CROATIAN ACADEMY OF SCIENCES AND ARTS
Department of Biomedical Sciences in Rijeka
UNIVERSITY OF RIJEKA

NEURODEGENERATIVE DISEASES - DEMENTIAS

Editors: Vladimira Vuletić and Daniel Rukavina

Proceedings of the 2nd Rijeka Forum on Neurodegenerative Diseases held on 17th October 2018 in Rijeka, Croatia

ZAGREB – RIJEKA
2019.

CROATIAN ACADEMY OF SCIENCES AND ARTS
Department of Biomedical Sciences in Rijeka
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45. obljetnica Sveučilišta u Rijeci
385. godina visokog obrazovanja u Rijeci
uniri
UNIVERSITAS STUDIORUM FLUMINENSIS
SVEUČILIŠTE U RIJECI

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Cataloguing-in-Publication data available in the Online Catalogue of the National and University Library in Zagreb under CIP record 001038673.

ISBN 978-953-347-283-6

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CONTENTS

Daniel Rukavina

EDITORIAL

Three years ago, in discussions with Dr. Vladimira Vuletić, Chairman of the Department of Neurology at the Clinical Hospital Center in Rijeka, we came to the idea of organizing meetings in Rijeka, on the topic of neurodegenerative diseases. The idea was that they will be held on an annual basis, each year bringing new aspects, approaches, and breakthroughs in this flourishing clinical and scientific field, set to be held under the auspices of the Croatian Academy of Sciences and Arts. Our intention was that meetings (called as Rijeka Forum) follow translational approach in the field of neuroscience, which we developed as the main idea and one of the principal goals of meetings held in Rijeka in the last five years under the auspices of the Croatian Academy of Sciences and Arts.

The topic of the First Rijeka Forum on Neurodegenerative Diseases (Rijeka, 17th October 2017) included discussions on Parkinsonism which is today the second-most common neurodegenerative disorder. In the focus of the 2nd Rijeka Forum on neurodegenerative diseases were dementias, particularly Alzheimer disease as the most frequent in this clinical entity.

The articles published in this book are contributions of invited speakers attending the 2nd Forum which was held in Rijeka on October 17th, 2018. Co-organizers of the Forum were the Clinical Hospital Center in Rijeka, the University of Rijeka Faculty of Medicine, and the Croatian Medical Association – Branch office Rijeka. The symposium was endorsed by the European Association of Neurology (EAN) and was held under the auspices of the University of Rijeka, which celebrated its 45th year of the foundation of modern University and 385 years of the University of Rijeka's establishment by the Jesuits. I would like to thank Dr. Vladimira Vuletić for her efforts and success to attract to Forums a group of outstanding speakers from abroad, leading scientists in the field of neurodegenerative diseases. These meetings created the atmosphere for opening the door to the next step in establishing the tradition.

The messages of contributions published in this book are very important for Society as well. The proportion of the population that is over 65 years of age has grown over the last decades and it is known that advancing age is the greatest-known risk factor for dementia. This is a world phenomenon and it is the same in Croatia. This is an enormous burden not only for the Health System, Society and families but an economic burden as well. The World Health Organization (WHO) recognized dementia as one of the public health priorities.

Dementia can arise from numerous conditions acting alone or in combination. Neurodegenerative processes are an umbrella term for a number of debilitating conditions that finally result in the death of neurons. Alzheimer's disease is the most common neurodegenerative cause of dementia and is currently incurable. Parkinson 's disease, which was a focus of our discussions at the First Forum, is also closely associated with the development of dementia.

In the articles presented in the first part of the book some basic mechanisms were discussed. Professor Hardy gave an overview of genomic analyses of neurodegenerative diseases identifying many genes involved in their pathogenesis. Professor Revesz presented from the neuropathologists perspective and professors Manganotti and Babić from neurophysiological and neuropharmacological aspects. Professor Vida Demarin gave a focus on approaches for prevention. Clinical aspects and pathophysiological mechanisms were in the focus of presentations of Professors Bogdanović, Padovani, Pirtošek and Vuletić. Cognitive problems in the field of demyelinating diseases of the central nervous system were highlighted by Professor Fredricson and other clinical aspects were in the focus of articles of Professors Borovečki and Klepac. We are delighted with the contribution of Professor Eric Smeets who gave an overview on clinical management of the very rare disease called Rett syndrome.

Daniel Rukavina, Professor emeritus
Department of Biomedical Sciences in Rijeka
Croatian Academy of Sciences and Arts

Vladimira Vuletić

EDITORIAL

Neurodegenerative disease is a brolly term for a range of conditions which primarily affect the neurons in the human brain. They are incurable and debilitating diseases that result in progressive degeneration and / or death of nerve cells. Neurons normally don't reproduce or replace themselves, so when they become damaged or die they cannot be replaced by the body. Examples of neurodegenerative diseases include Parkinson's, Alzheimer's, and Dementia of Lewy Body, Huntington's disease, Frontal Lobe dementia and Multiple sclerosis. The clinical picture varies among those diseases ranging from, problems with movement, memory, behaviour and other disabilities. In the European Region the burden of the neurodegenerative diseases is on 12th place and on the 6th place as a cause of death among all diseases. The burden of dementias is the most prominent between neurodegenerative disorders affecting about 1,3 – 1,5 % of entire population indicating a pandemic proportion. As we know, dementia is a big social and health-economic issue. The world is getting richer. But wealth brings its own burdens. Prosperous people live longer and old age carries a high risk of dementia — a condition that is so far neither preventable nor curable, thus dementia is currently in the focus of worldwide basic and clinical research. Dementia affects many aspects of the life of an afflicted person, as well as those around him, especially those who are on day-to-day care. Despite the number of new scientific findings, the cause of the disease has not yet been highlighted, no adequate prevention of this disease is known, the existing treatment is still symptomatic, and there is no drug that can halt the disease progression. But still it is important to make a timely diagnose, to begin an early treatment and organize a comprehensive multidisciplinary care since the total indirect and direct costs encompass at least 0,2 % of GDP while appropriate intervention in dementia care a total cost can be decreased for 34%.

It is therefore necessary to educate health professionals at local and global level in early dementia management and in improvement of life quality.

In our clinic we started with modern and early diagnosis of neurodegenerative diseases and dementias with introducing neuropsychiatric assessment tools, laboratory testing of serum and cerebrospinal fluid, MR and functional imaging like PET FDG, DAT scan. For proper care we introduce multidisciplinary team in

our Centre for Cognitive problems. We opened advisory center and organized a lot of educative actions of public-health and teaching meeting for health professionals in field of neurodegenerative diseases and dementias. We started with research in those areas due to great collaboration with scientist from abroad. Thanks to academician Daniel Rukavina, head of the Department of Biomedical Sciences of the Creoatian academy of sciennces and arts, we organized yearly this Rijeka Forum of neurodegenerative diseases with leading names in the field of neurodegenerative diseases from centres of excellency around the World to share the experiences of the basic and clinical research. Our aim is to increase awareness and the latest knowledge of neurodegenerative diseases, from genetics, neuropathology, neurophysiology, neuroimaging and clinical point of view and to motivate our scientists to engage in world trends in research of these diseases and provide significant scientific contribution. There are tremendous efforts to understand the biological basis of these complex neurodegenerative diseases and dementia and to find a real drug that not only relieves the disease but also cures such conditions. Neurodegenerative diseases have in common that there are clusters of specific "damaged, misfolded and altered" proteins (different for different neurodegenerative diseases) in those nervous cells that are likely to be vulnerable. Today, we know about specific proteins involved in pathological change, like Alzheimer's disease occurs primarily by β-amyloid and tau-protein, Parkinson's disease, multiple system atrophy, and dementia of Lewy Bodies primarily α-synuclein etc. We hope that the treatment considering actions on these known proteins will be discovered soon and cure the neurodegenerative diseases and dementias. We hope that further research in this area will bring us the real insight in mechanism of dementias and other neurodegenerative diseases aiming towards the new treatment option and mitigating this pandemic situation.

This proceedings from the last Rijeka Forum 2019 is a summary of the most representative and updated lectures "a state of art" covering a wide scientific interest areas from genetics and epigenetics, neuropathology, neuroimaging, neuropharmacology, neurophysiology, clinical and preventive issues.

We made this textbook with articles of invited speakers on the last Rijeka Forum contributed to dementias to be a modern pragmatic resource that covers clinicians' and neuroscientists' interests and for beginners entering the field of dementia. We hope, that bringing together different range of information in this field and promoting a collaboration with invited speakers and experts, will burst the interest for dementia and will improve day-to-day management of dementias in Croatia.

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UDK: 616.8-056.7
DOI: 10.21857/mnlqgc07ny
Review article
Received: 27.1.2019.
Accepted: 28.3.2019.

GENETIC RISK FOR LATE ONSET NEURODEGENERATIVE DISEASES LARGELY REFLECTS FAILURE OF PROTEIN CLEARANCE PATHWAYS

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Summary

In this brief review I suggest that the pathology and genetics of the major neudegenerative diseases share common features but informative difference. Long Aβ overproduction, including by APP duplication leads to Alzheiemers disease, 4 repeat tau over production, including by MAPT duplication leads to tangle disease, and synuclein overproduction including by SNCA duplication leads to Parkinson's disease. These simple genetic cases are rare. The more common risk loci relate to the clearance of the deposits: microglia for Aβ, the ubiquitin proteasome for tau and lysosomes for synuclein Lewy bodies

Key words: Alzheimer, Parkinson, frontotemporal dementia, genetic, microglia, lysosomes, ubiquitin proteasome

Introduction

For the twenty years from 1990 onwards, great progress was made in identifying the causes of mendelian forms of the major neurodegenerative diseases [1, 2, 3]. Over the last 10 years, through genome wide association studies and exome and genome sequencing, we have made progress in identifying risk genes for the sporadic forms of these diseases [4, 5, 6]. This means we now have a wealth of data to suggest some general principles about what we are finding. In this brief review I outline these general principles. This is not intended to be a comprehensive review, but rather an attempt to draw these principles.

Alzheimer's disease

In Alzheimer's disease, Aβ is deposited and the mendelian genes for the disease, APP and PSEN1 and PSEN2 are respectively the substrate from which Aβ is derived and the enzyme, γ-secretase involved in releasing it by intramembranous cleavage. The pathogenic variants include APP duplications which, like trisomy 21, increase the amount of substrate, as well mutations which perturb the position of the intramembranous cleavage such that longer, less soluble Aβ is produced. APP is a highly abundant protein which is rapidly trafficked through the neuronal membrane. It is not clear whether deposition is initiated in the extracellular space or in the membrane as longer, less soluble Aβ species are produced [7].

The risk genes for late onset Alzheimer's diseases largely include two, probably overlapping groups of genes, microglial genes and lipid metabolism genes [8]. Many of these genes are upregulated in response to amyloid deposition in mouse models of amyloid deposition [9].

Hypothesis for Alzheimer's disease

The mendelian causes of Alzheimer's disease directly result in more amyloid deposition, starting in the membrane though a greater production of long Aβ fragments. In late onset disease, over production is not the problem, rather it is largely a failure to clear the Aβ initiated membrane damage by microglia

Frontotemporal Dementia with Tangle Pathology and Sporadic Tangle Diseases

The sole mendelian causes of frontotemporal dementia with tau pathology are mutations in the MAPT gene, including MAPT gene duplications [2]. Many of the pathogenic mutations either increase the proportion of 4-repeat tau or lead to the production of of tau proteins which bind less well to microtubules leading to greater cytosolic cncentrations of the protein. Tau is, in any event, a very highly expressed cytosolic protein which is degraded through the ubiquitin proteasome system [10].

