of these patients are female and the aspect of their gynecological health could not be neglected[2].
Complications of HCT vary upon of many factors such as preparation procedures before the transplantation, age of the patient, comorbidity, primer disease, time of transplantation and many other clinical characteristics[3]. Complications of HCT can be divided into two main groups upon the onset time: early complications that develop in the first 100 days after the procedure and late that occur after that time. Early complications include: hemorrhagic cystitis, veno-occlusive disease, thrombotic microangiopathy and different respiratory complications. Infections that could be bacterial, viral and fungal could also involve all organs and systems and its prevention and treatment is of major concern for survival and life quality. Graft versus host disease (GvHD) that could develop as an early and late complication is very serious event and among leading causes of death along with relapse of the underlying primary disease and infections. Late complications can involve almost every organ disturbing later life such as cataract, arrhythmia, osteoporosis, diabetes, dental problems etc.
Female reproductive system has been shown to be highly predisposed to the effect of HCT procedure. These complications have later onset and include: premature menopause, genital type of GvHD, cervical carcinoma, human papilloma virus reactivation, vaginal infections and sexual dysfunctions. It is clear that allogeneic HCT has negative impact on fertility often causing premature ovarian insufficiency and infertility, and even complicating possible pregnancy. All the mentioned gynecological problems negatively impact the quality of women life after HCT which should be considered and prevented multidisciplinary.
In this review we will discuss the impact of allogeneic HCT on female reproductive system with special considerations on long-term consequences.

The effect of allogeneic hematopoietic cell transplantation on ovarian function

It is well known that HCT procedure and its previous preparation management effect ovarian functions at several levels. This negative influence on ovaries impact the female well being, health and fertility demanding gynecologic care at several stages and collaboration between health professionals[4]. The most important potential consequence of HCT procedure is ovarian insufficiency which is characterized by loss of ovarian function with hypergonadotropic hypogonadism, decreased uterine and ovarian volumes and most prominent symptom of secondary amenorrhea. Our results have also confirmed elevated levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in women who underwent HCT as compared to controls[5]. Ovarian insufficiency is most common complication affecting more than 90% of patients depending on age and therapeutical regimens[6]. In our study all the patients were affected probably due to the advanced age since median age was 42 years[5].
The exact mechanism of HCT impact on ovarian function has not yet been elucidated, although pretransplant conditioning regimen has been well appreciated. Indeed, conditioning regimens that include high-dose alkylate treatments associated or not with total body irradiation can severely damage the ovaries[7]. On the other hand, reduced-intensity conditioning did not result in significant improvement of ovarian function pointing that other mechanism could be involved in the subject[8]. It has been shown that even graft-versus-host disease could target granulosa cells of the ovarian follicles, thereby significantly reducing fertility and causing ovarian insufficiency[9]. This explains why pharmacological GVHD prophylaxis could help in preserving fertility after HCT[9]. In addition, long-lasting steroid treatment used in GvHD management can have additional negative impact on ovarian function[10].
Ovarian insufficiency is not always irreversible condition with younger age and higher estradiol levels being positive predictors of ovarian restoration[11]. Advanced age is independent risk factor, with the age of 30 being consider as cut-off value for irreversible ovarian damage[10]. Underlying disease has also influence on ovarian failure since it has been shown that acute lymphoblastic leukemia and lymphoma increase the risk of premature menopause[10]. As expected allogeneic transplantation also increased the risk of ovarian damage as compared to autoimmune transplantation.
Since ovarian insufficiency is characterized by various symptoms of estrogen depletion, such as hot flushes, mood disorders, sleep disorders, etc, what negatively impact the quality of life it is important to prevent, diagnose and treat this disorder.

The effect of allogeneic hematopoietic cell transplantation on cervix

It is well known that immunocompromised women, including those after hematopoietic stem cell transplantation, have an

increased risk of cervical cancer[12]. Since this mainly squamous carcinoma develops in stepwise pattern, it is reasonable that different grade squamous intraepithelial lesions also occur with higher prevalence after HCT procedure[13]. We have shown that less than 4% of patients after HCT have normal results of cervical Papanicolaou smear as compared to 76% in general population[5]. Similar results have been published by Negri and coworkers who extended the surveillance of patients and have shown the regression of the changes in many cases[14]. The addition of busulfan in chemotherapeutic regimens increased the number of abnormal cervical smears[14]. As expected, allogeneic HCT increases cervical abnormalities as compared to autogenic HCT[15]. Moreover, younger age and previous atypia in cervical Papanicolaou smears enhance the risk for post treatment abnormalities[15]. Recent study introduced the term therapy- related atypia that has been shown in around 11% of patients if cervical smear test was sampled within 100 days after HCT[16]. These cytological changes mimic precancerous lesions, but cervical surgical procedure and human papilloma virus tests were all negative. Repeated sampling showed the regression of cytological changes pointing that clinical informations are of crucial importance for patient management. All abnormal tests were found in patients treated by busulfan-containing chemotherapy, while no changes were observed after total body irradiation or nonbusulfan-containing chemotherapy[16].

The pathogenesis of different cervical abnormalities include long-term chemotherapy, graft versus host disease and immunosuppressive therapy that all result in decrease cellular and humoral immunity. Although all these procedures have beneficial roles in transplant protection, they also predispose patients to different bacterial and viral infections, such as human papilloma viruses that are in the basis of all cancerous cervical changes. It is unclear weather newly found cytological abnormalities are the results of new infections or reactivations of latent HPV virus in the setting of immunosuppression[17]. In addition, genital GVHD and unrelated HLA-matched donor were shown to be risk factors for developing cervical cytological abnormalities[17]. Opposite from mild cervical cytologic abnormalities, Holowaty et al. have reported the risk of progression for moderate dysplasia was 16% within 2 years and 25% within 5 years (18). The risk for cervical carcinoma was significant within 2 years after the abnormal Papanicolaou smear test[18]. Moreover, it has been shown that patients after HCT have double risk for occurrence of solid tumors in a period of 10 years as compared to general population with GVHD being an independent risk factor for squamous cell carcinoma[19].

Other reproductive issues after hematopoietic cell transplantation

It is well known that different modalities of treatment used in procedure of HCT effectively destroy the patient's bone marrow with subsequent pancytopenia which can result in severe morbidity. One aspect of this condition is thrombocytopenia which can induce thrombocytopenia-associated menorrhagia, particularly in women who had experienced irregular vaginal bleeding before the HSCT[20]. On the other hand, it has been shown that there is no correlation between severe menorrhagia and a general bleeding predisposition in other body sites[21]. Although thrombocytopenia-associated menorrhagia can affect up to 40% of patients undergoing HCT and can severely affect the morbidity and life quality of those patients, there are only few publications on the most effective treatment of this condition[21-23]. Beside the tranexamic acid that has been used for the treatment of menorrhagia of different origin, other effective treatment for thrombocytopenia-associated menorrhagia include gonadotropin-releasing hormone analogues and depo-medroxyprogesterone acetate[21]. It is also advisable to perform initial pelvic sonogram to diagnose gynecologic disorders that can alleviate menorrhagia and to remove intrauterine device, since it can predispose for pelvic infections during a period of pancytopenia[21].

Chronic GVHD is a serious complication of HCT procedure that occur in 30% to 50% of transplants from human leukocyte antigens-matched siblings and 60% to 70% from matched unrelated donors[24]. This condition usually develops over several weeks and months and involving inflammation, cell-mediated immunity, humoral immunity and fibrosis in its etiology[25]. The most common affected organs are: skin, mouth, eyes, liver, and intestines. Genital tract is involved in around 25% of patients with mostly vulvar disease manifested as erosions and fissures[26]. Vulvar and vaginal scarring are less common complications that can result in vaginal obstructions and labial fusion[27]. Patients with these complications usually complain of genital pain, burning, dysuria, swelling, soreness, dryness and dyspareunia. The most effective treatment include: local estrogen therapy, topical steroids and immunosuppressants with surgery in most severe cases of disturbed anatomy.

Osteoporosis is another potential complication in patients undergoing HCT due to the several mechanism. The most common causal mechanism is the lack of estrogens associated with ovarian insufficiency, lack of ovulation and consecutive amenorrhoea[28]. Other possible causes include different conditioning regimens, huge cytokine re-lease at the time of transplant, long-lasting immunosuppressive therapy and impaired intake and metabolism of calcium and vitamin D. Since osteoporosis can severely impact patient's morbidity and mortality, it is important to diagnose it and to start early treatment such as lifestyle modification, calcium and vitamin D supplementation, bisphosphonates and hormonal therapy[29].

Due to the previously described ovarian insufficiency, fertility is severely impaired after allogeneic stem cell transplantation with estimated overall conception rate under 1%[30]. Several factors contribute to this low conception rate. The most important

negative factors are advanced age at the time of HCT and regimens that include busulfan. Nowadays, oncologic patients are interested in fertility preservation in general. There is a growing number of cases with successful procreation after malignancy including those using classical oocytes/eggs freezing procedure or novel strategies such as ovarian tissue freezing. It is clear that these techniques require multidisciplinary approach including oncologists, reproductive gynecologist, surgeons, and others.

Conclusion

Reproductive sequels are among most common complications after hematopoietic stem cell transplantation which negatively affect the quality of life both in short and long time periods after the procedure. On the other hand, these problems are often underestimated by professionals whose concern is more in overall survival and life-treating complications. Since due to the medical improvement life span after HCT is constantly growing, focus should be pointed to better recognition and treatment of different gynecological disorders enabling maximum reproductive health and procreation if possible. This should be a concern of different specialists ensuring better quality of life in patients after HCT procedure.

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Battelfield Acupuncture and Femoral Nerve Block for Treatment of Postoperative Pain in Major Orthopedic surgery

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Abstract:

Introduction: Postoperative pain after major orthopedic surgery is extremely severe and especially after revision surgery where bone destruction is extensive. The role of postoperative analgesia is very important. Opioid analgesics are commonly used for this purpose in continuous infusion in combination with the intravenous administration of paracetamol, metamizole and ketoprofen.

Materials and methodes: The patient was admitted for revision surgery after a total hip endoprosthesis was installed. The patient is allergic to most analgesic medicines including fentanyl, alfentanyl, tramadol, buprenorphine, paracetamol, piroxicam, propifenazone, codeine, caffeine, diclofenac, ibuprofen. Only Ketoprofen and Oxycodonum are allowed analgesics.

In this case, postoperative analgesia was difficult because of the very narrow choice of analgesics. Researchers applied a regional femoral nerve block in combination with battlefield ear acupuncture, which has a pronounced analgosedative effect.

Pain was measured with an audio visual scale and allowed analgesics were added as needed

Results: The patient was satisfied with achived analgesia and the side effects of analgesics were avoided.

Conclusions: Battelfield ear acupuncture in combination with nerve block is a very effective method in the treatment of postoperative pain in major orthopedic surgery.

Keywords: Major orthopedic surgery, Analgesia, Battelfield ear acupuncture, Nerve block

Sažetak:

Akupunktura bolnog polja i blokada bedrenog živca za liječenje postoperativne boli u velikoj ortopedskoj kirurgiji

Uvod: Postoperativna bol nakon velike ortopedske kirurgije izuzetno je jaka, posebno nakon revizijske operacije, gdje je uništavanje kostiju opsežno. Uloga postoperativne analgezije vrlo je važna. U tu se svrhu obično koriste opioidni analgetici u kontinuiranoj infuziji u kombinaciji s intravenskom primjenom paracetamola, metamizola i ketoprofena.

Materijali i metode: Pacijent je primljen na revizijsku operaciju nakon ugradnje totalne endoproteze kuka. Pacijent je alergičan na većinu analgetskih lijekova uključujući fentanil, alfentanil, tramadol, buprenorfin, paracetamol, piroksikam, propifenazon, kodein, kofein, diklofenak, ibuprofen. Samo su Ketoprofen i Oxycodonum dopušteni analgetici. U ovom je slučaju postoperativna analgezija bila teška zbog vrlo uskog izbora analgetika. Istraživači su primijenili regionalni bedreni bedreni živac u kombinaciji s akupunkturom uha na bojnom polju, koja ima izražen analgosedativni učinak. Bol se mjerila audiovizualnom skalom i dodavali dopušteni analgetici po potrebi

Rezultati: Pacijent je bio zadovoljan postignutom analgezijom i izbjegnute su nuspojave analgetika.

Zaključci: Akupunktura uha Battelfield u kombinaciji s blokadom živaca vrlo je učinkovita metoda u liječenju postoperativne boli u velikim ortopedskim operacijama.

Ključne riječi: Velika ortopedska kirurgija, analgezija, akupunktura uha Battelfield, blok živca

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Introduction

After revision surgery of the total hip endoprosthesis, moderate to severe postoperative pain occurs due to severe bone destruction. It is very important to control postoperative pain becouse inadequate analgesia can delay adequate rehabilitation, prolong hospital stay and increase treatment costs[1,2,3].

Opioid analgesics are commonly used in the treatment of postoperative pain, which is known to have a large number of side effects. They are often combined with other analgesics (paracetamol, methamizole, NSAIDs) which also have numerous side effects. Therefore, it is necessary to determine the optimal dose that will suppress the pain while causing as few side effects as possible[4,5,6].

The National Institutes of health and the World Health Organisation approved acupuncture as a safe and effective method of treating pain[7,8].

Inserting needles into acupuncture points releases endorphins, enkephalins and dynorphins, which are important substances in the mechanisms of analgesia. Many studies prove this[9,10,11].

Analgesic sedation protocol Battlefield ear acupuncture is used to treat many pain conditions. Author Niemtzow start to use it in 2001. Needles are inserted on ear five specific spots. It cause changes the processing of pain in the central nervous system. Release of beta-endorphins allows short-term analgesia and release of anti-inflammatory cytokines allows long-term analgesic effects. This therapy reduces headaches, neuropathic pain and musculoskeletal pain[12,13].

Meta-Analysis and systematic rewiew analised Battlefield ear acupuncture studies. Pain scores were significantly reduced, there were no significant side effect and patients were satisfied[14].

Femoral 3-in-1 nerve block discontinue sensation and motor power in 3 nerve distributions (femoral nerve, lateral femoral cutaneous neve, obturator nerve). It is usefull for treatement of postoperative pain on hip area.

Regional nerve blocks have a benefit in reducing pain after procedures on hip area and significantly reduce need for opioides.[15]

Materials and methodes

The participant was admitted to the department of orthopedics for revision surgery after the total hip endoprosthesis was installed. The participant was allergic to most analgesic drugs including fentanyl, alfentanyl, tramadol, buprenorphine, paracetamol, piroxicam, propifenazone, codeine, caffeine, diclofenac, ibuprofen. Only Ketoprofen and Oxycodonum were allowed analgesics. Spinal anesthesia was performed for surgery. Pain was postoperatively measured by a visual analogue scale (VAS) in which 0 indicates the pain-free status and 10 the strongest pain possible. Analgesia was determined based on the VAS scale. Postoperative analgesia was difficult to performe because of the narrower choice of analgesics. The ivestigators first choice was 3 in 1 femoral nerve regional block in combination with Battlefield ear acupuncture that has a strong analgo sedative effect.

Femoral block 3 in 1 was performed with ultrasound control, 10 ml of 2% Lidocain and 10 ml of 0.5% Levobupivacaine were administered around the nerve. Battelfield ear acupuncture was performed with disposable sterile needles that were placed at five points of the ear (Omega2, ShenMen, Zero point, Thalamus, and Gyrus cinguli) on both ears and left for 30 minutes and then removed.

During the 24h postoperative period, the patient additionaly received Ketoprofen 2 x 100 mg iv and Oxycodon 20 mg iv for analgesia. The strongest pain was recorded after spinal anesthesia was weaken and just before the application of nerve block and acupuncture, and the VAS scale was 8 and 9. Thereafter, the pain gradually decreased to VAS 5 and 4 and overnight to 3 and 2.

Results

The participant was very satisfied with achived analgesia. The use of a large amount of analgesics was avoided and also a number of potential side effects. Conclusion is that the combination of nerve block and Battelfield acupuncture is very effective in treating pain after extensive orthopedic surgery.

Discussion

Battelfield ear acupuncture was developed by Niemtzow who investigated a model of ear acupuncture for effective analgesia. Battelfield ear acupuncture provides a significant analgesic effect in a very short period after administration[16].

MRI studies suggest that hypothalamus, thalamus, gyrus cinguli, and cerebral cortex are involved in the modulation of pain in the central nervous system by the Battlefield method[17].

The analgesic effect of acupuncture has been proved in many controlled clinical trials on large samples of participants. This effect is mainly caused by increased release of endorphins (endogenous opioid neuropeptides)[18].

Acupuncture causes an increase in beta-endorphin levels from the pituitary-hypothalamic region in the cerebrospinal fluid. The use of opiate antagonists abolishes analgesia achieved by acupuncture[19].

Acupuncture affects the sympathetic system and the opioid receptors of the spinal cord[20].

Very fast, effective and long-lasting analgesia is achieved by femoral nerve block 3 in 1 for severe pain in the hip area. The method is very simple and safe[21].

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Ventricular Assist Device Support in Advanced Heart Failure Patient with Congenitally Corrected Transposition of the Great Arteries and Dextrocardia- Case Report and Review

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Abstract:

Congenitally corrected transposition of the great arteries (ccTGA) is congenital cardiac malformation with an incidence of 0.5% of all patients with congenital heart defects. Dextrocardia is reported among these patients up to 20%. We report a 52-year old female patient with ccTGA and dextrocardia with situs solitus. Due to congestive heart failure refractory to medications and high pulmonary vascular resistance multidisciplinary team decided for long term unloading with ventricular assist device as a bridge to heart transplant candidacy. In September 2017 intrapericardial ventricular assist device (centrifugal continuous flow, fully magnetically-levitated technology) was implanted in failing systemic ventricle. Accurate imaging (transthoracic echocardiography with contrast, transoesophagic echocardiography, cardiac MSCT) in multidisciplinary heart team is pivotal in successful implantation of small size intrapericardial VAD in patient with complex anatomy as ccTGA and dextrocardia. Because the existing literature consists mainly of case reports, management should include the stepwise introduction of the treatment modalities and close monitoring of the clinical response as well as heart multidisciplinary team.

Keywords:

congenitally corrected transposition of the great arteries; dextrocardia; ventricular assist device; heart failure

Sažetak:

Podrška za ventrikularne pomoćne uređaje kod pacijenta s naprednom srčanom insuficijencijom s kongenitalno korigiranom transpozicijom velikih arterija i dekstrokardijom - prikaz i pregled slučaja

Kongenitalno korigirana transpozicija velikih arterija (ccTGA) kongenitalna je srčana malformacija s incidencijom od 0,5% svih bolesnika s urođenim srčanim manama. Dekstrokardija je zabilježena među tim bolesnicima i do 20%. U ovom radu prikazujemo 52-godišnju pacijenticu s ccTGA i dekstrokardijom sa situs solitusom. Zbog kongestivnog zatajenja srca otpornog na lijekove i visokog plućnog vaskularnog otpora multidisciplinarni tim odlučio se za dugoročno rasterećenje s ventrikularnim pomoćnim uređajem kao prijelaznim rješenjem do indikacije za transplantaciju srca. U rujnu 2017. ugrađen je intraperikardijalni ventrikularni pomoćni uređaj. Precizno slikanje (transtorakalna ehokardiografija s kontrastom, transoezofagična ehokardiografija, MSCT srca) u multidisciplinarnom srčanom timu ključni su za uspješnu implantaciju intraperikardijalnog VAD-a malih dimenzija kod pacijenta sa složenom anatomijom poput one u ccTGA i dekstrokardija. Budući da se postojeća literatura sastoji uglavnom od izvještaja o slučajevima, odluke u liječenju trebale bi uključivati postupno uvođenje modaliteta liječenja i pomno praćenje kliničkog odgovora, kao i multidisciplinarnog tima za rad srca.

Ključne riječi:

kongenitalno korigirana transpozicija velikih arterija; dekstrokardija; ventrikularni pomoćni uređaj; zastoj srca

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Introduction

Congenitally corrected transposition of the great arteries (ccTGA) is congenital cardiac malformation with an incidence of 0.5% of all patients with congenital heart defects. Morphologically, ccTGA comprises a combination of atrioventricular and ventricular-arterial discordance ("double discordance")[1]. CcTGA is accompanied by associated cardiac lesions in up to 80% of cases, ventricular septal defects (VSDs) being most common of all in 60% to 80% of cases and pulmonary stenosis in ≈ 50%[1,2]. Prevalence of ccTGA is 0.5%, with dextrocardia reported among 20% of them[3,4]. Patient with isolated ccTGA are often asymptomatic for decades, but as right ventricle (RV) and tricuspid valve (TV) support systemic circulation, higher afterload can over tome lead to gradual dysfunction and failure of systemic ventricle and systemic atrioventricular valve. Patients with congenitally corrected transposition of great arteries (ccTGA) present with heart failure commonly in the fourth or fifth decade of life[3,4]. Because therapeutic options are limited and probability of increasing number of individuals with TGA with longer survival, management of these patients needs an effective strategy[5,6].

Case report

We report a 52-year old female patient with ccTGA and dextrocardia (Figure 1) with situs solitus. In 2008, she was first admitted to our institution because of heart failure, and diagnosed with ccTGA combined with dextrocardia.

For approximately ten years she was treated with heart failure medications, angiotensin-receptor blockers, beta blockers, spironolactone which subsequently changed to pelerine. Optimal therapy improved her condition to well compensated ccTGA over longer period of time. In the January 2017, despite optimal medications, she developed congestive heart failure and required repeated hospitalisations with symptoms of congestion and low cardiac output with elevated NT-pro-BNP levees up to 10752 pg/mL. Her cardiac functional status decreased to NYHA (New York Heart Association) class IV. Laboratory test results indicated liver and renal dysfunction. She was treated with inotropic support and careful volume management to maintain euvolemic status. Inotropic therapy was administered in addition to intravenous prostaglandine infusion. However, her condition deteriorated to INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Profile 2. Echocardiography confirmed the presence of ccTGA and dextrocardia with situs solitus, with ejection fraction of dilatator and trabeculateted systemic ventricle less than 20%. Preoperative echocardiography (Figure 2) systemic ventricular end-diastolic dimension and endsystolic dimension were 6.0/5.5 cm, and a non-systemic ventricular ejection fraction of 40%. Patient also had severe atrioventricular systemic valve insufficiency, morphologically tricuspid valve, and mild atrioventricular non systemic valve insufficiency, morphologically mitral valve. She had mild pulmonic valve insufficiency with mild spumoni obstruction due to protrusion of the membrane of basal part of interventricular septum. No aortic valve insufficiency and no ventricular septal defect was found. She was at that time evaluated for heart transplantation and placed on the cardiac transplant waiting list.

Despite medication her condition deteorated, so invasive haemodynamics measurements were repeated revealing RVP 71/6/19mmHg, PCWP 29mmHg, CI 1,39 L/min/m2, MPAP 45mmHg, PVR 6,24WU. Pulmonary hypertension and pulmonary vascular resistance may have induced right heart failure in the transplanted heart, so multidisciplinary heart transplant team

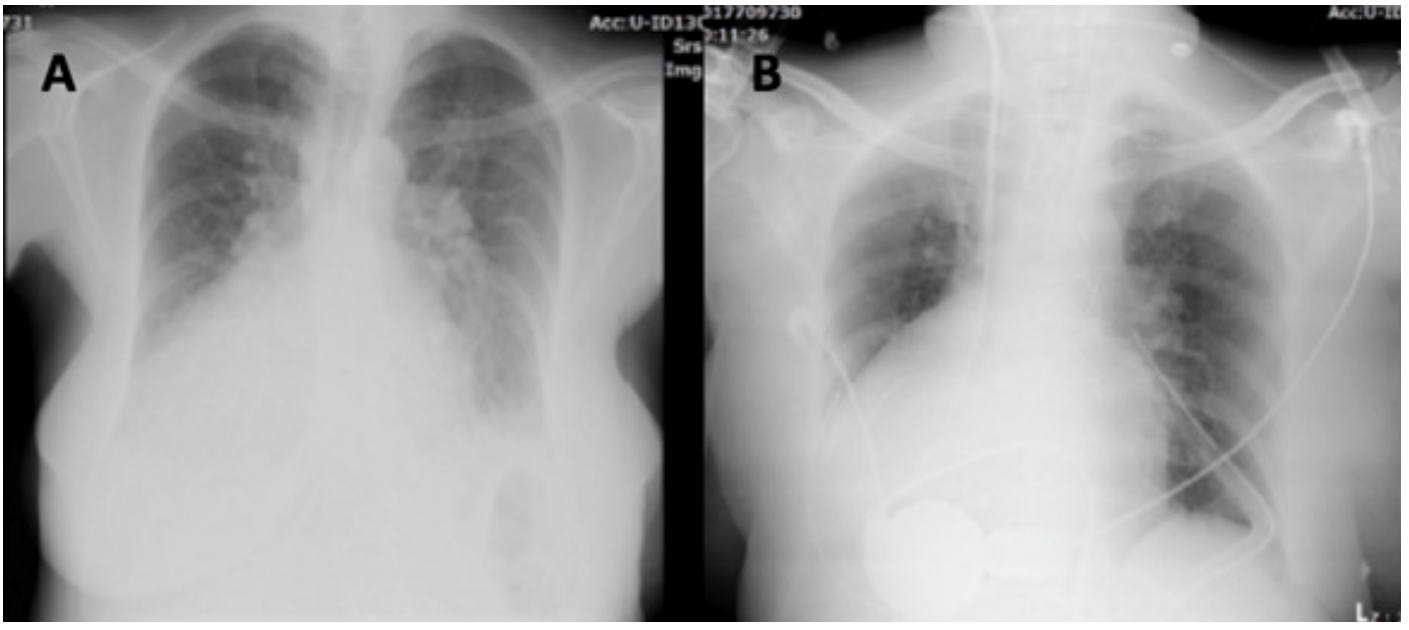


Figure 1. RTG showing ccTGA and dextrocardia with situs solitus A. before ventricular assist device implantation and B. after ventricular assist device implantation

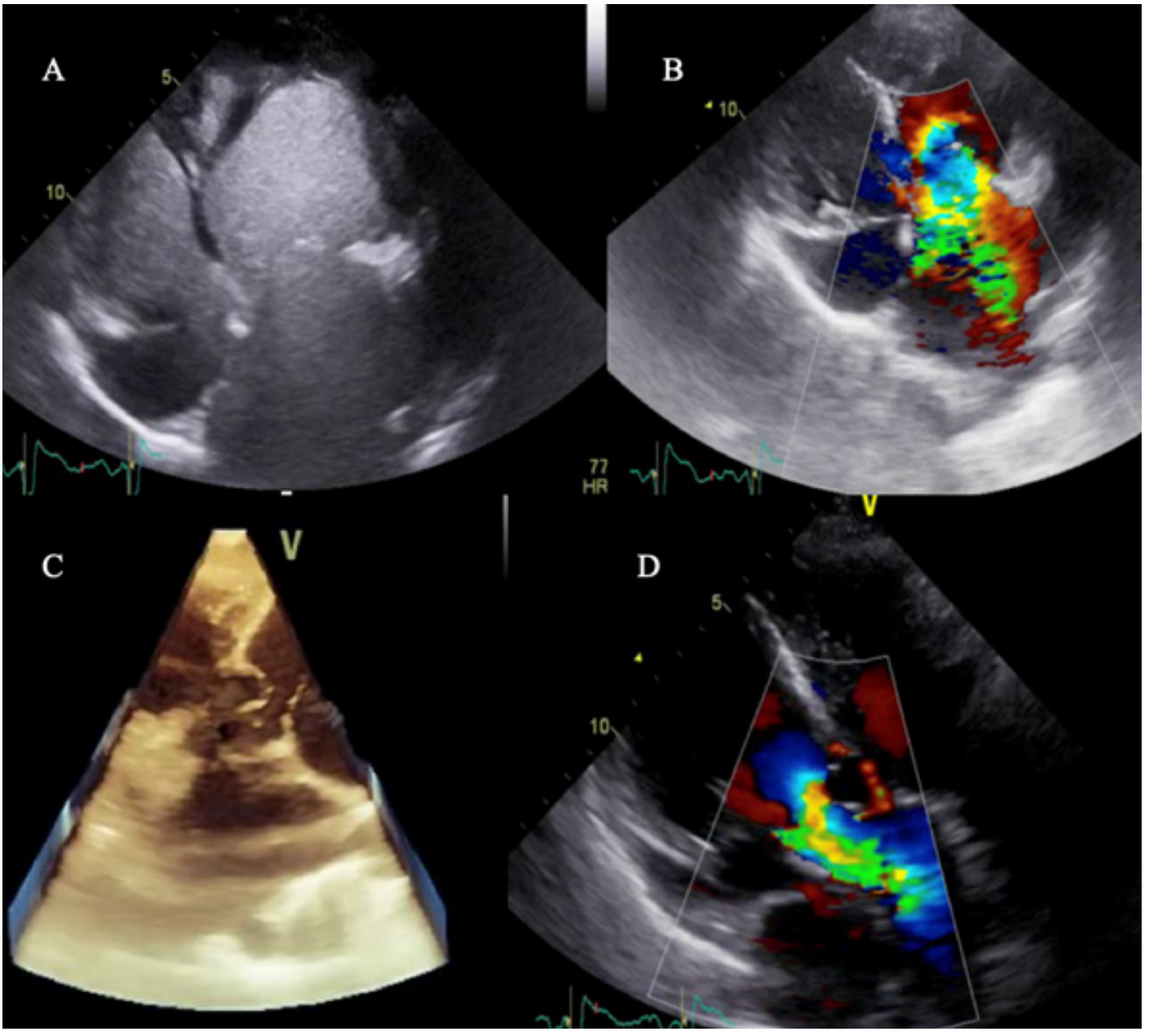


Figure 2. Transthoracic echocardiography A. ccTGA and dextrocardia with situs solitus, with ejection fraction of dilated and trabeculateted systemic ventricle less than20%. B. severe atrioventricular systemic valve insufficiency (morphologicaly tricuspid valve) C.D. mild pulmonic valve insufficiency with mild subpumonic obstruction due to protrusion of the membrane of basal part of interventricular septum.

decided for long term unloading with ventricular assist device as a bridge to heart transplant candidacy. In September 2017 intrapericardial ventricular assist device (centrifugal continuous flow, fully magnetically-levitated technology) (Figure 4) was implanted at midline position. We used preoperative optimization of subpulmonic ventricle as in all patients with biventricular failure, comprised of aggressive dehydration with diuretics in combination with inotropic therapy levosimendan prior to VAD implantation. We aimed to unload and optimize the subpulmonic ventricle to achieve mechanical circulatory support for systemic ventricle alone by targeting central venous pressure (CVP) of less than 10 mm Hg. Postprocedural hospital course was complicated by mild subpulmonic (nonsystemic) ventricle failure managed by inotropic support and pump adjustment. Operative technique cardiopulmonary bypass was used. The ventricular cavity was closely inspected before cardiopulmonary bypass was on because it is morphologically a right ventricle with many more trabeculations and possible sites for thrombus formation. The device was inserted to the inferior, diaphragmatic surface of the morphologic RV free wall. As an nonobstructed inflow optimal positioning of the inflow cannula is paramount, we achieved that by using intraoperative transesophageal echocardiography (TOE) to find the optimal device implantation site. We used pre and perioperative transoesophageal echocardiography (TOE) for guidance and positioning the inflow cannula (Figure 3) in the morphological right ventricle (systemic ventricle), positioning and extracting moderatory band which could induce inflow cannula obstruction, complicated by dextrocardia present in our patient. TOE guided placement of the inflow cannula was done when the heart was still full before going on cardiopulmonary bypass and positioned as dextrocardia, as failing systemic morphologic RV was dilated and a globular shape. Transesophageal echocardiography was also used to confirm cannula position after coming off bypass. Careful resection of adequate amount of muscle trabeculation or muscle bands to prevent obstruction to the inflow cannula was done, and papillary muscles were preserved. Outflow cannula was placed beneath the sternum and attached at in the lateral right side of ascending aorta. In early postoperative period, clinical course was complicated with mild failing of subpulmonic ventricle, managed with medication therapy of