The commonest sporadic tangle disease is progressive supraclear palsy. Genetic analysis of supranuclear palsy has shown that genetic variability at the MAPT locus is the strongest risk factor but that other risk factors include elements of the unfolded protein response and the ubiquitin proteasome system [11].

Hypothesis for Tangle Diseases

Mendelian tangle diseases is caused by mutations which increase the cytosolic concentrations of 4 repeat tau. Sporadic diseases are in part predisposed to by failures of the response to tau deposition in the cytoplasm: these include the unfolded protein response and the ubiquitin proteasome system

Parkinson's Disease and Lewy body disease

The protein deposited in Parkinson's disease and Lewy body dementia is synuclein. Synuclein is an abundant small, membrane associated protein which is metabolized through the lysosomes [12]. Synuclein gene missense mutations and duplications and triplications are one cause of the disease. The other mendelian and risk genes for Parkinson's disease include many lysosomal genes [13].

Hypothesis for Lewy body Diseases.

Overproduction of synuclein is one cause of disease: failure to metabolise synuclein, largely through the lysosome is another.

Overarching Idea

I would suggest that in all these protein deposition, neurodegenerative diseases, the disease can be caused by over production of the deposited protein, Aβ in the case of Alzheimer's disease, tau in the case of the tauopathies and synuclein in the case of the Lewy body diseases. These are all abundant proteins and have been suggested to be close to their critical concentrations [14]. Overproduction is clearly one way to lead to deposition and disease initiation: the other is to have deficiencies in the clearance mechanisms and this is the predominant reason in late onset and sporadic disease. In each case, the deposited protein is from a different cellular compartment, Aβ in the membrane, tau in the cytoplasm and synuclein on the membrane surface, and in each case the failing clearance mechanism is different… microglial for Aβ, ubiquitin proteasome for tau and lysosomes for synuclein.

This suggests two broad avenues for therapy...substrate reduction… APP, MAPT and SNCA… or the potentiation of the relevant clearance mechanisms.

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UDK: 616.892.3
DOI: 10.21857/y54jofpzlm
Review article
Received: 23.2.2019.
Accepted: 28.3.2019.

PATHOLOGICAL ASPECTS OF NEURODEGENERATIVE DEMENTIAS

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Summary

The aim of this chapter is to provide an insight into the neuropathological changes of neurodegenerative diseases underlying the clinical manifestations of dementia. Such diseases represent a rather heterogeneous group of conditions with different aetiologies, genetic background and pathological features. An overarching feature of the conditions, discussed in this chapter is that neuropathologically they are characterised by the presence of intracellular proteinaceous inclusions and, in Alzheimer's disease and a small number of other conditions, additional extracellular insoluble protein deposits are also present. As our knowledge about the genetic background of neurodegenerative diseases and the nature of disease-associated inclusion-forming proteins has significantly increased, a molecular classification of neurodegenerative diseases has become possible. In this chapter the neuropathological features of the most important neurodegenerative dementias are discussed.

Key words: Neurodegeneration, Protein folding disorders, Alzheimer's disease, Lewy body disorders, Frontotemporal lobar degenerations

Introduction

Neurodegenerative diseases represent a significant group of neurological conditions, which are characterised by gradual clinical deterioration, caused by progressive loss of neuronal function due to involvement of functionally related

neuronal groups and networks. Clinically they manifest in a number of presentations such as movement disorders and different forms of dementias.

In this chapter, we describe the major neuropathological features of some of the common diseases, clinically presenting with dementia. All of these are categorised as protein folding or conformational disorders characterised by misfolding and aggregation of disease-specific proteins resulting in the formation of either intracellular inclusions and/or extracelluar deposits (Figure 1).

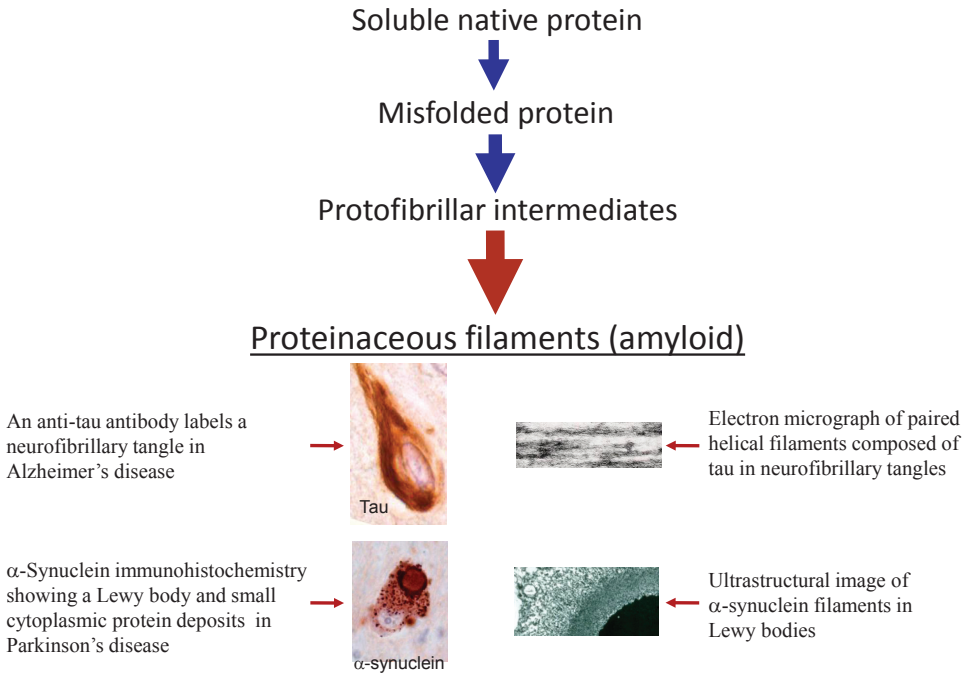

Figure 1. Schematic illustration of conversion of native proteins into insoluble amyloid.

Table 1. Molecular classification of neurodegenerative dementias

Disease	Type of protein deposit	Toxic protein	Precursor protein	Common genes in familial forms
Diseases with amyloid plaques and NFT				
Alzheimer's disease	Amyloid plaques CAA	Aβ	APP	*APP, PSEN1, PSEN2*
	NFT	Tau	Tau	
Synucleinopathies				
Dementia with Lewy bodies	Lewy body	αSyn	αSyn	*SNCA*
	Amyloid plaques	Aβ	APP	
Parkinson's disease with dementia	Lewy body	αSyn	αSyn	*SNCA, LRRK2*
	Amyloid plaques	Aβ	APP	
Frontotemporal lobar degenerations				
FTLD-TDP				
Type A	NCI, NII, DN, GI	TDP43	TDP43	*GRN, C9orf72*
Type B	NCI	TDP43	TDP43	*C9orf72*
Type C	DN	TDP43	TDP43	-
Type D	NII, DN	TDP43	TDP43	*VCP*
FTLD-FUS				
aFTLD-U	NCI, NII, GI	FUS	FUS	-
NIFID	NCI, NII, GI	FUS	FUS	-
BIBD	NCI, NII, GI	FUS	FUS	-
FTLD-Tau				
Pick's disease	Pick body, RA, OI	Tau	Tau	-
CBD	NFT, NT, AP, CB	Tau	Tau	-
PSP	NFT, NT, TA, CB	Tau	Tau	-
GGT	NFT, NT, GNI, GGI	Tau	Tau	-
AGD	NFT, NT, GI	Tau	Tau	-
FTDP-17 *MAPT**	NFT, NT, GI	Tau	Tau	*MAPT*

Abbreviations: Aβ = amyloid-β peptide; aFTLD-U = atypical frontotemporal lobar degeneration with ubiquitin-positive, tau and TDP43-negative inclusions; AGT = argyrophilic grain disease; AP = astrocytic plaque; APP = amyloid-β A4 precursor protein; αSyn = α-synuclein; BIBD = basophilic inclusion body disease; CAA = cerebral amyloid angiopathy; CB = coiled body; CBD = corticobasal degeneration; DN = dystrophic neurite; FTDP-17 *MAPT* = frontotemporal dementia and parkinsonism linked to chromosome 17 due to mutation of the *MAPT* gene; FUS = fused in sarcoma protein; GGI = globular glial inclusion; GGT = globular glial tauopathy; GI = glial inclusion; GNI = globular neuronal inclusion; NCI = neuronal cytoplasmic inclusion; NIFID = neuronal intermediate filament inclusion disease; NFT = neurofibrillary tangle; NII = neuronal intranuclear inclusion; TA = tufted astrocyte; TDP43 = TAR DNA-binding protein 43

Formation of proteinaceous filaments of amyloid nature is the end-result of a multistep process initiated by protein misfolding. The lower part of the figure illustrates the immunohistochemical and ultrastructural characteristics of the two most frequent intraneuronal lesion types, the neurofibrillary tangle and Lewy body.

The increase in knowledge of the cellular events and biochemical alterations associated with the neurodegenerative process, and the discovery of the genetic background of many of the neurodegenerative conditions have allowed the introduction of molecular classifications of neurodegenerative dementias, which is followed in this chapter (Table 1).

Diseases characterised by extracellular protein aggregates and neurofibrillary tangle formation

The presence of extracellular amyloid plaques, composed of one of a limited number of disease-specific amyloid peptides [1], and neurofibrillary degeneration are the pathological hallmarks of diseases in this group. Such features characterise Alzheimer's disease, which is the most important member of this groups, but also familial British dementia and familial Danish dementia as well as some forms of hereditary prion disease [1]. The main neuropathological features of Alzheimer's disease will be provided in this chapter, for other rare diseases we refer to standard texts and reviews [2,3].

Alzheimer's disease

Alzheimer's disease, which is the most common neurodegenerative condition, is mostly sporadic. The much rarer familial forms with an autosomal dominant pattern of inheritance are associated with mutations in one of three genes, which are the amyloid-β A4 precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes. In sporadic cases a number of genetic risk factors have been identified [4].