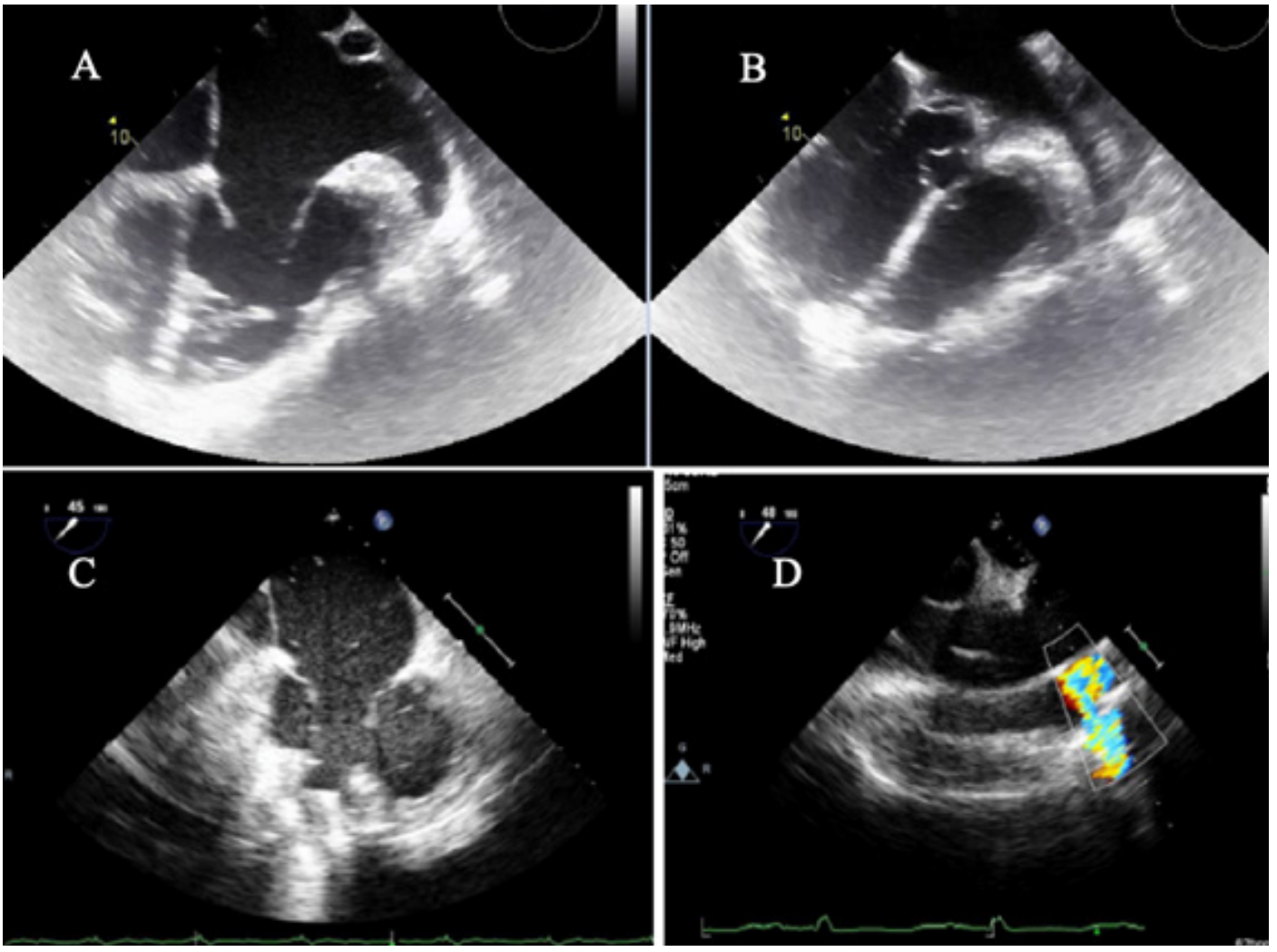


Figure 3. Preoperative A.B. transoesophageal echocardiography –ccTGA and dextrocardia with situs solitus, and C.D. postoperative transoesophageal echocardiography showing the position of the inflow cannula.

dobutamin and diuretic iv. Patient was discharged four weeks after implantation of ventricular assist device, taking pharmacological treatment of varfarin, acetylsalicylic acid, angiotensin- receptor blocker, beta blocker, eplerenon and is doing well, currently in NYHA class II. Eight months right heart catheterization was done revealing now PVR of 3,1 WU as result of good unloading of systemic ventricle by ventricular assist device.

Discussion

Congenitally corrected transposition of the great arteries (ccTGA) is congenital cardiac malformation with an incidence of 0.5% of all patients with congenital heart defects often combined with other cardiac malformation, in few cases with dextrocardia as in our patient.

Patients with transposition of great arteries (TGA) undergone a routine arterial switch operation (ASO) within the first week of life in In Europe in 25–30% of patients[7]. This very early approach is controversial and upper age limit for a primary ASO in TGA cannot be determined. In case of late failure of the systemic ventricle after the Senning or Mustard operation is controversial, and treatment options are medical management or cardiac devices possibly followed by heart transplant, or staged anatomical repair. Medical therapy for congestive heart failure include serial echocardiographic follow-up combined with exercise testing when needed for detection of early ventricular or valvular function changes[8]. Mild systemic ventricular dysfunction with mild-to moderate valvular regurgitation can be treated conservatively with afterload reduction using angiotensin-converting enzyme inhibitors, b-blockers and diuretics[8,9]. Progressive aortic insufficiency and arrhythmias add to morbidity and mortality of these patients[10].

Also use of left VAD for RV failure following the Mustard operation has been described[11]. But approximately one-quarter of these patients will need a heart transplant[8,12].

Patients presenting with advanced right ventricular or biventricular failure, severe valvular dysfunction, arrhythmias resistant to therapy or heart block should be enrolled in the heart transplant program[8,12]. Heart transplant is a well-established treatment strategy and is likely to be a superior option to anatomical conversion challenging[12,13].

Patients with congenital heart disease, as in our case ccTGA present with unique challenges for mechanical assist device implantation because of their individual specific anatomical features or previous operations. Systemic and pulmonary vascular resistances (PVR) add to the complex interplay of the preceding factors as in our case where we decided to implant VAD in systemic ventricle for unloading the systemic ventricle and thus to decrease PVR over time. Few reports describe the possibility of using long -term VAD support as an alternative treatment option for ccTGA patients with end-stage heart failure either as a bridge to transplant or destination therapy treatment strategy[13-17].

In our case ventricular assist device implantation was feasible using different specific to our patient cannulation site positioned and verified by echocardiography and pump performance before

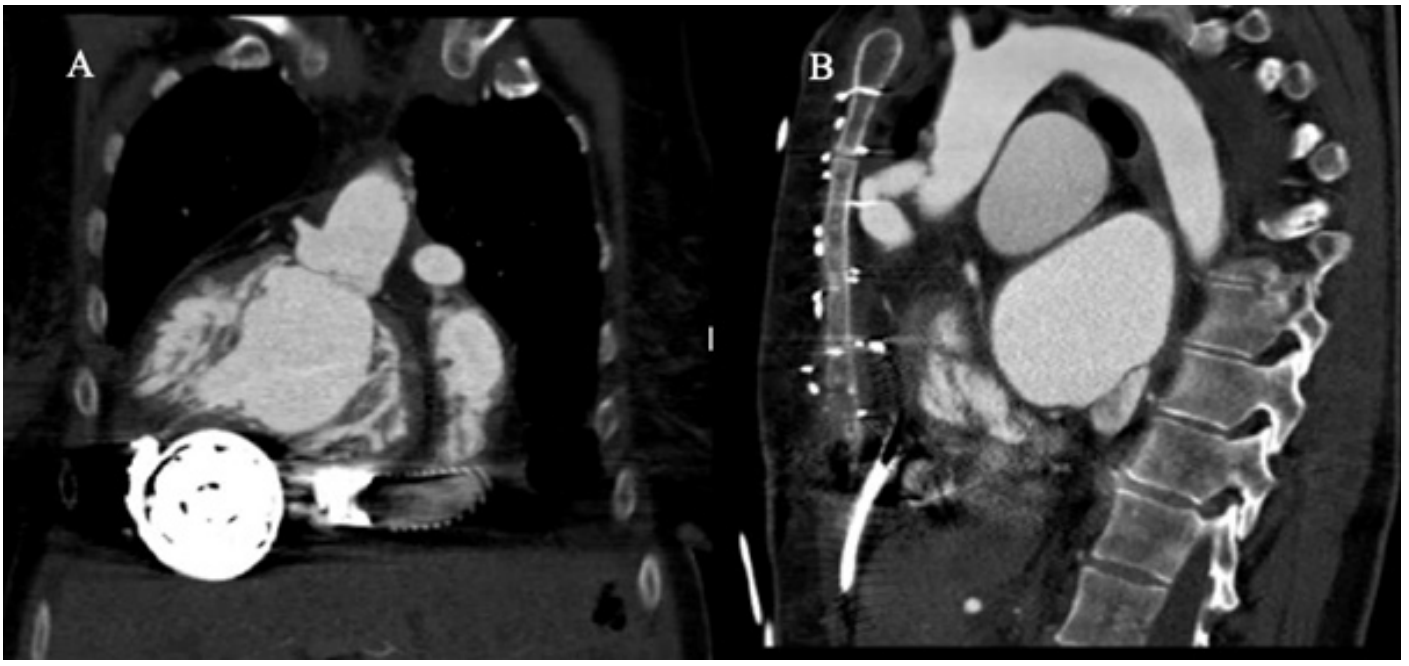


Figure 4. Multy slice Computer Tomography (MSCT) showing A. position of ventricular assist device in systemic ventricle and dextrocardia and B. mild kincking of outflow graft beneath sternum with no hemodinamic significance

leaving the operating room.

Conclusion

Implantation of ventricular assist device in systemic ventricle in ccTGA has been described in small groups of patients and in our knowledge in a couple patients with ccTGA combined with dextrocardia[13-17]. Accurate imaging (transthoracic echocardiography with contrast, transoesophagic echocardiography, cardiac MSCT) in multidisciplinary heart team is pivotal in successful implantation of small size intrapericardial VAD in patient with complex anatomy as ccTGA and dextrocardia. Because the existing literature consists mainly of case reports, management should include the stepwise introduction of the treatment modalities and close monitoring of the clinical response as well as heart multidisciplinary team.

Author contributions:

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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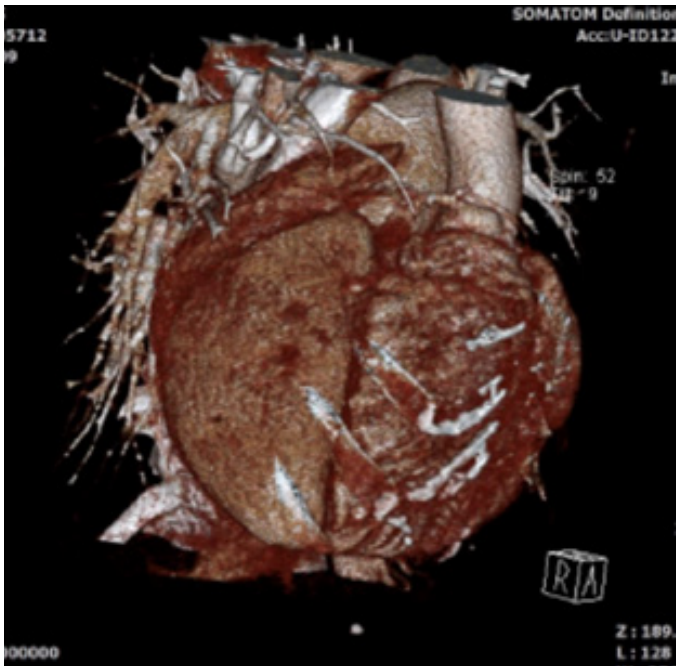


Figure 5. 3-D reconstruction showing systemic, morfhologicaly right ventricle.

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Indistinctly Synchronous Lung and Base of the Tongue Adenocarcinoma: Case Report and Discussion of Possible Patterns of Disease Development

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Abstract:

Lung adenocarcinoma accounts for about 40% of all lung cancers and is characterized by distinct cellular and molecular features. Distant metastases from primary lung cancer are frequent, however metastasis of the tongue is quite rare and unexpected. If there is existing evidence of metastasis in tongue, primary tumor is most probably generally disseminated and prognosis is poor. Such patients require a complete staging workup to evaluate the extent of disease, because tumor stage plays a major role in determining the choice of treatment. In this case report we want to present an unusual case of simultaneous lung and base of the tongue adenocarcinoma and discuss the possible patterns of disease development.

Keywords: lung adenocarcinoma, tongue, metastasis

Sažetak:

Nejasno sinkroni adenokarcinom pluća i baze jezika: prikaz slučaja i rasprava o mogućim obrascima razvoja bolesti

Adenokarcinom pluća čini oko 40% svih karcinoma pluća i karakteriziraju ga različite stanične i molekularne značajke. Česte su udaljene metastaze iz primarnog karcinoma pluća, međutim metastaze u jeziku prilično su rijetke i neočekivane. Ako postoje dokazi o metastazama u jeziku, primarni tumor je najvjerojatnije širen, a prognoza loša. Takvi pacijenti zahtijevaju cjelovitu obradu kako bi se procijenio opseg bolesti, jer stadij tumora igra glavnu ulogu u određivanju izbora liječenja. U ovom slučaju želimo predstaviti neobičan slučaj istodobnog adenokarcinoma pluća i baze jezika i razgovarati o mogućim obrascima razvoja bolesti.

Ključne riječi: adenokarcinom pluća, jezik, metastaze

Case Report

The 66-year-old Caucasian male patient was referred to our Department with histologically proven adenocarcinoma of the base of the tongue. His primary symptom was difficulty in swallowing and breathing although patient was not dysphonic and was on regular diet. Patient also reported occasional haemoptysis in last two months. The patient was a smoker with a long history of significant consumption of alcohol and sawdust exposure starting 45 years ago, and no history of previous tumor disease. Clinical examination revealed a left-sided tumor located at the base of the tongue, partially covering the epiglottis. MSCT scans revealed an exophytic, mushroom-like tumor of the left side of the base of the tongue connected to the epithelium by a thin pedicle with practically no infiltration of the surrounding tissue. No suspected positive lymph nodes were found in the neck.

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Furthermore, routine chest MSCT scan additionally revealed a tumor measuring 30 mm in diameter located in the lower left lung. Subsequently CT-controlled transthoracic fine needle biopsy was performed and histopathological analysis revealed a tiny focus consistent with adenocarcinoma. Routine PCR analysis for EGF receptor was performed, revealing negative results, but the specimen was inadequate for further immunohistochemical analysis to confirm the primary lung carcinoma. PET-CT showed no other tumor masses, except for the pulmonary and base of tongue tumor. At that stage the patient refused any kind of surgery and he was presented and discussed at the oncology group meeting, where the diagnosis of pulmonary adenocarcinoma cT1 N0 M1b, stage IVa, was made. Patient was treated with pemetrexed in combination with cisplatin chemotherapy protocol. After receiving two cycles of chemo, patient refused further therapy and medical assistance due to personal reasons. Two months later the patient presented to outpatient clinic complaining of having difficulty swallowing. MSCT scan showed a reduced size of pulmonary tumor with slightly increased tumor size at the base of tongue. Considering localization and need for subsequent reconstruction, comprehensive surgical procedure followed, including partial glossectomy, selective neck dissection (I-IV) and reconstruction with microvascular flap (radial forearm). Histopathological examination of the surgical specimen revealed an exophytic tumor on the base of the tongue, measuring 36 mm, composed of atypical epithelial cells forming alveolar, tubular and cribriform pattern with multiple necrotic foci. Neck dissection revealed a conglomerate composed of several positive lymph nodes in regions II and III. Immunohistochemical analysis revealed negative reactivity with Napsin A, CK5/6, TTF-1 and CK20, and partially positive reactivity with CDX-2 and CK7. The diagnosis was adenocarcinoma of the tongue with lymph node metastasis. PCR analysis for EGF receptor was negative. Oncology group decided to proceed with the treatment with pembrolizumab immunotherapy according to the protocol. After receiving 5 cycles of immunotherapy, MSCT scan showed clear status intraorally and in the neck, without evidence of any suspicious pulmonary mass. At present, 12 months after the treatment there are no signs of recurrent disease neither in the lung nor in the neck.

The accurate diagnosis of histologically identical simultaneous tumors is diagnostically challenging. Primary adenocarcinoma of the tongue is exceptional, therefore presented case has been considered as primary lung adenocarcinoma. The presence of lung cancer metastasis in the base of the tongue is a rare clinical entity and according to available literature several cases have been reported[1].

Due to lack of material obtained from the lung tumor with fine needle biopsy we could not perform immunohistochemical markers to confirm lung origin of the tumor (TTF-1, Napsin A) and to establish relationship between lung and base of the tongue tumor. Although, presented case has been considered as primary lung adenocarcinoma, we established three possible scenarios for such a disease development: 1.primary pulmonary carcinoma metastasing into the tongue, 2. primary base of tongue carcinoma metastasing into the lung, 3. or synchronous, independent pulmonary and base of tongue carcinoma.
For the third hypothesis, of two synchronous, independent tumors we do not have enough histological evidence to prove whether these tumors are of the same or different origin.
The second hypothesis, where base of the tongue tumor is primary and lung is metastasis, is possible but in our opinion is not likely. Main reason for this is exophytic grow, practically without infiltration of tongue tissue. Secondly, MSCT and PET-CT negative neck at first visit. Positive neck was developed several months after initial chemotherapy.
The first hypothesis, of the tongue tumor being metastasis of the lung adenocarcinoma, in our opinion, is the most likely scenario. Possible patterns of metastasing into tongue could be haematological spread or inoculation of cancer cells into mucosal epithelium. In our case spread through the blood stream is unlikely for two reasons. Firstly, the base of the tongue tumor would be the only metastasis and in all other reported cases tongue metastasis was one of many other metastases. Secondly, the blood stream metastasis would most likely present in the base of the tongue, submucosally, and not only intraepithelially. For these reasons we believe that the present case is not induced by hematological spread and the theory of epithelial inoculation with cancer cells originating from lung tumor is the most likely. Models investigated in animals confirm the possibility of such a pattern. We believe that the tongue metastasis was caused by inoculation of malignant cells by coughing and seeding into the lingual epithelium. Hayasaka et al.[2] reported a case of multiple endotracheal metastases of lung cancer after bronchoscopic intervention. Later regional neck disease was caused by lymphatic spread of tongue tumors and we base that opinion on the negative MSCT and PET-CT scans during initial and control check-ups.
To our knowledge, this is the only recorded case of simultaneous adenocarcinoma of the lung and the base of the tongue (as a single metastasis). Although, due to the lack of histological evidence, we could not establish clear pattern of disease development, we believe that this case report could contribute to a better understanding of the possible disease spread and subsequently its treatment.

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Nodular Pulmonary Sarcoidosis Mimicking Disseminated Malignant Disease

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Abstract:

Due to its varying and often mimicking appearance, sarcoidosis is considered one of the great imitators in medicine.

A rare form of pulmonary sarcoidosis, the nodular form, can be mistaken for disseminated malignancy. We present the case of 38-year-old patient, whose chest x ray demonstrated a large number of pulmonary nodules, more than 1 cm in diameter, predominantly in a peripheral distribution, with bilaterally enlarged hila, thus making disseminated malignant disease a part of differential diagnosis.

The sight of multiple lung nodules can be very suggestive for metastatic disease and misleading in everyday clinical practice.

Keywords: Sarcoidosis, Mimicking, Malignant disease, Nodules, Radiology; Nodular pulmonary sarcoidosis

Sažetak:

Nodularna plućna sarkoidoza prikazana kao imitacija diseminirane maligne bolesti

Zbog svoje raznolike prezentacije i brojnih sličnosti s drugim bolestima, sarkoidoza je znana kao veliki imitator u medicini. Jedan od oblika sarkoidoze, nodularna plućna sarkoidoza, lako se može zamijeniti s malignom diseminiranom bolešću. Prikazujemo slučaj 38-godišnjeg pacijenta, čiji je torakalni rendgenogram pokazao veći broj periferno smještenih plućnih nodusa promjera većih od 1 cm uz obostrano uvećane hiluse. Takav nalaz upućivao je na diseminiranu malign bolest kao jednu od diferencijalnih dijagnoza. Cilj ovog prikaza slučaja je podsjetiti kolege na nodularnu plućnu sarkoidozu kao jednu od mogućih dijagnoza u slučaju ovako sugestivnih nalaza kod pacijenata bez ranije poznate maligne bolesti.

Ključne riječi: Sarkoidoza, Oponašanje, Maligna bolest, Noduli, Radiologija, Nodularna plućna sarkoidoza

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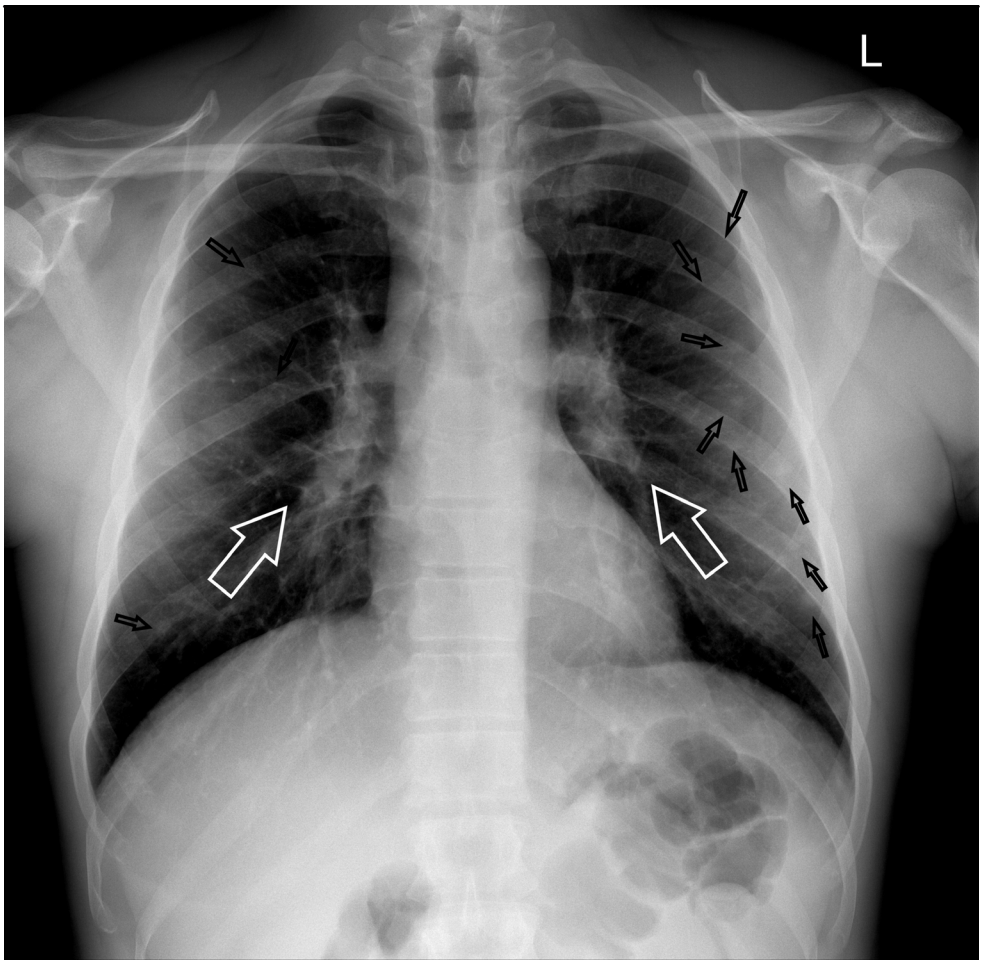


Figure 1. Chest X-ray shows large number of pulmonary nodules (black arrows), more than 1 cm in diameter, predominantly in peripheral distribution with bilateral enlarged hili (white arrows).

Introduction

Sarcoidosis is an idiopathic granulomatous disease which affects younger adults of all races, more commonly females, and those from northern Europe and Africa and the estimates of its prevalence in Europe ranges from 1 to 64 per 100 000 persons[1]

A considerable number of different organs and organ systems may be involved, the lungs being on the top of the list with 90% of the cases.

Diagnosis of sarcoidosis requires 3 elements: (a) radiographic and clinical findings consistent with sarcoidosis, (b) exclusion of diseases that present similarly, and (c) biopsy of the most accessible lesion, demonstrating noncaseating granulomas on histopathology[2].

When it comes to imaging, pulmonary sarcoidosis is best recognized for its typical presentation of mediastinal lymphadenopathy, occurring in 95% of the patients.[3]

Atypical radiographic presentation of pulmonary sarcoidosis varies, however, from alveolar opacities in alveolar sarcoidosis to distinct lung nodules in nodular form.[1]

The nodular form is the rarest form of pulmonary sarcoidosis and has an estimated prevalence of 2,4-4 %[4,5]. In most patients with nodular pulmonary sarcoidosis (NPS), radiographic imaging shows bilateral nodules measuring 1-7 cm in diameter and mediastinal lymphadenopathy[4,5,6]. However, NPS can display a whole array of other radiographic features apart from the above mentioned, such as pleural effusion, solitary mass, air bronchogram, cavitation, and pleural based masses. Knowing the radiographic appearance of NPS is important, since this may well be the only sign of the disease, as extrapulmonary involvement is not always present.[7,8]

One should also keep in mind that the NPS is not the only benign condition which can mimic metastasis of the lung. Various other benign diseases can present as multiple lung nodules as well, including infections, other granulomatous diseases and A-V malformations, amongst others[9].

Case report

A 38-year-old male Caucasian presented to his GP with two erythematous macules of the forehead which erupted suddenly 3 months ago. He has a 20 pack-year history of cigarette smoking and an inconspicuous family history. He underwent tonsillectomy in the childhood and nasal septum operation 7 years ago. He has been suffering from asthma for 8 years, and is treated with Seretide Diskus 50 mcg/100mcg- 1 breath as needed, with poor therapy compliance.

At the time of his visit to GP he reported no difficulties with breathing, no cough, no fever, and routine blood tests were within normal ranges.

He was referred to a dermatologist who scheduled him for a skin biopsy of the lesions on the forehead.

Subsequent skin biopsy report described noncaseating granulomas and the dermatologist advised a chest x ray suspecting sarcoidosis.

Chest x ray (Figure 1) demonstrated a large number of pulmonary nodules, more than 1 cm in diameter, predominantly in peripheral distribution with bilateral enlarged hila, and the radiology report included lung metastases with hilar adenopathy in the differential diagnosis.

Considering the described bihilar lymphadenopathy pulmonologist insisted on skin and lung sarcoidosis as primary diagnosis and ordered additional laboratory and lung function tests. The test results were all within the reference values: RBC=5.17[x-1012/L], Hb=149 [g/L], HCT=0.439 [L/L], MCV=84.9 [fL], MCH=28.8 [pg], MCHC=339 [g/L], RDW=13.0

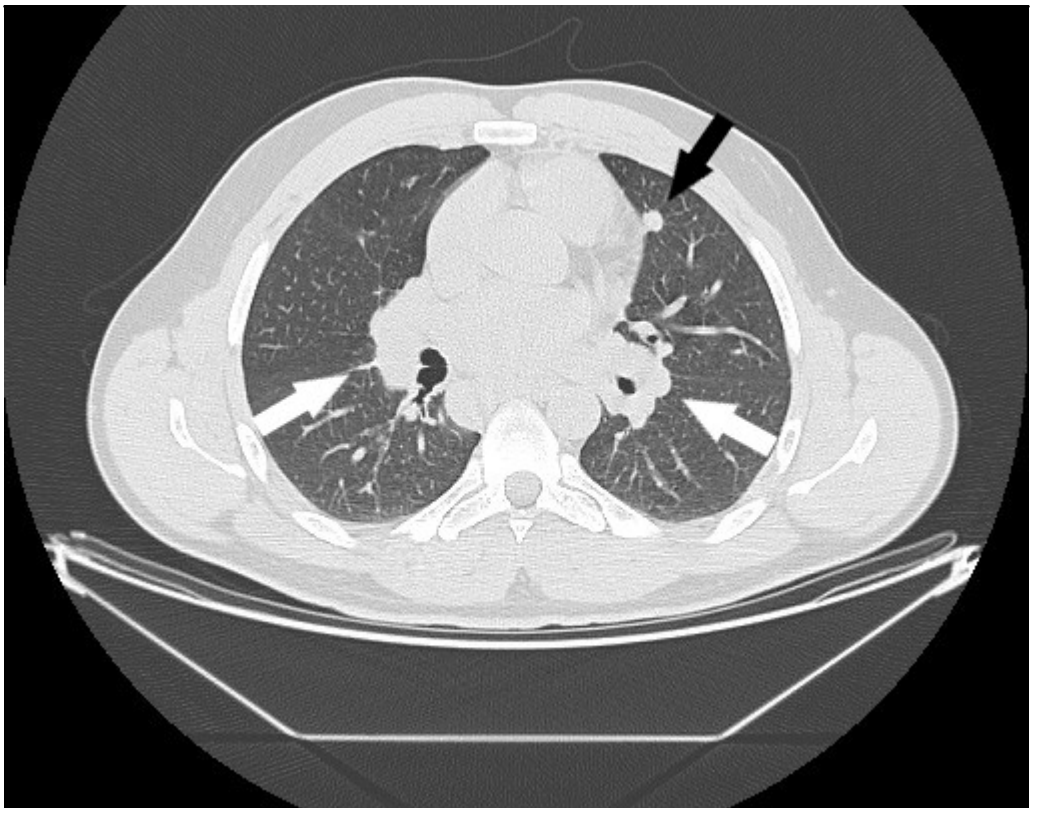


Figure 2. CT scan of the thorax in axial plane at the level of hili shows bihilar limphadenopathy (white arrows) and distinct lung nodule measuring 1,2 cm in diameter (black arrow).

[%], R-Ebl#=0.0 [x109/L], R-Ebl%=0 [/100 Lkc], TLC=5.0 [x109/L], EOS%=7.3, [%], BASO%=0.8 [%], NE%=61.4 [%], LYM%=17.6 [%], MONO%=12.9 [%], EOS#=0.37[x109/L], BASO#=0.04 [x109/L], ANC=3.07 [x109/L], LYM#=0.88 [x109/L], MONO#=0.65 [x109/L], PLT=219 [x109/L], MPV=10.7 [fL], GLU=4.3 [mmol/L], T-Bil=12 [umol/L], Urea=7.5 [mmol/L], CR=127 [umol/L], ALP=86 [U/L], ALT=28 [U/L], GGT=19 [U/L], LDH=225 [U/L], Ca=2.28 [mmol/L], P04=0.87 [mmol/L], CRP=1.9 [mg/L], GF-CKD=62 [mL/min/1,73m2], ACE=71 [U/L], Ca-portion=6.64 [mmol/L], Pportion=47.15 [mmol/L]; Urine Sp. Weight=1.027 [kg/L], PH=5.0, Lkc=0, Nitrites=0, Prot=+, GLC=NORM, Ketones=0, UBG=NORM, BIL=0, Blood=0, Erc=0-2, Lkc=0-2, Transitional epithelium cells=0-1, Mucus=+, Hyaline cylinders=2-4

The results of ensuing lung function tests were also within normal range: FVC 100 % (5,46 L), FEV1 98% (4,39 L), Tiff. 0,8, MEF 50 90%; DLCO 87% , Kco 102%, VA 87%.

Additional CT scan of the thorax (Figure 2) demonstrated multiple, well defined lung nodules up to 1,2 cm in diameter, again predominantly in a peripheral distribution with bilateral hilar and mediastinal lymphadenopathy. In all lung lobes no micronodules were detected in perilymphatic distribution. Clearly defined nodules were interpreted as granulomas consistent with nodular form of lung sarcoidosis.

The pumonologist confirmed the diagnosis and decided there was no need for bronchoscopy with bronchoalveolar lavage as well as mediastinal biopsy.

The patient started to experience pains in joints, which led the pumonologist to prescribe 30 mg of prednisone and replaced Seretide with Symbicort for asthma.

The pain in the joints ceased after few days and control x ray preformed after 4 months revealed the reduction of number and size of bilateral nodules and discrete reduction of bihilar lymphadenopathy.

Discussion

True pulmonary metastases that spread from primary solid organ tumors may vary in size and location, often favouring lung bases and the subpleural space. Although generally well defined, their borders can also be ill defined, and they can contain cavitations caused by bleeding and necrosis[9].

Sarcoidosis is a systemic granulomatous disease, which, like the rest of granulomatous diseases, may present itself with a cluster of granulomas in the lungs, as well as in other organs. Clearly defined nodules in organ's tissue can mimic disseminated malignancy.[10,11] Apart from nodular form of sarcoidosis, there are other granulomatous diseases that may lead to multiple nodules in the lungs, giving the impression of lung metastases, such as histoplasmosis and pulmonary hyalinizing granuloma[12,13].

Adding to the confusion, a number of other diseases can produce multiple pulmonary nodules, including pneumoconiosis, infectious (such as disseminated tuberculosis, invasive aspergillosis, chickenpox and measles), noninfectious inflammatory diseases (rheumatoid nodules, Wegener's granulomatosis), arteriovenous malformations, amyloid and infarcts[11].

These conditions should therefore also spring to mind when considering the right diagnosis.

Conclusion

Although the majority of sarcoidosis cases have a typical radiographic presentation involving hilar and mediastinal lymphadenopathy, with or without interstitial lesions in perilymphatic distribution, a small number of cases can be presented with distinct large parenchymal nodules, measuring from 1-7 cm in diameter, thus mimicking metastatic disease. It is therefore advisable to bear that in mind and include nodular form of pulmonary sarcoidosis as well as other possible benign conditions in differential diagnosis every time one sees large number of pulmonary nodules in a patient with not known primary malignancy.