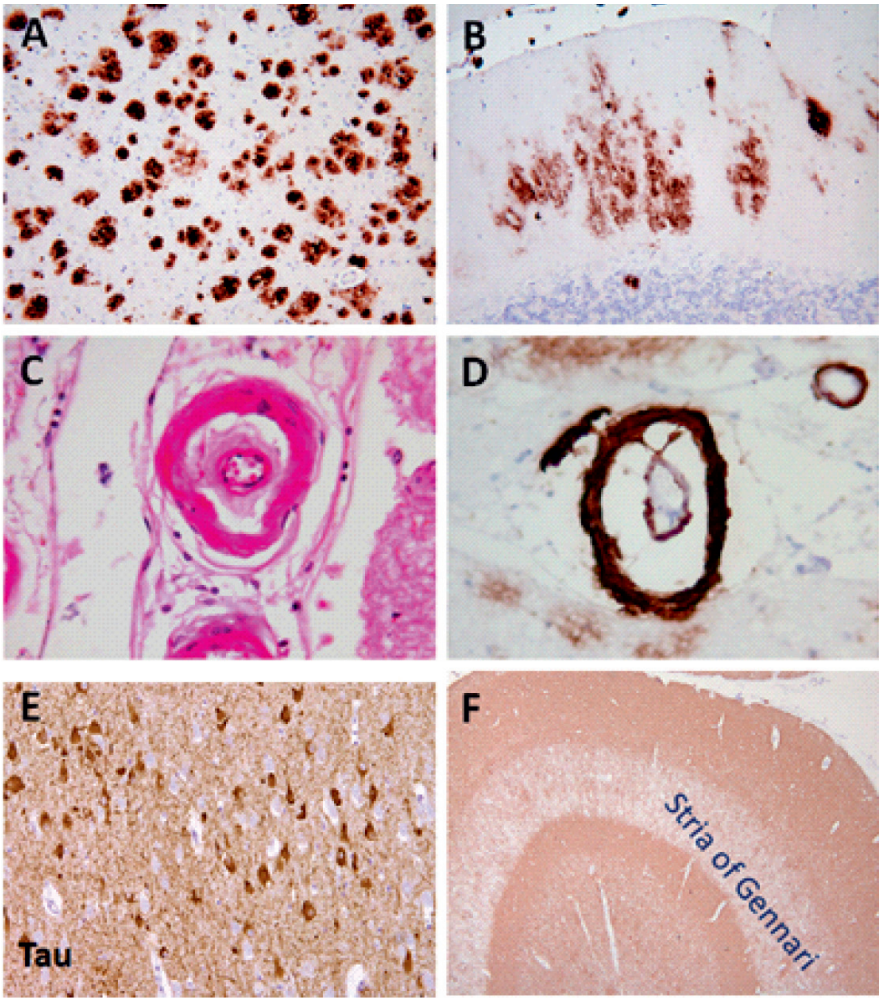

Figure 2. The main microscopic findings in Alzheimer's disease

A: The photomicrograph demonstrates numerous diffuse and mature Aβ-positive plaques in the frontal cortex. **B:** In advanced disease there is Aβ deposition also in the cerebellar cortex (**A** and **B:** Aβ immunohistochemistry). **C** and **D**: The presence of cerebral amyloid angiopathy (CAA) (**C**) due to Aβ deposition (**D**) in blood vessel walls is a common feature of Alzheimer's disease. Panels **C** and **D** illustrate severe CAA indicated by the presence of 'double barrelling' due to splitting of the blood vessel wall (**C:** haematoxylin and eosin preparation; **D:** Aβ immunohistochemistry). **E:** Numerous tau-positive neurofibrillary tangles and neuropil threads in the CA1 hippocampal subregion. **F:** In Braak and Braak stage VI the primary visual cortex also shows severe tau pathology (**E** and **F:** tau immunohistochemistry).

Alzheimer's disease has two cardinal neuropathological features. The first is deposition of the amyloid-β (Aβ) peptide into brain parenchyma forming amyloid plaques, and also in walls of cerebral blood vessels giving rise to cerebral amyloid angiopathy (Figure 2).

The Aβ peptide is processed from a much larger precursor protein, the amyloid-β A4 precursor protein (APP) by two secretases (β-secretase and γ-secretase) resulting in the production of predominantly 40 or 42 amino-acid-long variants of Aβ. The second major pathological feature is the presence of filamentous, argyrophilic inclusions in neurons called neurofibrillary tangles, which are composed of the abnormally hyperphosphorylated form of the microtubule-associated protein, tau (Figure 2). Accumulation of tau in dendrites gives rise to neuropil threads while tau deposition in axons, surrounding amyloid plaques, produces the plaque-associated neurites.

Neuropathological diagnosis of Alzheimer's disease

The post-mortem neuropathological diagnosis of Alzheimer's disease depends on the microscopic finding of senile/neuritic plaques and neurofibrillary degeneration in cases with clinical diagnosis of dementia.

The scheme originally proposed by Heiko Braak and Eva Braak nearly three decades ago and updated in 2006, differentiates six consecutive stages of stereotypical progression of the neurofibrillary tangle pathology [5]. According to this scheme the first structures affected in the cerebral hemispheres are the transentorhinal and entorhinal cortices (Braak and Braak stages I and II), followed by involvement of the hippocampus and other limbic structures (Braak and Braak stages III and IV) and finally isocortical cerebral areas (Braak and Braak stages V and VI). More recently the scheme has been modified, as involvement of the locus coeruleus has been suggested to proceed that of the medial temporal lobe structures [6]. The Aβ pathology has also been demonstrated to spread in a stereotypical manner and it has been shown that cerebral neocortical areas are first affected (Thal phase 1). From here the Aβ pathology progresses to affect medial temporal allocortical areas and the hippocampal formation (Thal phase 2), followed by involvement of the diencephalon and basal ganglia (Thal phase 3). In the most advanced stages the brainstem (Thal phase 4) and finally the cerebellum are also affected (Thal phase 5) [7].

Consensus neuropathological diagnostic criteria are used for establishing a probability post-mortem diagnosis of Alzheimer's disease [8]. For this the severity of three microscopic features needs to be determined: 1.) the frequency of neuritic plaques (absent, sparse, moderate, severe) 2.) the Braak and Braak neu-

rofibrillary tangle pathology stage (stages 0-VI) and finally 3.) the severity of the Aβ plaque pathology (Thal phases, 0-5). Consideration of all three components allows for the level of the 'Alzheimer's disease neuropathological change' to be established (none, low, intermediate and high levels) [8].

Lewy body disease, TAR DNA-binding protein 43-poitive (TDP43) inclusions, argyrophilic grain disease, vascular brain injury and hippocampal sclerosis may be associated with otherwise typical cases [9].

Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)

Both DLB and PDD are α-synucleinopathies as both are characterised by widespread Lewy pathology. Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia presenting in elderly individuals. Dementia is also a common late manifestation in Parkinson's disease. In PDD and DLB the clinical presentation may be similar; the two disorders are arbitrarily separated on the basis of the 1-year rule. Mutations of a number of genes have been shown to be associated with rare, familial forms of Parkinson's disease and genetic risk factors have been identified in the sporadic form of both diseases [10,11].

Neuropathological diagnosis of DLB and PDD

The neuropathological diagnosis of both DLB and PDD is dependent on the finding of widespread Lewy pathology (Figure 3). Semiquantitative assessment is carried out in compliance with the DLB Consensus Guidelines [12], which take into consideration the hierarchical progression of the Lewy pathology. On the basis of the distribution and severity of the Lewy pathology a case can be classified as belonging to one of five categories, which are 'olfactory bulb only', 'amygdala predominant', 'brainstem predominant', 'limbic (transitional)' 'and neocortical (diffuse)' variants. The presence of Alzheimer pathology, which is a consistent finding in both DLB [12] and in PDD [13], has to be assessed as the likelihood that in a particular case the dementia was caused by Lewy pathology is dependent not only on the severity of the Lewy pathology but also on that of the Alzheimer pathology [12].

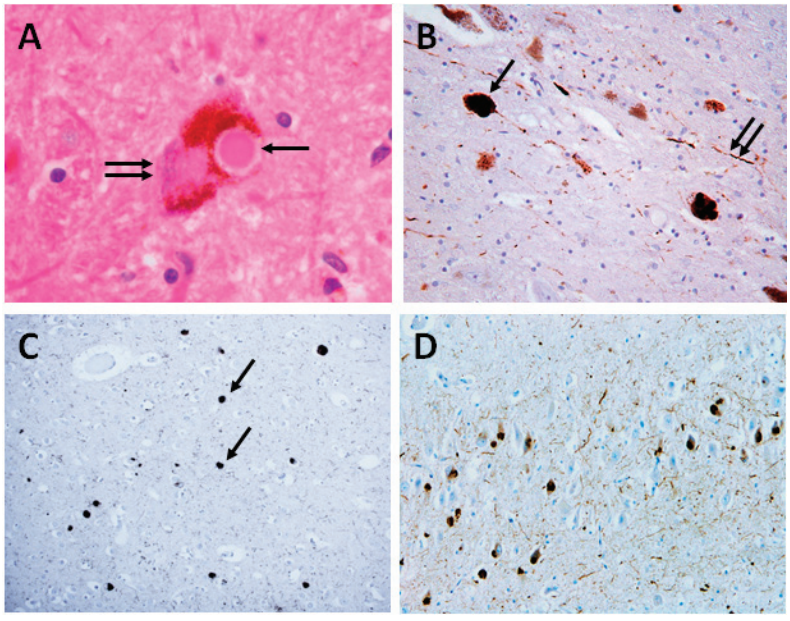

Figure 3. Lewy pathology in a case with dementia

A: A classical Lewy body (arrow) in one of the remaining pigmented neurons of the pars compacta of the substantia nigra. The same neuron also possesses a pale body (double arrow), which represents an earlier stage of Lewy body formation. **B:** Lewy bodies are strongly labelled with an anti-α-synuclein antibody (arrow) and α-synuclein-positive Lewy neurites are also present (double arrow). **C:** There are numerous cortical Lewy bodies (arrow) in the temporal neocortex. **D:** The CA2/3 hippocampal subregions are also affected by Lewy pathology (**A:** haematoxylin and eosin preparation; **B-D:** α-synuclein immunohistochemistry).

Frontotemporal dementias (FTD)

Frontotemporal dementia (FTD) is an overarching clinical term to describe a form of dementia which presents with a speech disorder (primary progressive aphasia or PPA) or with behavioural symptoms (bvFTD). After Alzheimer's disease FTD is the second most common form of dementia in the presenile age group (disease onset <65 years) [14,15]. Frontotemporal lobar degeneration (FTLD) is the neuropathological term used for a diverse group of diseases, in which atrophy and degeneration of the frontal and/or temporal lobes are characteristic. Some cases also show evidence of motor neuron degeneration underpinning the link between FTLDs and amyotrophic lateral sclerosis (ALS) (FTLD-ALS

spectrum). The major genes known to be associated with familial FTLD include the tau (*MAPT*), granulin (*GRN*), *C9orf72*, TDP43 (*TARDBP*), valosin containing protein (*VCP*) and charged multivesicular body protein 2B (*CHMP2B*) genes [15].

Classification

The recognition of the nature of the disease-proteins that can form inclusions in the vast majority of FTLD cases and the discovery of the genetic background of the majority of familial FTDs allowed the introduction of a molecular classification of FTLDs [16]. Depending on the nature of the proteinaceous inclusions, there are three major disease groups; FTLD with tau pathology (FTLD-tau), FTLD with TDP43-positive inclusions (FTLD-TDP) and FTLD with fused in sarcoma protein inclusions (FTLD-FUS). In a fourth group, designated as FTLD-UPS the protein component of the ubiquitin-positive inclusions remains to be identified while in a fourth, exceedingly rare group, no inclusions can be identified (FTLD-ni). In the three groups with known proteinaceous inclusions, there are several subtypes (Table 1).

1. FTLD-tau

Tau is a microtubule-associated protein with a role in maintaining the stability of the microtubules, the integrity of which is essential for maintaining normal neuronal cytoskeleton and a number of functions. In adult human brain tau is present in six isoforms due to alternative splicing of three of its exons (exons 2, 3 and 10). Abnormally hyperphosphorylated tau is the main component of inclusions in a number of neurodegenerative diseases including some of those presenting with FTD. The FTLD-tau group is further classified according to the tau isoform composition of the inclusions. Accordingly, the inclusions in Pick's disease and some FTDP-17 *MAPT* variants are composed of 3-repeat tau. In contrast, in diseases such as PSP, CBD and certain variants of frontotemporal dementia and parkinsonism linked to chromosome 17, associated with mutations of the *MAPT* (tau) gene (FTDP-17 *MAPT*) the inclusions are predominantly composed of 4-repeat tau isoforms. The presence of both 3-repeat and 4-repeat tau isoforms is characteristic in certain forms of FTDP-17 *MAPT* and also in sporadic primary age-related tauopathy (PART) [17].