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Franjo Kogoj's Role in the Yugoslav Academy of Sciences and Arts 1947–1972

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Abstract:

Up until now, extensive research has been conducted on the life and legacy of Franjo Kogoj (1894–1983) who was a prominent Croatian dermatovenereologist, full-time professor and Dean of the Zagreb School of Medicine, long-standing head of the University Department of Dermatology and Venereology, Zagreb University Hospital Centre, head of the Department of Dermatovenereology, Zagreb University School of Medicine, as well as a full member of the Yugoslav Academy of Sciences and Arts (YASA). In this paper, we shall present Kogoj's role in YASA after he was elected its full member in 1947, especially during his mandates as the first Secretary of the Department of Medical Sciences (1950–1958) and as Vice-President of the Academy (1958–1972). We shall follow his various publishing activities, international networking, as well as his role in the establishment of important medical institutions. The paper is based on Kogoj's articles published in Academy's periodicals, the documentation kept at the Academy's Division for the History of Medical Sciences and fragments of his material heritage preserved in the Croatian Museum of Medicine and Pharmacy of the Croatian Academy of Sciences and Arts.

Keywords: Franjo Kogoj, Yugoslav Academy of Sciences and Arts, Department of Medical Sciences YASA, dermatovenereology, Croatia, 20th century

Sažetak:

Uloga Franje Kogoja u Jugoslavenskoj akademiji znanosti i umjetnosti 1947-1972

O Franji Kogoju (1894. – 1983.), dermatovenerologu, redovitom profesoru Medicinskog fakulteta Sveučilišta u Zagrebu, dekanu i prodekanu u nekoliko mandata, šefu dermatovenerološke klinike tijekom četrdeset godina, redovitom članu Jugoslavenske akademije znanosti i umjetnosti, do sada je objavljen niz članaka. U ovom radu prezentirat ćemo njegovu ulogu u tadašnjoj JAZU nakon izbora za redovitog člana (1947.), kao prvog tajnika Odjela za medicinske nauke (1950. – 1958.) te kao potpredsjednika Akademije (1958. – 1972.), prateći njegove aktivnosti u realizaciji izdavačkih projekta, međunarodne razmjene, osnutka medicinskih ustanova i organizaciji kongresa. Pritom ćemo se većim dijelom koristiti Akademijinim publikacijama, dokumentacijom pohranjenom u Odsjeku za povijest medicinskih znanosti HAZU te dijelovima Kogojeve materijalne ostavštine, pohranjene u Hrvatskome muzeju medicine i farmacije HAZU.

Ključne riječi: Franjo Kogoj, Jugoslavenska akademija znanosti i umjetnosti, Odjel za medicinske nauke JAZU, dermatovenerologija, Hrvatska, 20. stoljeće

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Figure 1. Franjo Kogoj, author Vanja Radauš, Gliptotheque CASA

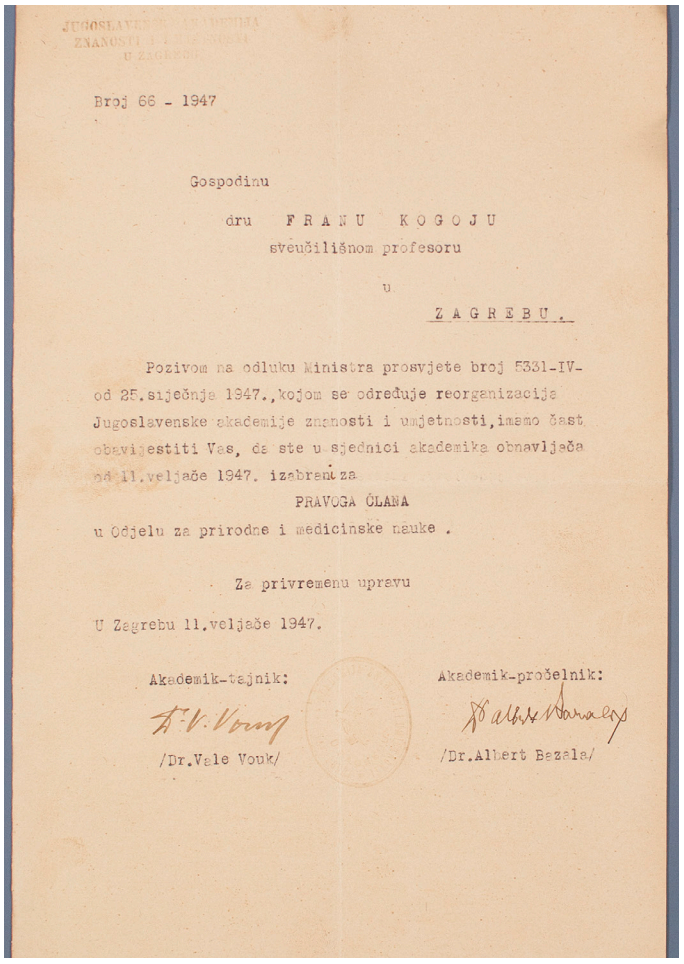
Franjo Kogoj's (1894–1983) role and contributions to the development of Croatian dermatovenereology have been examined in a series of articles[1-20], some of which were published by the Academy publications[21-25] (Figure 1). Unlike his printed works, Kogoj's material heritage has not yet been a subject of scientific analysis. For a number of years it has been stored in the Division for the History of Medical Sciences of the Croatian Academy of Sciences and Arts, later reassigned to the Croatian Museum of Medicine and Pharmacy of the Croatian Academy of Sciences and Arts (CASA) upon its foundation in 2014. The Kogoj Collection consists of framed photo portraits of 55 prominent dermatologists from all over the world, as well as 48 charters related to Kogoj's achievements and memberships in various professional societies, many of them international. Honorary diplomas, charters and acknowledgments have been awarded to Kogoj throughout his career for his distinguished role in the development of dermatovenereology, medicine and Croatian society in general. The greatest number of charters are related to Kogoj's honorary and other memberships in professional societies (in Europe and overseas) awarded to him in the period between 1930 and 1976, to memberships in other domestic and international medical societies (Croatian Medical Association, Slovene Medical Society, Yugoslav Medical Societies' Union) for the period between 1961 and 1977, and honorary plaques and acknowledgements (from schools of medicine in Zagreb, Sarajevo, Bratislava, Ljubljana and Rijeka) in the period from 1961 to 1975. The collection also includes diplomas and charters related to his membership in various academies that he received in the period from 1947 to 1975. This rich material forms the basis of an exhibition dedicated to Kogoj which will be opened in spring 2021, celebrating 100th anniversary of the Department of Dermatovenerology in Zagreb (established in 1921). This material is also a solid comparative foundation for revising the existing knowledge related to Kogoj's honorary and other memberships in various associations, as well as the reconstruction of his international networking.

Despite the fact that Kogoj became a full member of the Yugoslav Academy of Sciences and Arts (YASA) already in 1947, and that he was the secretary of the Department of Medical Sciences (1950–1958) and the Vice-President of the Academy (1958–1972), a detailed overview of his role in the Academy has not yet been published. In this article, we will present some of Kogoj's most important activities in the Academy, such as the establishment of medical institutions, international scientific exchanges, organization of symposia and lectures, as well as numerous publishing projects. To that end, we will use the data published in the Academy's bulletins (*Ljetopis* and *Rad*), the documentation kept at the Division for the History of Medical Sciences, as well as the segments of the material heritage stored in the Croatian Museum of Medicine and Pharmacy.

Full member of the Academy in 1947

Yugoslav Academy of Sciences and Arts was founded in Zagreb on April 29, 1861 by the Croatian parliament. After confirming its statute on March 4, 1866, the parliament elected the first 16 members of the Academy. Bishop Josip Juraj Strossmayer was named its patron, while the eminent Croatian historian Franjo Rački was elected President of the Academy. From 1941 to 1945, the Academy functioned under a new name – the Croatian Academy of Sciences and Arts – and again under its old name YASA after the Second World War. After the establishment of the democratic Republic of Croatia, the Croatian parliament on June 26, 1991 passed a new law on the Croatian Academy of Sciences and Arts. The Parliament named it the highest scientific and art institution in Croatia, while acknowledging its overall influence and historical role.

The Natural and Medical Sciences Department of the former Yugoslav Academy was founded in 1947. In that same year eminent representatives of various medical specialties and professors from the School of Medicine in Zagreb were elected as members: Branimir Gušić, professor of otorhinolaryngology;



Broj 66 - 1947

Gospodinu

dru FRANU KOGOJU
sveučilišnom profesoru

u

ZAGREBU.

Pozivom na odluku Ministra prosvjete broj 5331-IV- od 25.siječnja 1947., kojom se određuje reorganizacija Jugoslavenske akademije znanosti i umjetnosti, imamo čast obavijestiti Vas, da ste u sjednici akademika obnavljača od 11.veljače 1947. izabrani za

PRAVOGA ČLANA

u Odjelu za prirodne i medicinske nauke .

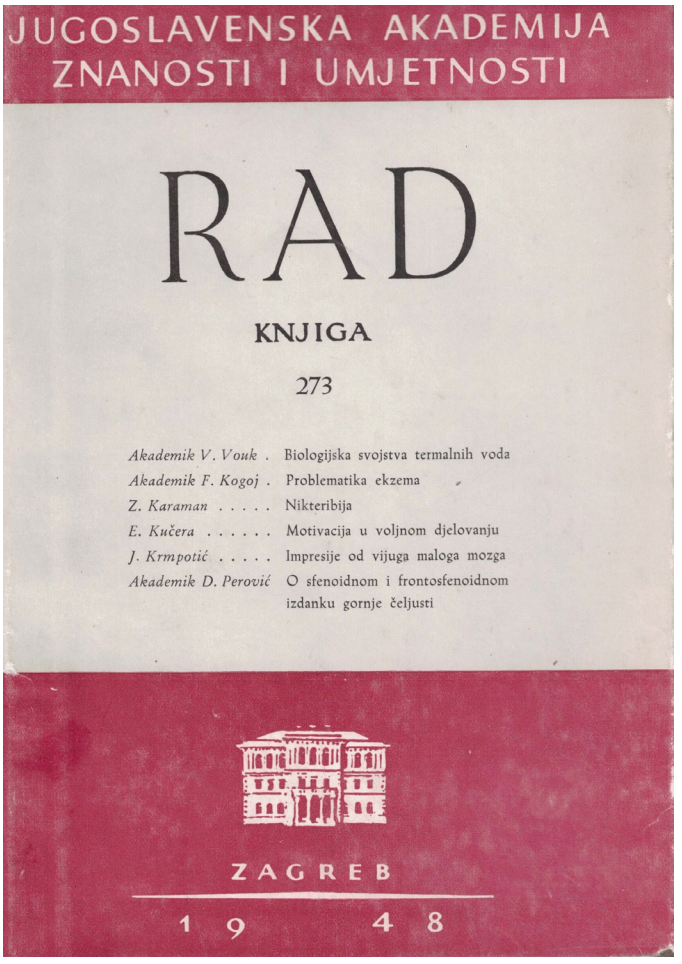
Za privremenu upravu

U Zagrebu 11.veljače 1947.

Akademik-tajnik:
/Dr.Vale Vouk/

Akademik-pročelnik:
/Dr.Albert Bazala/

Figure 2. Certificate of Franjo Kogoj's full membership in YASA, 1947, HMMF-4486



JUGOSLAVENSKA AKADEMIJA ZNANOSTI I UMJETNOSTI

RAD

KNJIGA

273

Akademik V. Vouk . Biologijska svojstva termalnih voda
Akademik F. Kogoj . Problematika ekzema
Z. Karaman . . . . . Nikteribija
E. Kučera . . . . . Motivacija u voljnom djelovanju
J. Krmpotić . . . . . Impresije od vijuga maloga mozga
Akademik D. Perović O sfenoidnom i frontosfenoidnom izdanku gornje čeljusti

ZAGREB

1948

Figure 3. Kogoj's first article published in the Academy's journal "Rad", vol. 273, 1948

Franjo Kogoj, professor of dermatovenereology and head of the Department of Dermatovenereology in Zagreb; and Andrija Štampar, professor of social medicine, who was elected as member of the Philosophy and Social Sciences Section[26] (Figure 2). Kogoj's biography, published in journal *Ljetopis* on the occasion of his membership in the Academy, states that he had previously published several monographs[27-30] and 87 scientific articles. At the age of 53, he was a corresponding and/or honorary member of several dermatovenereological societies, a member of several dermatovenereology journals' editorial boards, president of the Section for Dermatovenereology of the Croatian Medical Association and a participant in a number of Croatian and international conferences[31]. One year after his election to membership in the Academy, Kogoj published a paper on the complex topic of eczema and various theoretical models explaining its etiology, which was published in the Academy's *Rad*[32] (Figure 3). This comprehensive article reveals the breadth of Kogoj's erudition, as well as his capacity to observe and differentiate between various dermatological phenomena occurring in children and adults. Two years after being elected full member of the Academy, Kogoj gave a lecture *On Allergy*[33], a subject that continued to preoccupy him throughout his working life. In the same year, the Academy published Kogoj's second edition of the book *Terapija sifilisa* [The Treatment of Syphilis][34], in which he presented an original method of treating syphilis, which involved two crucial factors: critical moment and liqour quinquenio. He returned to this topic repeatedly as a lecturer and as an author.[35]

At the time when Kogoj was elected full member, the Academy consisted of the Department of Philosophy and Social Sciences, Department of Mathematical, Physical and Technical Sciences, Department of Natural and Medical Sciences, Department of Language and Literature and Department of Art and Music. The law on Yugoslav Academy from 1947 planned for the establishment of new scientific and art institutions. At the same time, natural and medical sciences were developing more rapidly, so the number of members from these fields grew. This eventually led to the splitting of the Department of Natural and Medical Sciences into the Department of Natural Sciences and the Department of Medical Sciences.

The Secretary of the Department of Medical Sciences, 1950–1958

After the Department of Medical Sciences was formed in 1950, Franjo Kogoj was named its first Secretary. He performed this duty in two mandates until the end of 1958. It was a very intensive period for the Academy, marked with growth and development of museums and scienfitic departments. Multiple institutes and museums were being integrated into the Academy. At that time, the Academy had its publishing department with a printing office, as well as a scientific library. The President of the Academy was Andrija Štampar (1888–1958), who had substantial international experience, including the crucial role in the establishment of the World Health Organization[36]. His qualifications proved to be more than beneficial to the Academy as well. Kogoj was also internationally renowned and, although a clinician, partial to viewing skin and venereal diseases through their interaction with ecology, geography and society in general. He dedicated a part of his investigations to professional dermatoses of factory workers[37]. Both Štampar and Kogoj



Figure 4. Josef Jadassohn (1863–1936), Wroclaw, 1931, HMMF-4549

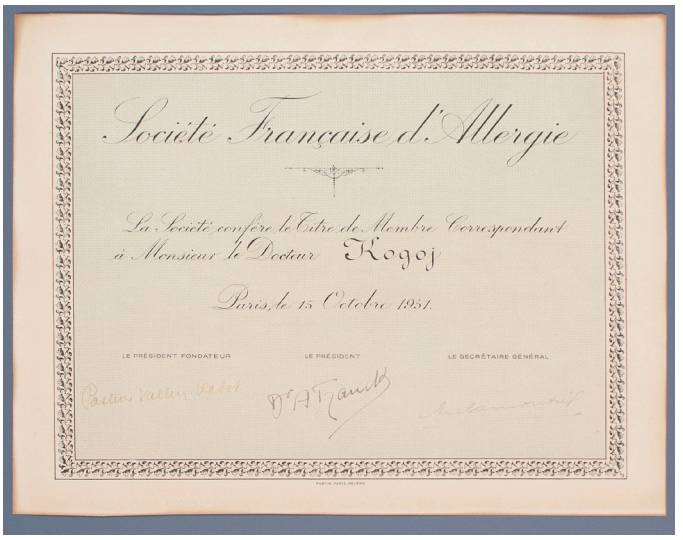
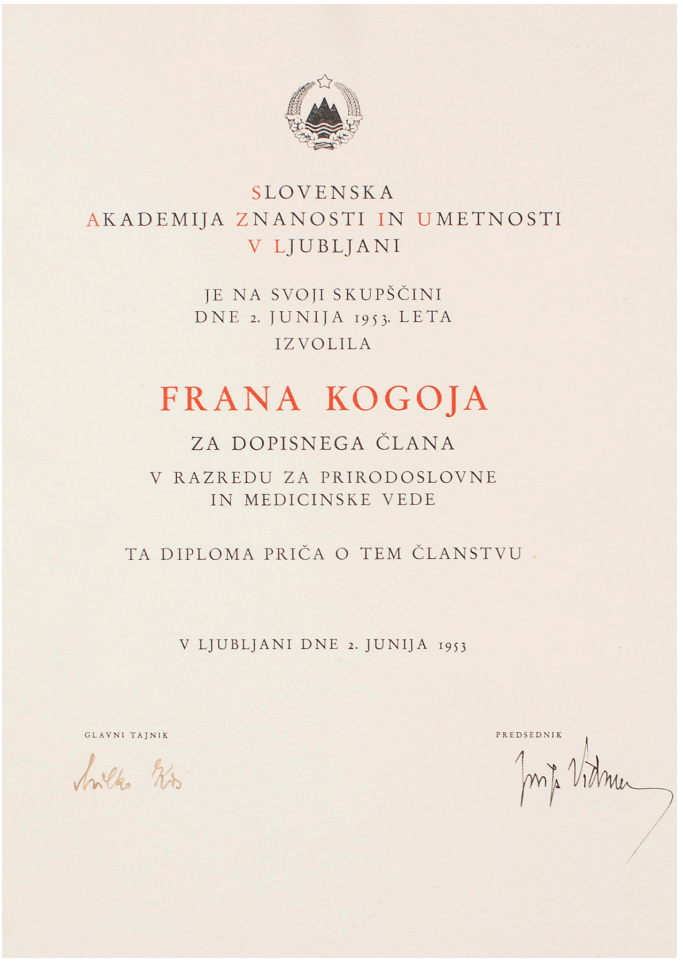


Figure 5 Charter of Franjo Kogoj as a corresponding member of the French Society of Allergology, Paris, 1951, HMMF-4476

advocated the globalization of medicine through their activities in the Academy. Prominent scientist were being invited to give lectures, while scientific journals and other publications were being exchanged and international and inter-academic connections were being developed. Academy also financially supported the participation of its members at international symposia. For example, in 1950 Kogoj received financial support to participate at the German Congress of Dermatologists in Heidelberg, at which he lectured about penicillin as an antisyphilitic drug. Kogoj returned to this topic repeatedly, especially during his field research of endemic syphilis in Bosnia[38].

During Kogoj's mandate, the Department of Medical Sciences worked diligently on the establishment of new scientific research centers. As the President of the Academy, but also as a member of the Department of Medical Sciences, Štampar initiated the establishment of the Institute for Workplace Hygiene in 1947, while Kogoj advocated for the establishment of an allergology institute[39]. Incorporating the ideology of the then popular social medicine, priorities were being set taking into consideration the interests of the working class and socially endangered population. Thus, the biggest support was given to those institutions that would identify and explore various factors compromising the health and well-being of the wider population. This aspect was reflected within the Department of Medical Sciences, which coordinated the Section for Medical Sciences and the Section for Veterinary Sciences, the Center for Leptospirosis, as well as the Biochemical Laboratory of the Institute for Workplace Hygiene. During 1952, the Academy merged all medical institutes and laboratories and established the Institute for Medical Research and Workplace Hygiene, which developed at an impressive pace. Its head was Branko Kesić, who also edited the journal *Arhiv za higijenu rada* [Archive for the Workplace Hygiene] established in 1950. Members of the Department of Medical Sciences at the time were: as full members Ivo Babić, Ivo Čupar, Branimir Gušić, Franjo Kogoj, Božidar Oklješa, Drago Perović, Andrija Štampar and Franjo Durst; and as corresponding members Branko Kesić, Ivo Tomašec and Otmar Trausmiller. The professor of anatomy at the School of Medicine in Zagreb Drago Perović regularly reported about the activities of the Section for Medical Sciences, while the veterinarian Božidar Oklješa referred about the activities of the Section for Veterinary Sciences. Meetings of the Section for Medical Sciences were not only dedicated to technical questions, but also incorporated lectures and discussions on various topics, especially those that were being prepared for publishing[40].

In the 1950s, the interest for allergy permeated various medical specialties. Kogoj's interest toward allergology had its roots in the time of his specialization, when he was impressed with experimental work and immunological research conducted in Josef Jadassohn's laboratories in Breslau (now Wroclaw in Poland). Thus, several photo portraits of dermatologists from Breslau form part of the Kogoj Collection, such as the photo portrait of Josef Jadassohn (1863–1936), the pioneer in allergology and the inventor of the patch test for contact dermatitis (Figure 4), and Hans Biberstein (1889–1965), who worked in Jadassohn's clinic and explored immunology and allergology. Kogoj's first papers on allergy were published in the late 1920s, and he continued to explore this topic throughout his career. Unsurprisingly, Kogoj gave an incentive in 1951 to organize a congress on allergy at the Academy, and the lectures given at the congress were published in *Rad* already in the following year[41]. His activities were also recognized internationally, so in 1952 he received the charter of the French Society of Allergology signed by its president Arnauldt Tzanck (Figure 5). Together with Albin Brnobić, in 1952 Kogoj founded the Allergology Section of the Croatian Medical Association, and was elected its first president[42]. In


SLOVENSKA
AKADEMIJA ZNANOSTI IN UMETNOSTI
V LJUBLJANI

JE NA SVOJI SKUPŠČINI
DNE 2. JUNIJA 1953. LETA
IZVOLILA

FRANA KOGOJA

ZA DOPISNEGA ČLANA
V RAZREDU ZA PRIRODOSLOVNE
IN MEDICINSKE VEDE

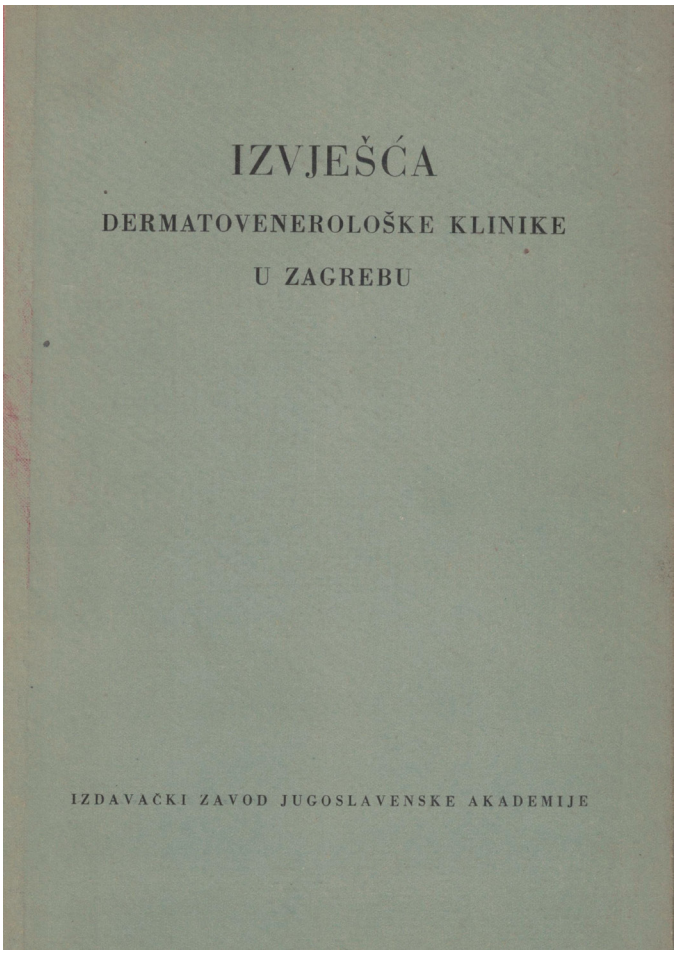
TA DIPLOMA PRIČA O TEM ČLANSTVU

V LJUBLJANI DNE 2. JUNIJA 1953

GLAVNI TAJNIK

PREDSEDNIK

Figure 6. Charter of Franjo Kogoj as a corresponding member of the Slovene Academy of Sciences and Arts, Ljubljana, 1953, HMMF-4487


IZVJEŠĆA

DERMATOVENEROLOŠKE KLINIKE

U ZAGREBU

IZDAVAČKI ZAVOD JUGOSLAVENSKE AKADEMIJE

Figure 7 Report of the Department of Dermatovenereology, ed. Franjo Kogoj, YASA, Zagreb, 1952

1953, he became a corresponding member of the Slovene Academy of Sciences and Arts (Figure 6).

Kogoj was undoubtedly responsible for inviting prominent dermatologists to the Academy as guest speakers. One of them was Alfred Marchionini (1899–1965), the German dermatologist famous for the 1950 establishment of the influential journal *Der Hautarzt*, which he edited for a number of years. From the same year there is also Kogoj's charter of his honorary membership at the Hamburg Dermatological Society, signed by Marchionini, as well as Marchionini's photo portrait with a dedication to Kogoj. Upon Kogoj's invitation, Marchionini gave a lecture at the Academy on April 22, 1952. Kogoj translated the abstract of the lecture, which was published in *Ljetopis*[43]. Under Kogoj's editorship, the Academy also published *Izvješća dermatovenereološke klinike u Zagrebu* [The Reports of the Department of Dermatovenereology in Zagreb], which addressed topics such as micoses, burns, syphilis and other conditions[44] (Figure 7). In his chapter in the Reports, Kogoj presented his idea of the antisyphilitic therapy, emphasizing that it was "being built on foundations that derive from the biology of white treponeme and from the biology of the diseased organism"[45].

In 1954, the Department of Medical Sciences published another issue of *Rad* (book 299), while Kogoj with his associates authored the four hundred-page book *Spolne bolesti* [Venereal Diseases] published by the Academy. The Department of Medical Sciences also started preparing a new publication on geriatrics, and several lectures were being given on this subject during the Department's regular meetings. The work on collecting medical and veterinarian terminology was also taking place. Given his important role in helping young scientists, Kogoj was assigned by the Academy's Council to participate at the CIOMS (Conseil des organisations internationales des sciences medicales) meeting in London in October 1954[46].

In 1955, Kogoj published a paper *O generaliziranoj kandidijazi* [On Generalized Candidiasis] in the Academy's journal *Rad*[47]. In the same year, he gave a lecture *O postanku nekih bolesti* [On the Genesis of Certain Diseases] at the Academy. The Academy granted him financial support to participate at the international congress in Lille, where he gave a lecture on professional dermatoses, as well as his trip to Munich, where he gave a keynote at the meeting of the Society of Dermatologists. At the time, the grants were being given only to the candidates that applied for active participation in the international congresses, while the candidate did not necessarily need to be Academy's employee or its member. In his reports of the annual meetings by the Academy's Assembly, Štampar emphasized this openness of the Academy "towards all who wish to advance science and art and its dedication to provide financial support"[48]. During 1955, the German dermatology journal *Der Hautartzt* published a paper by Alfred Marchionini dedicated to Kogoj on the occasion of his 60th birthday[49].

Among the many activities coordinated by the Department of Medical Sciences, one of the most progressive occurred within the Division for the History of Medicine of the Institute for Medical Research, led by the historian of medicine Mirko Dražen Grmek (1924–2000). In 1955, the Academy published

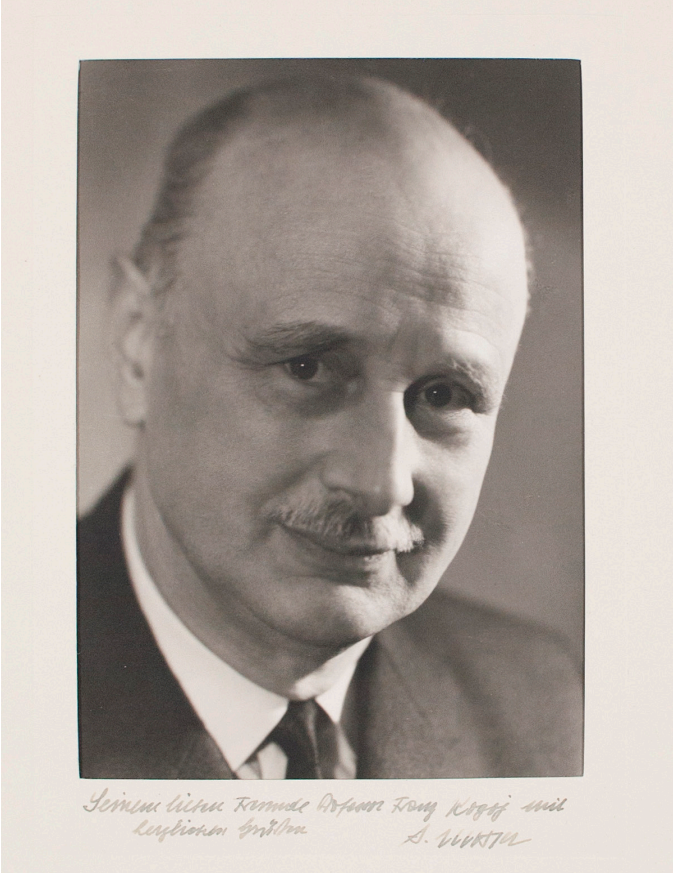


Figure 8. Anton Musger (1898–1983), corresponding member of YASA, Graz, circa 1960, HMMF-4562



Figure 9 Sven Hellerström (1901–1977), Stockholm, 1960, HMMF-4546

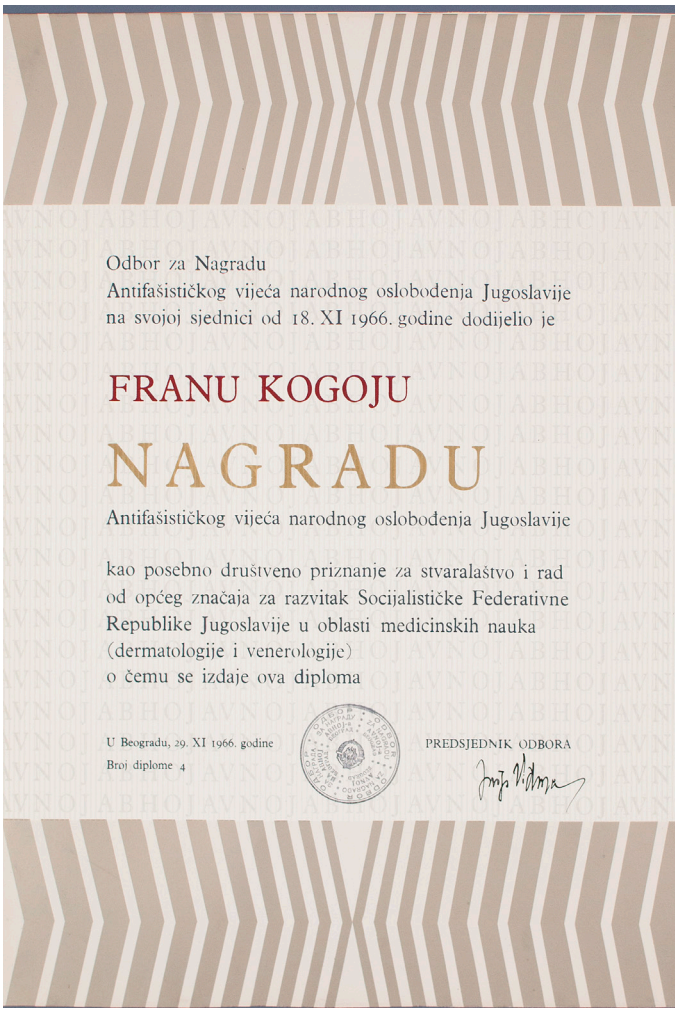
Grmek's work *Hrvatska medicinska bibliografija* [Croatian Medical Bibliography][50], while the members of the Department reviewed papers submitted by other historians of medicine. The Department sent Grmek on a study leave in Padua and Venice for two weeks, after which a lengthy report of the visit was published in *Ljetopis*[51]. At that time, the Department reflected the care which was being put into the development of the Croatian medical terminology. In 1955, Drago Perović reported that the project of cataloging the terminology had already commenced, and during one of the Department's regular meetings, he suggested the first one thousand terms, while also stimulating the discussion about the Croatian terms for tonsils[52].

Inter-academy contacts were established between related Academy departments of the former state. For example, together with Otmar Trausmiller, Kogoj participated as the Department representative at the meeting of medical departments of the Three Academies and the Science Society of Bosnia and Herzegovina held in Ljubljana on February 27, 1957[53]. In the same year, Kogoj participated at the international congress in Stockholm and entered the selection for the Preparatory Committee of the Twelve for the next dermatology congress, which was to be held in Washington in 1962[54].