Pick's disease (PiD)

PiD is characterized by severe frontotemporal atrophy, marked neuronal loss, gliosis, presence of swollen achromatic neurons (Pick cells) and rounded, tau-positive neuronal cytoplasmic inclusions, known as Pick bodies (Figure 4). Pick bodies are composed of 3-repeat tau isoforms and are argyrophilic with the Bielschowsky's silver stain. The presence of large numbers of Pick bodies in the granule cells of the dentate fascia and pyramidal neurons of the hippocampus is a characteristic feature of PiD. There are also tau-positive oligodendroglial cytoplasmic inclusions and astrocytic inclusions (ramified astrocytes).

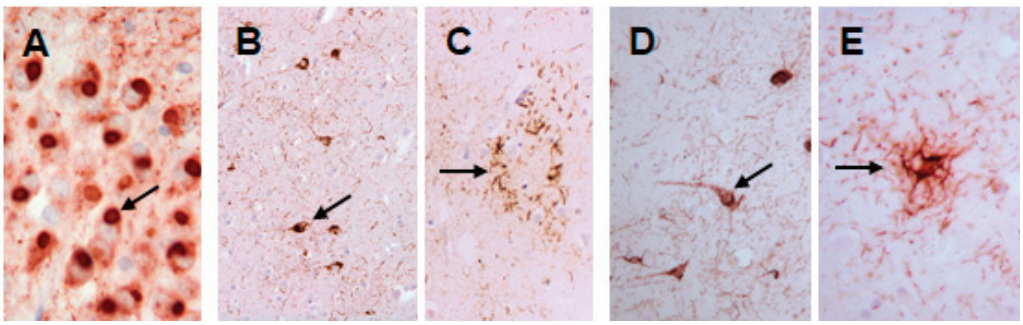

Figure 4. Pathological features of some forms of FTLD-tau

A: In Pick's disease the characteristic inclusion is the tau-positive Pick body (arrow), which are rounded, argyrophilic inclusions. Pick bodies are particularly common in the granule cells of the dentate fascia illustrated in panel **A**. Neurofibrillary tangles (arrow) (**B**) and an astrocytic plaque (arrow) (**C**) in the frontal cortex in a case with corticobasal degeneration. Neurofibrillary tangles (arrow) (**D**) and a tufted astrocyte (arrow) (**E**) in the frontal cortex in progressive supranuclear palsy (**A-E:** tau immunohistochemistry).

Corticobasal degeneration (CBD)

In CBD there is widespread neurodegeneration in cerebral cortex, basal ganglia, brainstem and cerebellar nuclei. In the affected cerebral cortical areas there is neuronal loss accompanied by astrocytosis and superficial spongiosis and swollen, achromatic neurons (Pick cells) may be seen. The substantia nigra and basal ganglia structures show neuronal lioss and astrocytosis. Neuronal tau (4-repeat tau) inclusions are found in affected cerebral cortices, subcortical grey nuclei, substantia nigra, other brain stem nuclei and cerebellar dentate nucleus. Tau-positive oligodendroglial inclusions (coiled bodies) are widespread in both grey matter and white matter. Tau deposition in distal astrocytic processes gives

rise to 'astrocytic plaques', which consist of annular arrays of short, tau-positive processes (Figure 4). They are most common in the premotor, prefrontal and orbital cortices and also in the striatum. Presence of astrocytic plaques is required for the diagnosis of CBD. Large numbers of tau-positive neuropil threads are also characteristic in CBD [18 - 20].

Progressive supranuclear palsy (PSP)

Although PSP is mostly classified as a form of atypical parkinsonism, in some patients behavioural variant of frontotemporal dementia (PSP-bvFTD) or primary progressive aphasia (PSP-PPA) may be the predominant clinical presentation. Similar to CBD, PSP is also a 4-repeat tauopathy with accumulation of abnormal tau in both neurons (neurofibrillary tangles and pretangles) and glia (Figure 4). Neuronal loss with astrocytosis is most apparent in the basal ganglia, brainstem and cerebellar nuclei. The tau-positive stellate-shaped astrocytes, called 'tufted astrocytes' are characteristic for PSP (Figure 4) and oligodendroglial coiled bodies are also present. While in the classical cases with Richardson's syndrome (PSP-RS) cases the tau-load is greatest in the basal ganglia and brainstem, in the cortical PSP variants such as PSP-bvFTD, PSP-PPA and PSP presenting with corticobasal syndrome (PSP-CBS), involvement of the cerebral cortices by tau pathology may be prominent [17-20].

FTDP-17 MAPT

Over 40 different pathogenic *MAPT* gene mutations have been identified as a cause of FTDP-17 *MAPT*. The primary effect of some of the mutations is at protein level while others affect alternative splicing of tau pre-mRNA [17]. In cases of FTDP-17 *MAPT* there is superficial spongiosis, nerve cell loss and astrogliosis in affected cortical regions, basal ganglia and brainstem nuclei and swollen, achromatic neurons may be seen. Tau-positive inclusions are present in affected structures and, determined by the effect of the *MAPT* mutations. The neuronal tau inclusion types comprise pretangles, neurofibrillary tangles and Pick body-like inclusions. The glial inclusions include oligodendroglial coiled bodies and in some subtypes tufted astrocytes or astrocytic plaques can be found [21].

2. FTLD-TDP

In FTLD-TDP the inclusions are composed of TDP43, which is a widely expressed RNA/DNA binding protein, found predominantly in cell nuclei. TDP43-positive pathology is present in both sporadic and familial FTLDs and it is responsible for ~50% of all cases. The TDP43 lesion types include neuronal

cytoplasmic inclusions (NCIs), neuronal intranuclear inclusions (NIIs) and dystrophic neurites (DIs) (Figure 5). An important feature of the pathology is that affected nerve cells loose the normal diffuse nuclear TDP43 staining (Figure 5) [16, 22].

The currently known genes, whose mutations are associated with familial FTLD with TDP43 pathology include the *GRN*, *C9orf72 and VCP* genes and rarely the *tank-binding kinase 1* (*TBK1*) and the *TARDBP* genes [15, 23].

There are four distinct subgroups of FTLD-TDP (types A, B, C and D), which can be differentiated from one another on the basis of morphological appearances and distribution of the TDP43 inclusions. In cases with 'type A' pathology a combination of NCIs, short DNs and NIIs is characteristic, while in cases with 'type B' pathology NCIs are predominant. In 'type C' the characteristic lesion type is the long twisted DN and NCIs are either absent or rare. 'Type D' pathology is associated with *VCP* gene mutations and NIIs and DNs are predominant lesion types in this variant (Figure 5). There is a correlation between pathological subtype, clinical presentation and genetics in FTLD-TDP [16].

In addition to TDP43 pathology, in cases with *C9orf72* expansion repeats, p62 and ubiquitin-positive 'star-like' inclusions are also found, which are most prominent in neurons of the hippocampus and cerebellum (Figure 5). Such TDP43-negative inclusions are composed of dipeptide proteins, generated from the translated expansion repeats.

TDP43 pathology, often limited to the medial temporal lobe is often seen in other neurodegenerative disorders including Alzheimer's disease and Lewy body disorders.

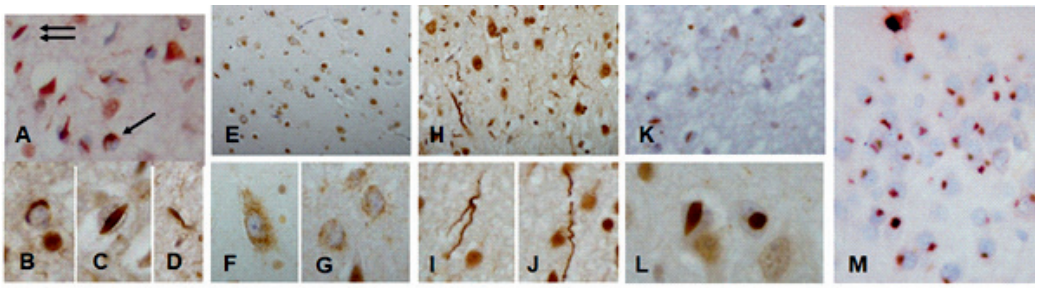

Figure 5. Pathological characteristics of FTLD-TDP

A: Temporal cortex in a case of FTLD-TDP, 'type A' with arrow pointing to a neuronal cytoplasmic inclusion (NCI), double arrow pointing to a neuronal intranuclear inclusion (NII). An NCI (**B**), an NII (**C**) and **a** short dystrophic neurite (DN) (**D**) are demonstrated with higher magnification in a 'type A' case. In 'type B' (**E**), which is the morphological phenotype associated with FTD-MND, the characteristic inclusion type is NCI (**F** and **G**). In 'type C (**H**),

characteristically associated with semantic dementia, the morphological hallmark lesion is the long DN (**H-J**). In 'type D', which is the morphological variant seen in familial FTD due to mutations in the *VCP* gene, there are frequent NIIs (**K** and **L**). In FTLD-TDP cases with *C9orf72* expansion repeat mutation, in addition to TDP43 pathology (types A or B), ubiquitin and p62-positive, TDP43-negative 'star-like' NCIs are present in the granule cell layer (GCL) of the hippocampus (**M**) and the cerebellum.

3. FTLD-FUS

In entities of the FTLD-FUS group the major disease protein is the fused in sarcoma (FUS) protein and the diseases are atypical FTLD with ubiquitin positive, tau and TDP43-negative inclusions (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD) [24, 25].

In aFTLD-U, FUS-positive NCIs are present in frontotemporal cortices, hippocampus, basal ganglia, thalamus and brainstem nuclei and also in spinal cord motor neurons and NIIs, which are also seen, have twisted vermiform, ring-like, straight or curved morphologies [25]. In NIFID the NCIs often appear as eosinophilic intracytoplasmic structures on the haematoxylin and eosin preparation and are often strongly positive for p62. NIIs also occur in NIFID with a proportion of the FUS-positive inclusions being also positive for α-internexin [24, 25]. The term BIBD derives from the pathological observation that the FUS-positive inclusions are basophilic on the haematoxylin and eosin preparation.

4. FTLD-UPS

Mutations in the *CHMP2B* gene is a rare cause of familial FTLD. In this entity the neuronal intracytoplasmic inclusions are ubiquitin-positive, but negative for tau, TDP43 and FUS [26].

Conclusions

In the entities discussed in this chapter specific disease-associated proteins form intracellular, and in some cases, extracellular protein aggregates. The knowledge of the biochemical characteristics of disease proteins together with understanding the genetic background of the majority of the familial entities, have allowed the introduction of a molecular classification of the neurodegenerative diseases. All this information provides a practical tool, which can be utilised in the neuropathological diagnosis of the cases.

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UDK: 615.217.2
DOI: 10.21857/yvjrdcq38y
Review article
Received: 20.1.2019.
Accepted: 10.5.2019.