Publishing business in the Academy developed according to its financial constraints. For instance, up until 1958 the Academy published fifty books annually, while in 1958 that number was almost halved at only twenty-six books due to a significantly smaller budget. In 1958 the number of employees also dwindled, since the Balneo-climatological Division, as well as the Division for Immunochemistry of the Institute for Medical Research were merged with the School of Medicine in Zagreb[55]. During 1958, *Simpozion o gerontologiji* [Symposium on Gerontology] was published and the activities related to the study of social pathology in the near future were agreed. Further on *Rad* number 316 was published and activities related to the research of medical terminology were continued, while those related to the veterinary terminology were temporarily suspended. Financial grants for congresses continued to be given to active participants, among others to Kogoj, who traveled to Krakow for the meeting of the Polish Dermatovenereological Society, where he was awarded a charter for honorary membership. Kogoj also received the financial grant for the Third International Congress on Allergy in Paris.

Vice-President of the Academy (1958–1972)

In January 1959, Fellow of the Academy Ivo Čupar replaced Kogoj as the Secretary of the Department of Medical Sciences. Kogoj was elected Vice-President of YASA on November 23, 1958, a position he held until March 15, 1972. As Vice-President and member of the Academy's Presidency, Kogoj was involved in the ongoing administrative work, especially the fostering of inter-academic and international cooperation. The Kogoj Collection enables the reconstruction of the networking behind some of the keynote lectures given by prominent international researchers in the Academy. Undoubtedly, the person behind Musger's (1952) and Marchionini's (1954) lectures was Kogoj, who maintained close contacts with both of them. Austrian dermatologist Anton Musger (1898–1983) was famous in our academic community for his initiative to hold interclinical colloquia between Graz and Zagreb, at which he also gave lectures. As an ex-rector of the University of Graz, Musger was present at the ceremonial meeting of the Teacher's Council of the School of Medicine in Zagreb held on December 20, 1967, when Kogoj was awarded a charter documenting his honorary membership at the School[56]. Musger also held a keynote lecture


Odbor za Nagradu
Antifašističkog vijeća narodnog oslobođenja Jugoslavije
na svojoj sjednici od 18. XI 1966. godine dodijelio je

FRANU KOGOJU

NAGRADU

Antifašističkog vijeća narodnog oslobođenja Jugoslavije

kao posebno društveno priznanje za stvaralaštvo i rad
od općeg značaja za razvitak Socijalističke Federativne
Republike Jugoslavije u oblasti medicinskih nauka
(dermatologije i venerologije)
o čemu se izdaje ova diploma

U Beogradu, 29. XI 1966. godine
Broj diplome 4

PREDSJEDNIK ODBORA

Figure 10 *Award by the Anti-Fascist Council for the National Liberation of Yugoslavia on the occasion of the 100th anniversary of YASA, Belgrade, 1966, HMMF-4507*

Noviji podaci o kožnoj retikulozi [New Data on Reticulosis of the Skin] in 1954, and on June 20, 1969 he was elected corresponding member of YASA57 (Figure 8).

A notice about the lecture held by the renowned Swedish dermatologist Sven Hellerström (1901–1977), responsible for his description of Lyme borreliosis, was published on the pages of *Ljetopis*[58]. It was accompanied with information regarding Kogoj's participation at the Congress of Dermatovenereologists in Stockholm in 1957, presided by Sven Hellerström, and included the portrait with Hellerström's dedication to Kogoj from 1960 (Figure 9). It is without a doubt that Hellerström, just like Musger and Marchionini previously, held his lecture in the Academy after being invited by Kogoj. Similar circumstances brought to Zagreb the British team of dermatovenereologists led by Geoffrey Barrow Dowling (1891–1976), whose undated photograph is also in the Kogoj's collection of photo portraits. Dowling was a skin diseases consultant for St Thomas' and St John's Hospital, where he encouraged histopathological research and pointed out benefits of applying high doses of calciferole in the treatment of lupus vulgaris. He also founded the famous Dowling Club, which enlisted Kogoj as one of its members in 1959. In that year, a group of British dermatologists headed by Dowling visited Zagreb's Department of Dermatovenereology, as well as the Academy, where "a public meeting" was held[59]. Despite high workload, Kogoj continued to publish in the Academy's *Rad*. In 1963, he gave a lecture in the Academy about Mal de Meleda, and in the same year this lecture was published by the Academy.

In the sixties, Kogoj sped up his activities related to allergology. During 1961, he organized the First Congress of Yugoslav Allergologists, as well as symposia on allergology in 1964 and 1967. It was his initiative on April 16, 1965 that led to the founding of YASA's Allergology Center on Hvar, "as a scientific research institute within the Academy's Department of Medical Sciences"[60]. Members of the Expert Committee of the Center were, according to the decision by the Academy's Presidency on July 1, 1965, Branimir Gušić, Arpad Hahn, Zlatan Sremec and Milorad Mimica, while Franjo Kogoj was the head of the Expert Committee and the Center itself. The Director of the Allergology Center on Hvar was Želimir Dujmović, who trained in the Netherlands specifically for this role. During 1965, Kogoj participated at a meeting of the German Society for Allergology in Freiburg and Budapest, again with the Academy's support[61].

On the occasion of the 100th anniversary of the Yugoslav Academy of Sciences and Arts in 1966, Kogoj received an award by the Anti-Fascist Council for the National Liberation of Yugoslavia, which is also preserved in his collection (Figure 10).
On June 30, 1967 elections for the Academy's Presidency were being held. Grga Novak was again elected President, while Kogoj was again elected Vice-President with 72 votes out of 74[62]. Kogoj was the recipient of prestigious charters for his contributions, especially in German speaking regions. Of particular importance is his election to the membership of the German Leopoldina (1966), the Austrian Academy of Science (1971) and the Swiss Academy of Medical Sciences (1964).

In the seventies, Kogoj still focused on allergology. He organized the Dies italico-jugoslavici medicinae destinati in 1968, 1971, 1972 and 1974[63]. In the period between 1967 and 1974, he was the Director of the Institute for Clinical Medical Research of the School of Medicine and the University Hospital Center Zagreb. In 1970, the Academy published Kogoj's book *Bolesti kože* [Skin Diseases][64]. The first number of *Glasnik Alergološkog centra JAZU* [Bulletin of the Allergology Center YASA], the first journal in Yugoslavia dedicated wholly to allergology, was published in 1972. This important undertaking, according to Vinko Bogdanić, would not be possible without Kogoj[65] (Figure 11). Kogoj's involvement in the Allergology Center's council and the editorial board of the Bulletin lasted until September of 1973, when the Department of Medical Sciences accepted Kogoj's resignation[66].
At the meeting of the Academy's Assembly on March 15, 1972, members of the Academy thanked Kogoj, whose mandate as Vice-President ended. On that occasion Fellow of the Academy Branimir Gušić stated that although he had participated only in the final three out of thirteen years of Kogoj's mandate in the Presidency, he knew that in the most difficult situations which required careful thinking, it was always Kogoj who knew how



SAVJET CENTRA ZA ZAŠTITU KULTURNE BAŠTINE
KOMUNE HVARSKE

ODAJE OVIME

PRIZNANJE

AKADEMIK PROFESOR DR. FRAN KOGOJ

ZA RAD NA OČUVANJU KULTURNE BAŠTINE
OTOKA HVARA

Time što je svojim blagorodnim čovjekoljubivim odnosom i autoritetom učenjaka podstakao mnoge humane manifestacije i ostvarenja Jugoslavenske akademije u Hvaru, čime je zadužio narod Hvara, komunu i ovaj Centar

HVAR, 1. rujna 1974

ČLAN SAVJETA:

PREDSJEDNIK:

Figure 11 *Acknowledgment for the preservation of culture heritage of the island of Hvar, Hvar, 1974, HMMF-4461*

to find the best solution. Among those who thanked Kogoj for his work in the Presidency was Grga Novak, who said: "During these thirteen years, which is not a short amount of time, he was always a best friend and a best adviser"[67].

Kogoj had an interest in a variety of topics in dermatovenereology, trying to assess the specificities of local dermatopathology in their relation to global knowledge. His work in the Yugoslav Academy of Sciences and Arts underlines this aspect, especially concerning his attempts to accommodate dermatovenereology within a broader social and cultural context. In that respect, Kogoj's legacy outlines the establishment and the development of institutions, scientific publishing, networking, cooperation and knowledge exchange, research in dermatovenereology and allergology, while contributing to the Croatian medical history and attempting to collect medical and veterinary terminology. Apart from this lasting legacy, Kogoj left the Academy a segment of his material heritage: a bust by Vanja Radauš, which his daughter Breda Kogoj Kapetanić donated to Gliptotheque CASA in 2015, as well as the collection of photo portraits and charters which are now kept in the Croatian Museum of Medicine and Pharmacy CASA.

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Orthopaedics is a medical speciality that deals with the study, prevention and treatment of diseases and injuries of the locomotor system. The word propaedeutics means "first lesson, preparatory training, pre-education, introduction to a science." A clinical examination is more than a half the diagnosis (sometimes a complete diagnosis), and without an accurate diagnosis, there is no successful treatment. Unfortunately, in technologically advanced medicine, clinical examination is an almost forgotten skill that requires appropriate theoretical knowledge, but also many years of practical experience.

The book Ortopedska propedeutika (English: "Orthopaedic Propaedeutics") is the result of many years of clinical experience of the author in working with patients and the participation of the author in all forms of teaching in orthopaedics and traumatology of the locomotor system. In it, the authors described clinical exams that serve precisely to master the skill of examination and making an accurate diagnosis in orthopaedics. The introductory part describes the general principles of clinical examination of the locomotor system, and the special part systematically describes and illustrates the most commonly used clinical tests in orthopaedics by individual regions of the body.



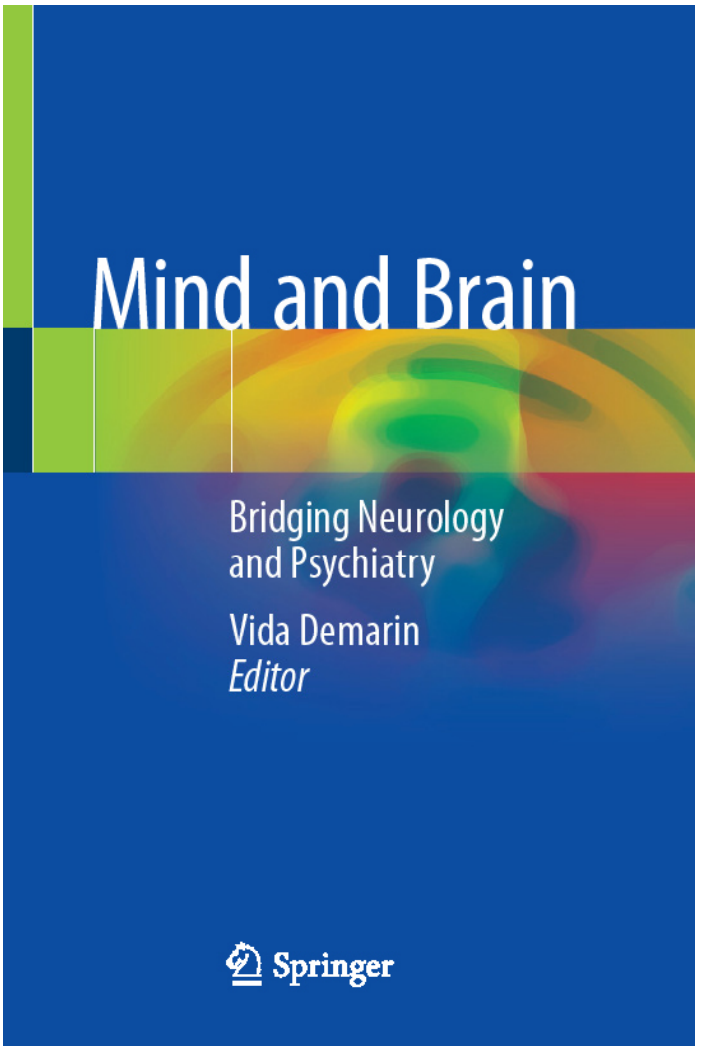
The deepest impression on the reader is left by the educational value, and as a special feature of the textbook, we mention the precision, systematicity and logical sequence and gradual presentation that make the work easy to read and understand. With interesting and well-chosen images and drawings that make it easier to understand the text and facilitate learning, the authors have made the book attractive and complete. The textbook contains nine chapters, with 763 photographs and 293 drawings (a total of 1056 illustrations), showing the performance of clinical tests, and 258 references.
With the content and scope of the provided knowledge, documented by original clinical photographs and drawings, the book is intended for a wider circle of readers and experts. It will primarily be useful for orthopedists, traumatologists, radiologists, paediatricians, physiatrists, family physicians, medical students in regular graduate and postgraduate specialist classes and in continuing education. It will also be a useful read for a wide range of professionals such as physiotherapists, occupational therapists, kinesiologists, nurses and technicians.

Apart from the authors, special thanks should be extended to eminent orthopedists and reviewers, prof. dr. sc. Sava Jovanović and prof. dr. sc. Domagoj Delimar, for his advice and wholehearted support during the creation of the book. A graphically really demanding book would not have seen the light of day without the great effort of the staff of Medicinska naklada, headed by prof. Andjom Raic. The book, which can compete equally with foreign editions, is unique because the medical literature on this issue in the Croatian language is very scarce. After a long time, local readers were greeted by a quality modern textbook.

Book review:
Mind and Brain, Bridging Neurology and Psychiatry

Publisher: Springer

Author:
Marko Pećina



The book Mind and Brain, Bridging Neurology and Psychiatry, discusses the link between the brain and the mind. Adopting an evidence-based neuropsychiatry approach while also touching on philosophical aspects, it examines the association between diseases of the brain and mental health, offering comprehensive insights into the emerging new discipline of psychoneuroendocrinoimmunology and its translation to clinical practice. The book particularly focuses on brain plasticity and on explaining the ability of the brain to learn new pathways in everyday situations and at the same time improve creativity.
It consists of 11 chapters within 140 pages, written by 17 authors.

From the Book introduction:
The brain as an organ and mind as its product and even more than that were for centuries a secret that many scientists tried to reveal. But only recently, during and following Decade of the Brain, with the introduction of neuroimaging methods, especially functional magnetic resonance imaging (fMRI) it was possible to get more data on these important topics. This was a kind of a „golden era" for neurology and psychiatry, disciplines that got tools for deeper searching and possibilities of getting answers to important questions, together with results from neuroscience and neurobiology.
This development enabled getting a broader field of the investigation, the interaction of several disciplines, new perspectives and a more comprehensive view of mind and brain interaction.
...
And today, with emerging a new discipline Psychoneuroendocrinoimmunology and its translation to clinical practice, our long-standing comprehensive approach to the interrelation and bridging of the mind and the brain could contribute to a better understanding of this challenging topic. As it is not possible to show in detail this huge area of interest, we have tried with the few examples in the following chapters to illustrate it from different perspectives.

The Book provides a wide variety of perspectives on the impact of mind–brain interaction, explaining how brain physiology affects brain pathology by using specific examples of diseases. It discusses brain diseases and mental health within the frame of the concept of mind.
Written by clinicians and leading experts in the field of brain physiology and pathology, this book is a valuable resource for medical professionals and postgraduate students.

Book review: Vulvology

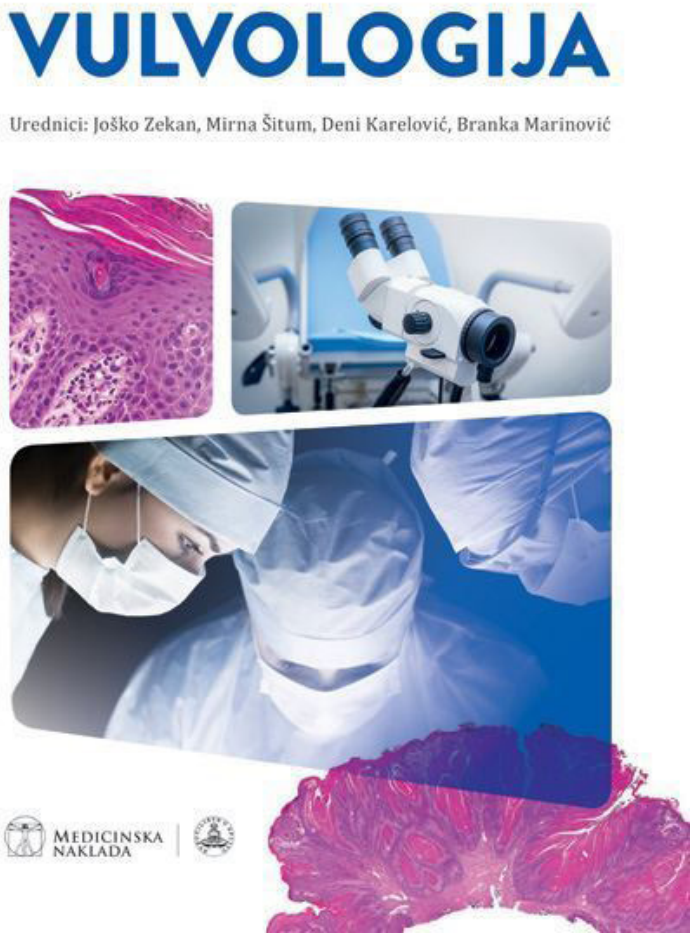
Publisher: Medicinska naklada

Author:
On behalf of the editors,
Mirna Šitum

The university textbook "Vulvology" is an interdisciplinary work of a team of editors, a detachment of renowned experts in the field of gynaecology and dermatovenerology, published in March 2020 by the publishing house Medicinska naklada in Zagreb, specializing in the medical literature. "Vulvology" is the work of editor Joško Zekan - professor of gynaecology, academician Mirna Šitum, a specialist in dermatovenereology, university professor of gynaecology Deni Karelović and university professor of dermatovenerology Branka Marinović who with their associates created materials as a logical entity that a modern breakthrough in the Croatian scientific and professional literature.