NEUROPHARMACOLOGICAL NEWS AND STUDIES IN NEURODEGENERATIVE DISEASES ESPECIALLY DEMENTIAS AND MULTIPLE SCLEROSIS

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Summary

Development of new chemical entities (NCE) for the treatment of Alzheimer's Disease in the last fifteen years has been followed with huge number of confirmatory studies which all have been negative but associated by high cost. Unfortunately, in spite of encouraging results from exploratory clinical studies, confirmatory trials are practically all negative. The most recent disappointing results are those associated with development of aducanumab and crenezumab. On the other side, NCE developed for the treatment of relapsing remitting multiple sclerosis made great progress, providing various new modalities of treatment. Of course, there are still a lot of unmet medical needs in the treatment of multiple sclerosis but current data available from exploratory clinical studies are very optimistic.

Key words: Alzheimer's disease, Multiple Sclerosis, Drug development, New-chemical entities.

Alzheimer's disease (AD) is a progressive degenerative disorder of the brain with increasing prevalence in the elderly population. A progression of Alzheimer's disease is characterised by deterioration in cognition (thinking, conceiving, reasoning), functional ability (activities of daily living), and a disturbance in behaviour and mood. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition.

The current treatment of Alzheimer's disease with central acting acetyl cholinesterase (AchE) inhibitors or memantine has been considered as modest, in spite of the recent meta-analysis which showed lower mortality rate among

AchE inhibitors consumers [1] which makes the research field wide open. In fact, various biological aspects of Alzheimer's disease pathology have been targeted in clinical research so far (e.g. amyloid processing, tau-hyperphosphorillations, microglia activation, inflammatory reactions and others), but in spite of favourable preclinical data, no one substance has met regulatory and clinical requirements in confirmatory randomized clinical trials (RCT), neither for symptomatic nor for disease modifying effect. Development of new treatment for neurodegenerative disorders like Alzheimer's disease (AD) and other types of dementia is currently the most disappointing field in CNS drug research. In facts after nearly twenty years no new drug has been approved to treat neither cognitive nor behavioral symptoms in subjects with Alzheimer's disease. More than 500 clinical studies have been executed involving more than 30.000 participants in Alzheimer's disease since 2000 and no one have met clinically significant primary endpoint in their confirmatory trial design. Therefore, many of the biggest worldwide leaders in pharma industry (GSK; Pfizer; Sanofi) have decided to get rid of research and development in neurodegenerative disorders.

Plenty of explanations have been offered including inappropriate preclinical models, inadequate dose selection during the translational process, lack of sensitive instruments who will capture small, but clinically significant changes, short study durations, occurrence of numerous research sites usually with limited experience in drug research and many others. Apparently, our knowledge on Alzheimer's disease biology is still quite limited, whereas the current concept of drug development targeting inter-neuronal amyloid deposition in the brain has not been confirmed, in spite of numerous clinical studies with various molecules. There are several ongoing confirmatory trials (aducanumab, crenezumab, and others) which are targeting enhanced study populations (prodromal or clinically early stage of Alzheimer's disease with evidence of amyloid burden either by molecular neuroimaging or cerebrospinal fluid (CSF) examination). These studies are very demanding, some of them have randomized more than two thousand subjects, but all of them have been associated with extremely high screening failures rates (>80%) which makes usual high cost Alzheimer's disease studies extraordinary expensive. We are desperately awaiting first results of these studies, although recent decision of aducanumab's sponsor (Biogen) to increase sample size due to efficacy data variability in interim analysis should not be regarded as the good news. In fact, the effect of aducanumab on accumulated amyloid in the human brains seen at phase I and II of clinical trials and published at several specialized conferences since 2019 have been considered as an encouraging, although the clinical effect on patients cognition were minimal.

World Leaders associated in G8 group of the most developed countries in the World in their Summit in December 2014 has concluded that Alzheimer's disease is the global priority in medical research with ultimate goal of making successful drug treatment available until 2025. Although political, this statement had the intention to evoke a new innovative approach to drug development in Alzheimer's disease. However, due to strong public pressure on Regulatory Authorities, (RA) it is quite possible that RAs will relax their requirement about minimal efficacy evidences needed for the approval of new drug for Alzheimer's disease. This will not be the first time, because it happened in 1995 when Food and Drug Administration (FDA) approved riluzole for the treatment of amyotrophic lateral sclerosis, regardless of initially negative but borderline evidence of the efficacy. Since then several other examples can be seen particularly among treatment of rare diseases (orphan drug indication). The current request for drug makers to get approval of new chemical entity (NCE) for the treatment Alzheimer's disease is to prove statistically significant difference in two studies between NCE and placebo in at least two of three domains which are including cognition, activities of daily living and global functions, using pre-defined assessment instruments, sample size and statistical plan.

Inability to find new and successful molecule to treat Alzheimer's disease leaded to enhanced research towards primary and secondary prevention of Alzheimer's disease. It seems that today's technology of molecular imaging of the brain can visualise presence of amyloid pathology several years prior to clinical onset of Alzheimer's disease. Therefore, there are several ongoing large clinical studies in so called pre-clinical Alzheimer's disease subjects where new molecules have been tested with idea to postpone the clinical onset of Alzheimer's disease Such studies are requesting very long NCE exposure between 3 to 5 years in several thousand subjects who have increased risk to develop Alzheimer's disease. The main challenge of such studies are to identify subjects with increased risk for Alzheimer's disease and selection of appropriate outcome measures to capture potential signal of change against placebo. The first results of these studies we expect in 2021.

Nevertheless, at the moment it is very difficult to see any molecule in development which will be able to meet G8 group expectation and being available for the treatment of Alzheimer's disease in 2025. Such molecule should be already in at least phase II of drug development, with already expressed strong clinical signals of the efficacy, but regrettably, nothing has been reported so far to encourage our optimism.

In such pessimistic environment, why therefore companies are still developing drug for Alzheimer's disease? It is very difficult to answer these questions, but one of the answers can be hidden in several historical examples where some companies have made huge profit during the drug development of the molecules which eventually failed RA requests. However, this a long story out of the scope in this article.

Opposite to new drug research for AD, the drug development for the treatment of relapsing remitting multiple sclerosis (RRMS) has made great progress since the first disease modifying treatment agent (DMTA) called interferon beta has been approved for the treatment of RRMS in the early nineties of previous century. Since then, plenty of new molecules have been developed, frequently with better and better efficacy profiles. Unfortunately, the occurrence of new and more potent molecules for the treatment of RRMS has not been associated with the improvement with their safety profiles. Therefore, among unmet medical needs in the treatment of multiple sclerosis which are including further delaying progression and avoiding disability; re-myelinisation and repair of degenerated neurons; neuroprotection and more effective reduction of active symptoms, reduction of the cost of treatment and prevention and ameliorating of adverse effects of current medication are the most important challenges of further drug development for multiple sclerosis.

In spite of the great progress made, the long-term treatment and prognosis of MS is still unknown, particularly related to progressive form of disease which is inevitable after RRMS phase or in case of the primary progressive MS (PPMS). Recently approved ocrelizumab is the first drug approved after old and toxic mitoxantrome for the treatment of progressive form of disease. The approval of ocrelizumab was made on the basis of one study [2] which showed slower progression of disease after 120 weeks in subjects exposed to ocrelizumab compared with subjects on placebo. However clinical implications of these results should be confirmed during the post-marketing research.

There are several ongoing confirmatory clinical studies in multiple sclerosis from which we expect additional therapeutic progress and improvement.

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UDK: 616-084:616.892.3
DOI: 10.21857/yrvgqtknj9
Review article
Received: 20.11.2018.
Accepted: 10.5.2019.

POSSIBILITIES OF DEMENTIA PREVENTION

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Summary

Dementia represents one of the greatest global challenges for health and social care in this century. More than 50 million people worldwide suffer from dementia, and this number is predicted to triple by 2050. Ageing is often associated with cognitive impairment. Therefore, prevention of cognitive impairment is an imperative. Dementia includes a heterogeneous group of disorders, the most common being Alzheimer's disease and vascular dementia. Most cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and smoking are not exclusively risk factors for vascular dementia but also for Alzheimer's disease. Genetic material and ApoE4 allele is about the only non-modifiable risk factor for Alzheimer's disease. Today we know that one important and modifiable risk factor is education. Better education means better protection against dementia. A large number of dementias are potentially preventable by early intervention. Early changes in the blood vessel wall can be detected by early ultrasound methods or early biomarkers. These methods allow us to detect changes before the disease becomes clinically evident. Early disease detection enables in-time management, and studies have shown that careful control of vascular risk factors can postpone or even reverse disease progression.

Key words: Alzheimer's Dementia, Vascular Dementia, Cognitive Impairment, Dementia Risk Factors, Dementia Prevention

Possibility of dementia prevention

Global ageing population is leading to greater numbers of older people, owing to factors such as increasing life expectancy and decreasing birth rate. Ageing is often associated with cognitive changes, which range from mild cognitive

changes to severe impairment causing dementia. This growing number of patients suffering from dementia represents the greatest challenge for health and social care in this century. Although Alzheimer's disease is the most common cause of cognitive decline in aged population, independent causes of cognitive dysfunction such as vascular disease, subclinical brain injury, silent brain infarction, and clinically overt stroke are important causes and contributors to cognitive dysfunction. [1], [2]

Mild cognitive impairment (MCI) is a clinical state of mild but clearly abnormal memory loss, without significant impairment in daily activities. In many instances, both clinically and pathologically, MCI represents a prodromal stage of Alzheimer's disease (AD). Some studies have shown that the presence of MCI in older subjects, regardless of the definitions and criteria used, increases the risk for developing dementia. [3],[4] Because cerebrovascular disease can cause mild cognitive deficits that affect multiple cognitive functions, the term 'vascular' mild cognitive impairment (VaMCI) was proposed. [5], [6] Patients diagnosed with VaMCI are in transition towards Alzheimer's disease. [7] Vascular cognitive impairment (VCI) encompasses all cognitive disorders associated with cerebrovascular disease, from developed mild cognitive deficits to dementia. VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury, and cognitive impairment affecting at least one cognitive domain. The most severe form of VCI is VaD. [1], [2]

Dementia is a clinical syndrome characterized by the impairment of cognitive functions, such as memory, language, praxis, recognition and executive function, with the loss of functional capacity. [8] Dementia may be caused by a heterogeneous group of disorders, the most of common being Alzheimer's disease and vascular dementia. While cardiovascular risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and smoking, are particularly relevant in the development of VaD, they also play a role in AD. [9], [l0], [11], [12], [13], [14] Thus, both conditions may represent different spectrums of cerebral vascular disease depending on the extent of microvascular changes. [15] An association between impaired function of cerebral micro vessels and cognitive impairment in patients with mild to moderate AD was shown in a study by Silvestrini. [16] Because some cardiovascular risk factors are modifiable, investigating the mechanisms by which they contribute to AD pathology and the manifestations of dementia may have implications for prevention. Also, lifestyle factors at a younger age, such as physical, cognitive and work activity, diet and mild to moderate alcohol consumption, may be protective against AD. [17]

The diagnostic evaluation of dementia is complex, with various criteria applied. The clinical diagnosis depends on the definition of cognitive deficits and the differentiation between normal age-related changes and pathological conditions. Because the variability of cognitive function among the elderly is great, it is difficult to quantify precise normative limits in this population group. [18] The clinical diagnosis of dementia should always take into account the individual's decline from the premorbid level of functioning. [18] In addition to the difficulty in differentiating between early AD and normal ageing, the distinction among the various dementing illnesses presents a diagnostic challenge.

Recently, the Lancet Commission presented a new life-course model showing potentially modifiable, and non-modifiable, risk factors for dementia. [2] [19] According to this model, it is estimated that 35% of dementia cases could be prevented if we eliminate risk factors. A key recommendation is to focus on interventions to build up resilience and brain reserve, to activate neuroplasticity, detect and to treat risk factors and to live a healthier lifestyle. This life course model shows us the need for preventative actions from early childhood, or even, from birth. As we already know, the most common form of dementia, the Alzheimer's disease, is in large part modulated by genetics. Genetics is one non-modifiable risk factor, meaning that with birth we either have already inherited ApoE4 allele, or not. Along with other genetic material, this is among the only non-modifiable risk factors. All other risk factors belong to potentially modifiable risk factors and they account for about 35%. In early childhood, we need to start taking care of another risk factor for dementia, and that is education. Studies have shown that lower grade of education brings a higher risk for dementia, pointing to a conclusion that education protects against the onset of dementia. Education also influences the course and the outcome of the disease in terms of a pattern of cognitive decline and underlying brain pathology. Study shows that adult life work complexity, social network and complex leisure activities also reduce the occurrence of dementia. [2] [19]

When we reach midlife, we are at risk of developing hearing loss [20], hypertension, and obesity. These three things attack us at the age of 40 or 45 (45 is officially the beginning of middle age), and if we partner with them for the rest of our middle age or longer, they bring us to an increased risk for developing dementia. [19] So, keeping fit, taking care of the extra weight, as well as early recognition and treatment of hypertension will not only guard our body from disease but also our brain.

The potential public health impact of hearing loss in the context of dementia is substantial, given the high worldwide prevalence of hearing loss in older

adults. What we urgently need is an inter-disciplinary effort to bring together hearing and mental health and to investigate further early hearing loss in the context of brain and cognitive ageing. [20] Later on in life we will need to take care of smoking, depression, physical inactivity, social isolation, and diabetes. [19], [21], [22], [23]

The National Academy of Sciences in 2017 reported that there are no specific interventions that have sufficient evidence to warrant a public health campaign for the prevention of dementia except: cognitive training, blood pressure management in people with hypertension, and increased physical activity. [24], [25] In 2017, the presidential advisory from the American Heart Association/American Stroke Association, tried to decide on a definition of initial optimal brain health in adults. [18] The working group identified seven metrics to define optimal brain health in adults, and these originated from well-known Life's simple 7 [26], identified by Ralph Sacco in 2011. He then identified four ideal health behaviors; non-smoking, physical activity, healthy diet, and a body mass index under 25 kg/m^2, and three ideal health factors such as untreated blood pressure under 120/80 mmHg, untreated total cholesterol under 200 mg/dL and fasting blood glucose less than 100 mg/dL. Along with these recommendations in order to maintain cognitive health, it is advised to incorporate control of cardiovascular risks and suggest social engagement and other related strategies. There is always an opportunity to improve brain health through adult prevention and other interventions.

Overall, white matter fiber-tracking on MRI evidenced an early signature of damage in hypertensive patients when otherwise undetectable by conventional neuroimaging. In perspective, this approach could allow identifying those patients that are in initial stages of brain damage and could benefit of therapies aimed at limiting the transition to dementia and neurodegeneration. [27] In adults with high baseline blood-pressure, those using any blood-pressure lowering drug, regardless of drug class, had a reduced risk for developing all-cause dementia and Alzheimer's disease compared with those not using blood-pressure medication. It's also interesting, that this meta-analysis looked not only at dementia but also Alzheimer's disease specifically, and found a benefit of blood-pressure lowering. This suggests that the onset of Alzheimer's disease may be slowed through treatment of high blood pressure. [28]

Several studies showed that increased arterial stiffness has greater value in predicting cognitive decline in healthy subjects, than blood pressure. [29] It is superior to blood pressure in predicting cognitive decline in all domains and in explaining the hypertension-executive function association. Arterial stiffness,

especially in hypertension, may be a target in the prevention of cognitive decline. [29]

An increasing number of studies confirm the positive correlation of obesity and inflammation with cognitive impairment. [30], [31] There is sufficiently strong evidence, from a population-based perspective, to conclude that regular physical activity [32] and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) [33] reduce the risk of cognitive decline and may reduce the risk of dementia. Also, there is sufficiently strong evidence to conclude that a healthy diet and lifelong learning/cognitive training may also reduce the risk of cognitive decline, thus enhancing the inborn mechanism of neuroplasticity. [34], [35]

Findings indicate that older men with the history of depression are at increased risk of developing dementia, although depression in later life is more likely to be a marker of incipient dementia than a truly modifiable risk factor. Older people with depression may be better viewed as potential targets of indicated prevention strategies, rather like people with mild cognitive impairment. [21]

The window of opportunity for beneficial effects of physical activity seems to be broad, and may extend to people who become active later in life. However, beyond already available general recommendations for health promotion, it is very challenging to draw specific practical recommendations from the current evidence regarding the type, frequency, intensity, and duration of physical activity that could protect against AD. It is likely that physical activities that have additional social and cognitive stimulation components may be most effective. The multi-domain approach to dementia prevention also seems more promising compared with the traditional, single-domain approach. [23]

Loneliness predicted greater dementia risk, whereas being married and having many close relationships with friends and family were related to a lower risk of dementia. Further epidemiological research is needed to understand the possible causal nature of these associations, including the likely underlying mechanisms. [36]

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is the first multi-domain lifestyle intervention that has shown that a combination of lifestyle interventions is able to prevent or slow down cognitive decline. [37] Lots of evidence from epidemiological studies indicates that these different modifiable lifestyle factors are related to dementia and Alzheimer's disease. The intervention areas were diet (Nordic diet), exercise, cognitive training (individualized) and vascular risk monitoring. The results

showed a reduction of cognitive decline by 30%. There are now 3 multi-domain trials going on globally. The FINGER study was taken as a model. The FINGER study included 1109 participants in the analysis: 362 APOE ε4 allele carriers (173 interventions and 189 controls) and 747 non-carriers (380 interventions and 367 controls). The difference between the intervention and control groups in annual neuropsychological test battery total score change was 0.037 (95% CI, 0.001 to 0.073) among carriers and 0.014 (95% CI, −0.011 to 0.039) among non-carriers. Intervention effect was not significantly different between carriers and non-carriers (0.023; 95% CI, −0.021 to 0.067). Healthy lifestyle changes may be beneficial for cognition in older at-risk individuals even in the presence of APOE-related genetic susceptibility to dementia.

Assuming a causal relation and intervention at the correct age for prevention, relative reductions of 10 or 20% per decade in the prevalence of each of the 7 risk factors would potentially reduce the prevalence of AD in 2050 by between 8 and 15% - between 8,8 and 16,2 million cases worldwide. After accounting for non-independence between risk factors, around a third of Alzheimer's disease cases worldwide can be attributed to potentially modifiable risk factors. Incidence of Alzheimer's disease can be reduced through improved access to education, reduction of vascular risk factors (through the use of effective methods such as physical inactivity, non-smoking, diagnosing and treating midlife hypertension, obesity, and diabetes) and depression. [38], [39]

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UDK: 616.892.3
DOI: 10.21857/m16wjc6j79
Review article
Received: 29.1.2019.
Accepted: 28.3.2019.

ALZHEIMER DISEASE AND ALZHEIMER-LIKE DEMENTIAS

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Summary

Alzheimer's disease (AD) is the main cause of dementia and accounts for 60% of dementia syndromes in people older than 75 years. Memory impairment, especially impairment of episodic memory, is one of the first symptoms of typical AD. Alzheimer-like clinical picture is often assumed to be the underlying cause of dementia in elderly patients. Thus, it is highly important to establish the correct diagnosis and be aware of medical conditions that may by presenting with memory impairment mimicking AD. The correct classification of AD and non-AD is mandatory to study disease mechanisms or new treatment possibilities. Episodic memory is an essential cognitive function that supports our ability to form an autobiographical history and helps us to create a concept of the past and the future. The hippocampal network, including the parahippocampal gyrus, hippocampus, and neocortical areas, play a major role in the process of memory consolidation and retrieval. The diagnostic procedure of memory impairment is firstly based on a comprehensive clinical investigation that should comprise a detailed medical/medication history, proxy report of the perceived symptoms, neuropsychological testing, and a neurological and psychiatric examination. Additional investigations, such as a magnetic resonance imaging (MRI) scan, 18fluorine-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET), cerebrospinal fluid (CSF) examination, electroencephalography (EEG) and AD biomarkers (β-amyloid42 [Aβ42], ratio Aβ42/Aβ40, total tau protein [t-tau], and phosphorylated tau [p-tau]), may further help to establish the correct diagnosis. Application of the novel clinical criteria based on biomarkers has shifted a diagnostic procedure "to the left" and has introduced a new concept termed preclinical AD where clinically normal

individuals with biomarker evidence of AD pathology were hypothesized to be on the trajectory towards symptomatic AD. Use of biomarkers have carried out individuals with mild cognitive impairment who are amyloid-negative but neurodegeneration-positive addressing a conceptually separate clinical entity named suspected non-Alzheimer disease pathophysiology (SNAP). SNAP clinical progression can mimic AD that makes final diagnose and treatment options uncertain in the clinical centers that are not using biomarkers in the assessment of cognitive impairment. Medial temporal tau pathology without amyloidosis might be a major constituent of SNAP. The term primary age-related tauopathy (PART) has been proposed as a useful practical clinical construct to describe this phenomenon in very old individuals. Besides slow progression of memory impairment a slow evolution of behavioral and mood changes is not uncommon. Increased awareness of AD and non-AD clinical entities may ultimately help clinicians to establish timely clinical diagnose and to start an adequate/personalized therapeutic intervention.

Key words: dementia, biomarkers, amyloid, tau, SNAP, Primary Age Related Tauopathy, cognitive testing, Pet-Amyloid, neuropathology, therapy

Epidemiology

In recent decades, interest in dementia and Alzheimer's disease (AD) has been intensifying due to demographic changes that have led to an increase in the population of old people throughout the world. Dementia is one of the most common chronic diseases of people over the age of 75. Dementia among young people aged 60 and less is less common but after 60 the prevalence is doubled with every five-year interval, which is 1.5% between 60-69 years old and almost 40% in 90-year-olds. In 2015, almost 47 million people worldwide were estimated to be affected by dementia, and the numbers are expected to reach 75 million by 2030, and 131 million by 2050, with the greatest increase expected in low-income and middle-income countries. [1] It is widely accepted that the dementia prevalence in the western population is about 1,3-1,5 % while the incidence of the new cases is about 0,23% per year [2]. The most common form of dementia is AD, which accounts for about 60% of all dementias, 10-15% of vascular dementia (VD), 10-15% of Parkinson's dementia (PDD) and Lewy Body dementia (LBD, 5-10% of frontotemporal lobe dementia (FTLD) [3].

Economic impact

There is no comprehensive analysis of economic impact of dementia and specifically AD in Croatia. Thus, we have to use a data from western countries to be able to understand the substantial extend and impact of AD on individuals,

families and society. AD has a substantial economic impact for each person. A multinational study performed in Spain, Sweden, the UK, and the USA in 2011 [4] had estimated that societal costs amount to about €14 500 per year in patients at home with a high level of autonomy in activities of daily living (ADL), but rises up to €72 500 per year in patients who need residential care. In 2014, the direct cost of AD for payers in the USA alone was estimated to be $214 billion [5]. For Comparison the entire cost (indirect and direct) of cancer was estimated at $290 billion in 2010 [6].