Vaginal diseases form a large and significant but often neglected part of pathology in the daily clinical practice of many medical disciplines, and especially gynaecology and dermatovenerology. In addition to the extensive spectrum of dermatoses, most of which are chronic and which significantly reduce the quality of life of patients, the last few decades have seen an increase in the incidence of premalignant and malignant lesions of the external female genitalia in younger age groups. In diagnostic and therapeutic procedures, close cooperation of several professions is often necessary, which leads to the need to harmonize knowledge, terminology and therapeutic procedures. Therefore, a new interdisciplinary specialization - vulvology - has been formed in the scientific and professional literature. The editors, wanting to keep up with modern trends in medicine and actively participate in them, decided to offer professional readers this multidisciplinary, richly illustrated with original photo documentation, a textbook covering almost all pathological entities that appear in the external female genitalia.
34 authors participated in writing the textbook by writing 30 chapters, 221 pages of text, 29 tables and displaying 129 original photographs.

According to its structure and content, the textbook "Vulvology" is a textbook intended mainly for medical students, but also for specialists and other students in the field of biomedicine and health, which include topics from gynaecology and obstetrics, dermatovenereology, infectology, microbiology, paediatrics and pathology. in graduate school and physicians of family medicine and other specialities.



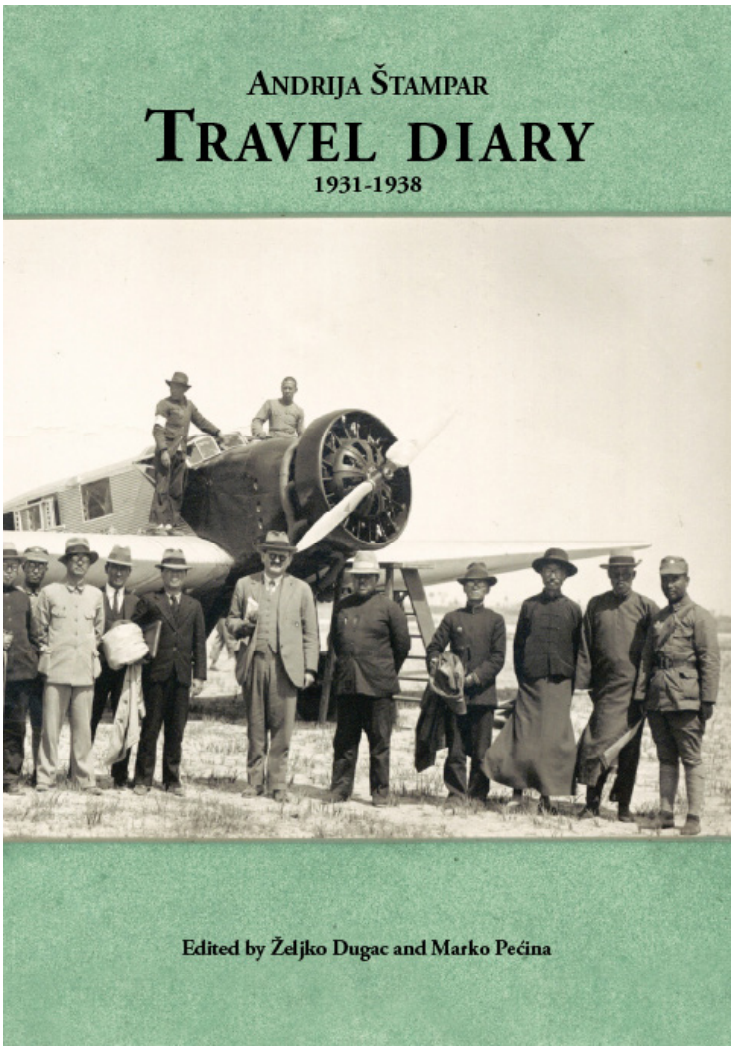
In their texts, the authors used recent literature and proven scientific and professional knowledge, but also rich personal clinical experiences, and the editors dedicatedly coordinated all texts and contributions to make uniform clinical and teaching units easy to learn.

The textbook was positively evaluated by reputable reviewers and experts in the field in which this textbook deals and these are professor Goran Grubisic, professor Josip Đelmiš, professor Neira Puizina Ivić and professor Sunčanica Ljubin Sternak.
We are sure that this completely new literature in the world of medical publishing in the Republic of Croatia will be a useful read for all those who nurture an interdisciplinary and holistic approach to the patient.

Book review: Andrija Štampar travel diary 1931-1938

Publisher: Croatian Academy of Sciences and Arts, School of Medicine Zagreb, Srednja Europa

Author:
Luka Filipović-Grčić



It is hard not to reflect on the unusual coincidence, that the book containing travel diaries of one of the heroes of modern medicine and humanitarianism, Andrija Štampar, was published amid a global pandemic of COVID-19. Such were the circumstances, that, due to the epidemiological restrictions, the book didn't even receive a proper promotion. The book itself is a translation of Štampar's diary published in 2008. This, english edition, was copublished by the Croataian Academy of Sciences and Arts, School of Medicine, University of Zagreb, Andrija Štampar School of Public Health and Srednja Europa d.o .o. This collaboration seems fitting, since Štampar served as president, dean and founder of these institutions. His diary was edited by prof. Željko Dugac and academician Marko Pećina, and translated by Boris Blažina. Andrija Štampar undertook these travels as an expert working for the League of Nations Health Organization, the Rockefeller Foundation, Chinese government of Chiang Kai-shek and invited lecturer at numerous universities. He was primarily preoccupied with advancing public, especially rural health, a task he began in his homeland and pursued his entire life. The travels are organised into nine chapters, namely: Journey to the USA and Canada, Firs journey to the Far East, Journey to Turkey and Bulgaria, From the Journey Through Spain, Second Journey to the Far East, Third Journey to the Far East, In the USSR, Another Journey Through Europe, and In America. From today's perspective it is interesting to compare the world of 1930s with present. At the onset of 2020 COVID-19 pandemic the world was amazed by the speed of Chinese buiders who managed to construct and fully equip the Houshenshan hospital in Wuhan in just 15 days. This stands in stark contrast to the dire circumstances in China from the time of Štampar's journeys, when he encountered mostly substandardly built, underequipped and understaffed hospitals and unsanitary living conditions of the large share of the population. This was by no means new for him, as he came from a background with rural hygiene not much better than that of the Chinese countryside. Born into a teacher's family in a small village of Drenovac on the outskirts of the Austro-Hungarian Empire, he experienced all the misery brought upon his neighbours by poverty, lack of education and public health and resolved to change it. His life and work demonstrates how drastically things can improve in a single lifetime. However, his job is not done as millions of people in the 21st century still wait for decent sanitary infrastructure and basic health care. Therefore let this book serve as an inspiration to those looking to continue in Štampar's footsteps in making this world a better place.

Symposium "New Coronavirus from China: Biosecurity Threat and Challenge for Healthcare Professionals"

Authors:
Alemka Markotić
Ljiljana Žmak
Rok Čivljak
Ivan Christian Kurolt
Vida Demarin

The symposium "New Coronavirus from China: Biosecurity Threat and Challenge for Health Care Professionals" was held at the Croatian Academy of Sciences and Arts, on February 14, 2020. In late 2019, a severe respiratory infection caused by SARS-CoV-2 started to spread rapidly, resulting in high morbidity and mortality rates in Wuhan, China, and continued to spread even faster worldwide, causing immeasurable health and economic challenges.

The goal of this symposium, organized by the Croatian Society for Biosafety and Biosecurity in cooperation with the Croatian Academy of Sciences and Arts and the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, was to gather a large number of experts in the field of biosafety, infectious diseases, microbiology, epidemiology, molecular biology, as well as other health experts to discuss current possibilities in the treatment, diagnosis and prevention of the Coronavirus disease 2019 (COVID-19).

Due to the exceptional interest in the symposium, it was organised simultaneously in the large hall of the Croatian Academy of Sciences and Arts and the Library of the Croatian Academy of Sciences and Arts, which were linked by a video link. However, the interest in the symposium exceeded the capacity of these two conference rooms, thus the entire symposium was broadcasted live on YouTube. The symposium was also recorded, which enabled future watching both on YouTube and on the websites of the Croatian Society for Biosafety and Biosecurity, the Croatian Academy of Sciences and Arts and the University Hospital for Infectious Diseases "Dr. Fran Mihaljević".

Speeches at the symposium were held by leading exprets in the field. First, the director of the University Hospital for Infectious Diseases "Dr. Fran Mihaljević ", professor Alemka Markotić reminded the participants of the causes and consequences of previous dangerous infectious diseases epidemics and pandemics, from plague in the Middle Ages to Ebola in the 21th century. Academician Josip Madić spoke about coronaviruses in veterinary medicine, while professor Antoinette Kaić Rak, Head of the World Health Organization Office in the Republic of Croatia, spoke about the new coronavirus as a global threat.

The Minister of Health, Vili Beroš, was also a speaker at the symposium, reporting on the results of the meeting of the Ministers of Health of the European Union countries held on February 13 in Brussels. Professor Beroš convened the meeting as minister of health, as Croatia is currently holding the presidency of the Council of the European Union. The main goal of the meeting was to ensure better coordination of measures to combat the threat of coronavirus spread. The meeting pointed out possible issues in the procurement of medicines and medical equipment from China. Minister Beroš expressed satisfaction that such a meeting was organized in a short time, emphasizing that it is a success of Croatian diplomacy.

Bernard Kaić, MD, PhD, Head of the Infectious Diseases Epidemiology Service at the Croatian Institute of Public Health presented the epidemiological features of the recent coronaviruses causing-severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the new coronavirus, SARS-CoV-2. The clinical features of the COVID-19 were described by assistant professor Rok Čivljak, Deputy Director of the University Hospital for Infectious Diseases "Dr. Fran Mihaljević". Assistant professor Marko Kutleša, Head of the Department of Intensive Care Medicine and Neuroinfectology, at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević" covered the treatment of patients with severe respiratory infections admitted in the intensive care unit. Ivan Christian Kurolt, PhD from the University Hospital for Infectious Diseases "Dr. Fran Mihaljević", who established positive reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid test for SARS CoV-2 in late January, and head of the Biosafety Level-3 (BSL-3) laboratory gave a speech about the molecular diagnosis of the new coronaviruseDr. Kurolt.

The first case of COVID-19 in Croatia was confirmed on February 25. Over the next two weeks, sporadic COVID-19 cases were reported, after which the number of new cases recorded per day gradually increased. Measures taken to limit and prevent the spread of SARS-CoV-2, prompt diagnosis and treatment of COVID-19 patients, have ranked Croatia among the world's top countries that have so far successfully fought this dangerous pandemic.





5th Croatian Symposium on Vascular Medicine CROVASCULAR 2020 - Angiology Update 2020

Author:
Mislav Vrsalović

The Croatian Symposium on Vascular Medicine, "Angiology Update 2020", held on March 6th 2020 was the 5th in a series symposium, annually organized by the Department of Medical Sciences of the Croatian Academy of Sciences and Arts, Sestre milosrdnice University Hospital Centre Zagreb and Croatian Cardiac Society. Traditionally, it takes place in a beautiful Revival Hall located in the National Home Palace in Zagreb.

The symposium aimed to gather experts in the field of vascular medicine and to serve as a platform for experience exchange, discussion and debate on the latest advances in prevention, diagnosis and treatment of vascular diseases, emphasizing the importance of holistic approach to the vascular patient.

The experts were not only from Croatia but also from neighbouring countries thus providing an international character to the symposium.

Lots of specific topics, such as antithrombotic therapy in angiology (both in patients with peripheral artery disease and venous thromboembolism alongside patients with atrial fibrillation and endovascular interventions), endovascular treatment of peripheral artery disease and cerebrovascular disease, endovascular management of the aortic diseases and acute vascular syndromes (pulmonary embolism, acute coronary syndrome and acute ischemic stroke) were covered through the sessions.

The president of the Organizing committee Professor Mislav Vrsalović, head of the Department for Vascular Diseases, Sestre milosrdnice University Hospital Centre, in his welcome speech highlighted the importance of early diagnosis and treatment of vascular diseases, not only because of the better quality of life, but also because of potential decrease in total cardiovascular mortality for those patients. Vascular diseases, particularly peripheral arterial disease, although relatively common clinical entity, is often diagnosed in an advance stage of disease, likely due to lack of sensibility among medical professionals and patients. Thus, it is of utmost importance that every cardiologist should be sensitive concerning the diagnosis and management of patients with peripheral arterial disease, as many of them are seen and managed for concomitant cardiac conditions.

On behalf of the Croatian Academy of Sciences and Arts, the Symposium was opened by Academician Vida Demarin, who noticed that a huge number of participants, confirms the increased interest for angiology, at the same time identifying the role of Croatian Symposia on Vascular Medicine in promoting awareness for vascular diseases.

The president of Croatian Cardiac Society, Academician Davor Miličić, emphasized the importance of physician education, from the very beginning of the career. Accordingly, basic skills such as appropriate physical examination, is as important as are sophisticated pharmacological and surgical treatment methods.

Professor Mario Zovak, head of Sestre milosrdnice University Hospital Centre, highlighted the long tradition of vascular medicine in this hospital.

The symposium was divided into four sessions, and the speakers were eminent cardiologists, angiologists, interventional radiologists, vascular surgeons, neurologists and professors from School of Medicine, Universities of Zagreb, Split, Rijeka and Osijek. Cardiovascular prevention, treatment of comorbidities in vascular patients (arterial hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation), new recommendations about peripheral artery disease, prolonged anticoagulation therapy after venous thromboembolism and treatment of venous thromboembolism in oncologic patients are some of the discussed topics.

It was a great pleasure to welcome our dear guest Professor Aleš Blinc form University Hospital in Ljubljana, who opened the third session on acute vascular syndromes with a topic about fibrinolytic therapy in pulmonary embolism treatment. The presentation resulted in an interesting and fruitful discussion among the participants.

Professor Vrsalović closed the Symposium citing the most recent European Society of Cardiology guidelines: Patients with vascular diseases could not be treated properly without an interdisciplinary holistic approach to the patient. A multidisciplinary "vascular team" approach should be used for the treatment of peripheral arterial disease, venous thromboembolism, acute ischemic stroke, and acute aortic syndromes. In the end, he announced and invited the audience to the 6th Symposium on Vascular Medicine next year.





2020 Earthquake - the consequences on the School of Meidicine University of Zagreb

Authors:
Filip Đerke
Luka Filipović-Grčić

In the earthquake that hit Zagreb on March 22, the facilities of the School fo Medicine in Šalata were significantly damaged, and a week and a half later, Dean Marijan Klarica came out with an approximate assessment of the damage. According to his extensive report, their rough estimate rises to more than half a billion kuna.

Professor Klarica points out that the damage caused by the earthquake on the facilities of Medicine means very difficult working conditions at the faculty for an unpredictably long period. The damage after the earthquake on the buildings in Šalata, which houses teaching facilities, a medical library, classrooms, laboratories for scientific and professional projects and activities, is such that for a long time it will be dangerous to enter and use buildings, the dean wrote in the notice for students.

Professor Klarica points out that they managed to save most of the valuable equipment, chemicals, work materials and protect important documentation. "All of this is housed in the only surviving building of the Croatian Institute for Brain Research," explains the dean, adding that the damaged buildings will be able to be entered briefly by a few pieces of equipment, only after inspecting statics and removing larger pieces of plaster that could endanger those who enter objects.

Reconstruction of the damaged facilities of the Faculty of Medicine will take months, with which it will be possible to start only when the anti-epidemic measures are stopped. Until then, the building of the Croatian Institute for Brain Research will be "the heart of the Faculty's vital activities." The Dean also listed in detail all the damage to Medicine and explained how five teams are currently working on urgent and vital remedial interventions.



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