Costs of (non)diagnosing AD

Insufficient diagnostic services are the biggest obstruction to establish of proper care for patients with dementia. Although a novel therapeutic approach is still not available at present, timely and correct diagnosis is a prerequisite for access to care and current symptomatic treatment. As the primary care should be the carrier of information regarding dementia, it is estimated that only 20–50% of demented patients have a documented diagnosis in primary care, and this proportion is substantially lower in low-income and middle-income countries [7]. For those underdiagnosed dementia patients, the economic costs are largely covered by caregivers and by patients themselves. The early identification and diagnose of AD pathological changes in the brain becomes mandatory.

Risk factors

The most common risk factors are genetic (mutations on 1, 14 and 21 chromosomes and presence of APOE 4 genes in a late age), vascular (high pressure, diabetes, obesity, cardiovascular disease, depression and alcohol) and psychosocial (reduced cognitive reservoir and physical inactivity) nature. Of the other factors, nutrition, head trauma and hormonal changes can play a smaller role [8].

Neuropathology

The brain of a patient with AD was characterized by atrophic changes of gyrus and deep and broad sulcus.Atrophic changes are more pronounced in young patients than in older patients for the same clinical picture. Macroscopically atrophical changes start in temporal lobe followed by parietal, frontal and occipital reflecting the sequential and temporal spreading of pathology. Associative regions are more affected than the primary areas. One of the first and most atrophied areas is the hippocampus and the parahippocampal region. These regions are used to evaluate bio-degeneration at Magnetic Resonance (MRI) or

Computerized Tomography (CT). Other subcortical areas are less affected at the beginning of the disease. [9, 10] The main microscopic changes in AB are characterized by the presence of senile plaques, neurofibrillary tangents and neuronal degradation. In addition, the presence of glial cells is increased. Senile plaques of the most circularly extracellular formations in the neuropil of the gray matter of the brain and consist of fibrillar forms of amyloid proteins and clusters of degenerate axons and dendrites. The appearance of senile plaques also depends on the type of histological dye and is often referred to as diffuse, neurite, amyloid, mature plaques or plaques with the central amyloid nucleus or so called "core" plaque. For practical reasons, they are divided into diffuse and neuritic reflecting the stage of maturation [11]. At the beginning of the disease amyloid plaques accumulate in the neocortex while the hippocampal regions are free of them. With the duration of the disease, the plaques are "lowered" to the central parts of the large brain and small brain and the stubborn tree. Intracellular changes typical for AB are neuronal tangles that consist of accumulated hyperphosphorylation proteins. Unlike amyloid plaques, neuronal tangles begin to accumulate in the parahippocampal region in the entorhinal cortex and breed against the hippocampus and in the subsequent phase toward the neocortex. In other words, the amyloid empties "from below" and the tangled "bottom up" [12]. The distribution and pathology of pathology and the regional pathology of pathology determine the clinical picture and the development of the disease. Other neuropathological changes are important changes in the blood vessels that arise in the amyloid accumulation leading to amyloid angiopathy, and by specific neuronal death, synapse degeneration in specific brain regions [13], and the increasingly present inflammatory component that appears as a defense mechanism of brain tissue toward nonphysiological accumulation of that "Biological garbage". Patients with mild-to-moderate clinical AD with predominant tau neuropathology lacking Aβ plaques in the medial temporal lobe, have been frequently described in worldwide cohorts [14,15]. Historically, tau pathology accumulate in elderly persons thus pathologic it was suggested the continuum ranging from focally-distributed neurofibrillary tangles observed in cognitively normal aged through the pathology observed in persons with dementing illnesses that have been referred to as "tangle-predominant senile dementia" (TPSD), "tangle-only dementia", "preferential development of NFT without senile plaques", and "senile dementia of the neurofibrillary tangle type" (SD-NFT), among other neuropathological terminology. Recently it was introduced the new term PART ("primary age-related tauopathy"), reviewing the relevant studies in the clinical and pathologic literature [16].

Patophysiology of AD

How to explain this cascade of change and find it in a common hypothesis, the most important issue of the nineties of the last century. In 1992, the working hypothesis of Alzheimer's Disease was suggested, "Amyloid Cascade Hypothesis", which still has 25 years after the proposal is a hypocritical hypothesis despite many criticisms, but it has not been rejected yet.Modern DIAGNIC approaches AB, animal experimentation experiments, and directions for the development of new drugs against AB are underlined by this hypothesis. Hepatitis suggests that the excessive accumulation of beta-amyloid physiological protein, which is the product of the metabolic rate of the entire protein, APP (amyloid precursor protein) is the main trigger of the pathological process. The accumulated beta-amyloid accumulation, which leads to a conformational change of the protein itself, which becomes toxic to the brain cells as an oligomer, is 1) accumulated in the presynaptic part of the synapse, binds to different intranasal proteins and affects the reduction of LTP and the secretion of the LDP protein. In the next stage, the oligomers interact with glutamate, acetylcholine, noradrenaline and GABA and reduce their effects at the end of 3) a direct influence on the phosphorylation of tau protein which leads to cytoskeletal cell destabilization the formation of neurofibrillary tangents and dying of the cell. Parallel to the neurodegenerative process, there is a glial and inflammatory reaction that accelerates the process of decay and destabilization of cellular structures and leads to the cessation of cognitive function and dementia [17].

Amyloid cleaning

Production and cleansing of Amyloid is a normal physiological process. Clearing of toxic molecules such as amyloid occurs mostly via cerebrospinal fluid but also via modified glial and lymphatic system or so-called glymphatic pathway. With the help of anti-amyloid antibodies that each person creates retreats amyloid from interstitial spaces and drains over the blood and kidneys. Aging brings a decrease in the amount of antibodies, which reduces drainage and decreases the maintenance of amyloid balance in the brain and its accumulation in plaque form. All factors that can affect the drainage pathways and the formation of antibody directly affect the physiological amyloid cleavage processes. On the other hand, increased amyloid formation in the brain due to various causes (mutations, cerebrovascular problems etc) overwhelms the cleaning system and leads to secondary amyloid accumulation. Uncontrolled accumulation of amyloid leads to cascades of pathological events described above [18].

Inflammatory processes

Inflammation or inflammatory process is a normal tissue reaction, in any changed steady state in the brain. In Alzheimer's disease, the inflammatory reaction plays an important role in repairing injury and restoring the tissue to its functional state. In Aging, amyloid accumulation grounds inflammation, which, along with the role of reparation, causes and accelerates the formation of amyloid and reduces the soluble and neuroprotective forms of the amyloid precursor protein. This is called the kindergarten phenomena. Acute phase proteins and inflammatory cytokine proteins are specific molecules that release when diseased neurons interact with astrocytes and microglia [19].

Genetics of Alzheimer's Diseases

Patients with early AD who are between 30 and 60 years of age represent a population of 10 % of all AD patients. In about half of these patients, the genetic causes lie in the hereditary mutations of one of the three genes whose form AD that is called the familial form (FAD). For other patients with an early onset, it is still unclear what changes cause early symptoms. A child whose mother or father inherits a genetic mutation has 50/50 chance to inherit this mutation and get a disease. FAD is caused by one of the many mutations in chromosomes 21, 14 and 1 [20]. The pathological consequence of these mutations is the production of abnormal amyloid protein form where a 21 chromosome mutation causes changes in the amyloid precursor protein (APP) while mutations at the 14 and 1 chromosomes cause abnormal changes to presenilin 1 or 2 proteins [21]. Each of these mutations at the end of the pathological path leads to the formation of fibrillar amyloid forms and the formation of plaques, previously mentioned. Several world projects have begun to explore and follow genetic forms that have shown that brain changes are occurring almost 20 years earlier than the first outbreaks of memory function. This knowledge is used today in understanding and late forms of AD. Late AD forms occurring after 65 years prevail in almost 90% of cases. Since that causes of late forms are not always understood, it is considered that genetics, the environment, and the lifestyle in combination affect the onset of the disease. The solitary gene has not been discovered but genetic risk factors are described where one form of apolipoprotein E (APOE) gene on chromosome 19 increases the risk of amyloid formation and accumulation. Apolipoprotein E appears in several forms or alleles. APOE e2 is a rare form in the population and is considered to provide protection against AD. APOE e3 is the most common form in the population and plays a neutral role in AD. APOE

e4 increases the risk for AD and starts the disease earlier in time. A person with two alleles e4 has the highest risk of developing AD and the accumulation of amyloid changes in the brain more than carriers of APOEe2 or e3. It is important to note that the succession of APOE e4 alleles does not mean that a person will unavoidably develop AD because there are people carrier of APOE e4 who never develop the disease. The main neuropathological hallmarks of AD is the same in FAD and late onset AD but distribution and amount may differ [22].

General Principles of Alzheimer's Disease Diagnosis

The early and timely diagnose of AD and other dementias is a mandatory task for every practitioner starting from the primary care to the highest specialized care. The paradigmatic shift in understanding the pathophysiology of AD and increased knowledge of dementia disorders have already contributed to the earlier diagnosis and the earlier initiation of therapy that is crucial for the patient and his environment. Concerns for patients and family members for changes in cognition must be taken with the utmost seriousness and the etiologic factor must be able to be identified. The early behavioral and personality changes such as depression, neuroticism and anxiety have to be treated intensively because untreated lean towards to deteriorate cognitive functions. For such a comprehensive and systematic approach, national guidelines are important. Croatia still does not have such guidelines or national register that hampers the same diagnostic and patient treatment. Such register may act as a quality indicator of diagnostic procedures and treatment options and an important source of information for scientific and clinical studies.

Diagnostics of AD is based on the group of well determined and established steps enable the physician to give a valid diagnosis or differential diagnosis of the condition. Based on the amyloid cascade hypothesis the revolution in making of diagnose of AD is reached by using a wide palette of clinical biomarkers mainly biochemical and imaging. Development of inclusion clinical criteria in combination with biomarkers has increased the accuracy of the AD diagnose and shift diagnostic procedure "to the left" timely when a first subjective cognitive impairments could be noticed.

Recently the two clinical scientific groups around a) National Institute of Aging-Alzheimer's Association in USA and b) International Working Group (IWG) have suggested a set of new clinical criteria for AD that has been harmonized for wide use in the routine clinical praxis (23, 24, 25]. The clinical biomarkers are specifically focused on determination of neurodegeneration by analysis

of MRI/CT, PET-FDG or tau in CSF or present of specific amyloid pathology by PET-Amyloid ligands or changes of amyloid and phospho-tau in CSF [26].

Is it important to set up an accurate and timely diagnosis of AB? Some of the most important reasons are:

- To exclude or confirm other diseases that may give the symptoms of dementia, which changes the therapeutic approach.
- To inform patient and family members or caregivers about diagnosis, possibly hereditary traits, symptoms, duration, therapy, and prognosis. Ultimately it contributes to the patient's better understanding of the disease, risk factors, therapy and disease perspectives .
- To provide the most appropriate therapy not only to cognitive problems but also to others that occur during the development of the disease such as depression, hallucinations, illusion or psychomotor impairments.
- To understand the patient's functional autonomy and to help maximally to keep it as long as possible.
- To plan and provide assistance to the patient by the local community and its social welfare services and to communicate with all the stakeholders involved in the care of dementia pacific. Getting a diagnosis of dementia should help the patient gain access to day-to-day activities and various forms of practical help.

The process of dementia diagnosis and therefore AD should consist of two levels: basal and extended.

Basic procedure via primary care should include: anamnesis, hetero-anamnesis, somatic and neurological status, basic / baseline blood analysis, simple cognitive testing, functional capacity evaluation, and one of the imaging techniques (CT / MRI). A structured report must provide specific information about the beginning and the course of cognitive problems, especially memory impairments, spatial orientation, and speech problems. In the early stages of my illness, the patient gives satisfactory information about himself and subjective problems, but it is very important to get the information from the caregivers and bring them in the context of getting a complete picture of the development of the disease.

Furthermore, the importance of getting the diagnose of dementia should be specifically shared with nearest generations of the patient's family to be able to understand the risks and the character of cognitive problems in the first or second generation. The magnitude of data on cerebrovascular changes and head trauma and on the medications taken by the patient is of great value for comple-

tion of diagnosis and initialization of the therapy. It is important to emphasize the importance and the focus of the question as to the ability to drive and possess a weapon.

Somatic, detailed neurologic and psychiatric status and cognitive and functional assessment are mandatory parts of diagnostic procedure. The cognitive scales, the MMT or MOCA, RBANS tests, and the Clock Test are the minimum that primary care physician should obtain.

The extended or specialist diagnostic procedure consists of detailed neuropsychological testing, CT / MRI completing, alternative brain imaging with PET-FDG or PET Amyloid and taking the CSF where AD specific biomarkers are required; Tau proteins (total , and phospho) , beta amyloid (40, 42 and 42/40 ratio) and NFL (neurofillament) (26). In cognitive function testing using **neuropsychological batteries**, several cognitive domains are tested which change is typical for AD. Typical domains are: episodic memory, visuospatial function, executive function, attention, speech and psychomotor speed [27]. Furthermore, the assessment of the patient's function is examined on daily activity scales, from assessing personal hygiene to the estimation of so-called instrumental functionality: using mobile phones, computers, banking fees, economic issues) and autonomy in taking medications. Scales are ADL and IADL or FAST scales**. CT scan or MRI** is attempted to find anatomical changes in specific regions related to cognitive decline, hence the hippocampus, amygdala, insula, parietal cortex, transient, frontal cortex are regions of primary importance in the description of atrophic changes [28]. Correct description describes the specificity of the AD diagnosis where SPECT usage is declining in Western countries, although blood flow information may contribute to differential diagnosis. The **PET-FDG** camera showing the regional activity of synaptic contacts and brain metabolism by depicting the typical differences in uptake of glucose that may help in in differential diagnosis of AB towards the Frontal Dementia, Depression and the Lewy Body Dementia [29]. PET Amyloid is one of the most advanced method of visualization of neuropathological changes in amyloid accumulation and represents a major advance. The FDA was approved for the routine use the PET -Amyloid ligands by 2012 and EMA in 2013 for the routine use**. PET-Amyloid** has pushed PET-FDG and SPECT on side as one of the methods of additional diagnostic choices [30]. Confirmation of the presence of amyloid (plaques) in the brain indicates a process of irreversible neuropathological degeneration and provides clinician with the possibility to establish timely diagnosis and start standard therapy. Positive PET Amyloid is also one of the AD certification criteria and inclusion of the patient into clinical studies. **EEG** is a method that directly cap-

tures brain cell activity. It has high sensitivity but the specificity is not sufficient for the diagnosis of AD alone. The decrease of alpha rhythm activity and increase in slow activates is characteristic for AD. EEG in AD is pathological very early in disease development what is unlike in FTLD. It is important to exclude epileptic activity. In some neurodegeneration, EEG findings are characteristic like in prion diseases or LBD [31]. **Lumbar puncture and CSF** analyzing amyloid proteins (A42 and A40 and A42/A40 ratio), and tau (Total Tau and Phospho-Tau) and NFL is a very simple and acceptable method for determining the pathological balance of proteins involved in the neuropathological dementia process of AD and other dementias [32]. The lowered amyloid A42, and the increase in total Tau and phospho-Tau is a highly specific sign for AD. The problem around the LP is that every laboratory has to develop and monitor its standards, regardless of the existence of reference values. Variations in values within and between laboratories can be as high as 15%, and today the ratio of protein ratios Tau / A42 or A42 / A40 is more in use. LP is applicable in routine and even at general practitioner level (Sweden) and, in addition to the neuropathological changes of dementia-specific proteins, allows analysis of Blood-Brain Barriers Infectious and immune parameters. The release of **APOE genotypes** has no clinical relevance for AD prediction but may help to interpret the disease and even personalized symptomatic therapy [33].

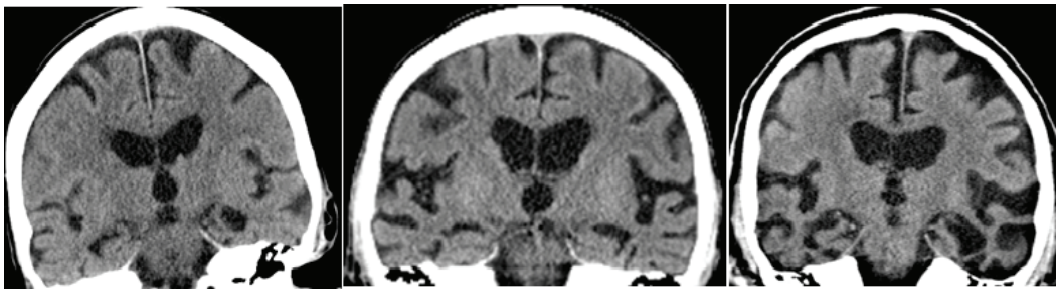
Clinical features of AD vs SNAP/PART

The group of the patients older than 65 but specifically over 80 years display normal cognition or mild cognitive impairment are amyloid-negative but neurodegeneration-positive by means of CSF and MRI biomarker and neuropsychological testing. Since that a clinical picture can mimic an early AD these patients can get a wrong diagnose of AD and get the wrong treatment if biomarker analysis is not performed. Thanks to the biomarker signature, a concept of suspected non-Alzheimer disease pathophysiology (SNAP) has been introduced. SNAP is present in ~23% of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals [34]. *APOE4* is underrepresented in individuals with SNAP compared with amyloid-positive individuals that further imply the lack of amyloid in these initial phases. Individuals with SNAP changes and still normal cognition or mild cognitive impairment have worse clinical and/or cognitive outcomes than individuals with normal levels of neurodegeneration and amyloid-β biomarkers. SNAP was first described in a study in which the National Institute on Aging–Alzheimer's Association (NIA–AA)

criteria of preclinical AD were examined. The most prominent difference was absent of amyloid pathology despite the similar neuropsychological profile [16].

The patterns of atrophy and hypometabolism in non-AD conditions often overlap spatially with the patterns seen in AD. This is the most obvious in the medial temporal lobe. Hippocampal atrophy is not the early feature only in AD but it can be seen in hippocampal sclerosis, TDP-43 pathology, anoxic–ischemic injury and Primary Age-Related Tauopathy (PART) such as argyrophilic grain disease, tangle only dementia [35]. Even hypometabolism is found in non-AD conditions similar as in AD with predominant temporo-parietal pattern of decreased glucose uptake, indicating that the AD-like hypometabolism in posterior association areas that is observed in PART can be explained by the fact that these areas are highly connected, both structurally and functionally, to the medial temporal lobe. This indicates that networks in these areas can be vulnerable to a variety of insults associated with AD, non-AD disorders and ageing. The same judgement applies to elevated total tau levels in CSF, which are seen in conditions other than AD, including ischemic cerebrovascular disease, traumatic brain injury, and Creutzfeldt–Jacob disease. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be easily identified pre-mortem at present despite that some specific clinical features during diagnostic procedure could be related to non-AD pathology. This specific concept is still under development, but several important steps are made in understanding the differential diagnostic picture of dementia of 80+ individuals suffering from PART. It I important that every practitioner is aware of this extremely common pathologic change (SNAP/PART etiology) since the final diagnose and therapy differ from AD or mixed AD/VaD. Cognitive impairment is often mild, and recent studies have identified a common biomarker profile consisting of specific temporal lobe atrophy and tauopathy without evidence of Aβ accumulation. MRI can reveal asymmetric involvement of the hippocampal atrophy characteristic for both AD and PART but unlike in typical Alzheimer's disease where atrophy of the hippocampus does not show an anterior and posterior gradient, atrophy in definite PART showed an anterior and left predominance. This observation is important for clinical use since there is evidence that the anterior and posterior hippocampus have different network connections with the posterior hippocampus involved with retrieval and encoding aspects of episodic memory. The lack of posterior hippocampal degeneration can be tested by diverse neuropsychological battery which may suggest different pathology, accordingly suggesting the clinical difference between AD and PART. Similarly, in semantic dementia involvement of anterior hippocampus is

the MRI hallmarks of this dementia which is characterized by relative sparing of episodic memory and hence it would not be surprising for PART to be associated with a semantic dementia like phenotype. While PART and SD may have some MRI similarities the entire clinical and neuropsychological phenotype, age of onset and additional anatomical changes clearly differ these two neurodegenerative entities (Figure 1.). Moreover, PART differs from AD, by low frequency of the APOE 4 allele. The frequency of the APOE4 allele in AD is 3–4 times higher than in definite PART. It is known that the APOE4, whose frequency decreases with age, has been linked to beta-amyloid hence PART has less or no amyloid pathology so typical for classical AD. Thus, PART has cognitive consequences that should be considered in the context of emerging therapies targeting tau in age-associated neurodegenerative diseases. In summary, PART is separate from AD and its distinction is enormously important for the clinical management of patients with cognitive impairment and for public health care planning [36].



A **B** **C**

Figure 1. CT coronary images at the level of the anterior hippocampus in patient with PART (A), late-onset Alzheimer's Disease (B) and Primary Progressive fluent Aphasia – Semantic Dementia (C).

Note predominant left > right anterior hippocampus atrophy in all three patients which should not be related to the Alzheimer Disease only. Patient A – Part is 85 y old, MMT 23/30, APOE 2/3 and normal CSF biomarkers, clinical predominant amnestic cognitive impairments and mild dementia. Patient B – late onset AD, APOE 4/3, CSF biomarkers for AD, MMT 20/30, clinical primary amnestic cognitive impairment and mild dementia, besides MTL atrophy mild/moderate cortical atrophy, Patient C – moderate advanced Semantic dementia in 75 y patient with characteristic severe atrophy of the left MTL and temporal pole that has spread towards opposite temporal lobe and left frontal cortex, normal CSF biomarkers, APOE 3/2, MMT 19/30, clinical progressive fluent aphasia as a

part of FTLD. Awareness of a pathognomonic atrophy of fusiform gyrus (white arrow) can indicate Semantic Dementia in the very early stage of this disease. Without use of biomarkers and careful image analysis patient A and C are commonly misdiagnosed as Alzheimer Disease that use to have vast consequences in post-diagnosed management of those phenotypes.

Therapy

One of the biggest clinical challenges of the end of the last century was to find a cure for AD and other dementias. The biggest progress as far as it was in the development of symptomatic medications for AD. These drugs could only slow down the development of the disease for up to a year or two but do not stop or cure. Even the modest effect of their effects could be measured by the quality of life of patients and for the social community signifying lower overall care costs. The last 15 years of development have led to progress in understanding pathophysiological processes in AD, understanding of risk factors and other causes of AD. Early Diagnosis AB with the previously mentioned CSF biomarkers and structurally functional brain imaging is an important prerequisite for developing more successful drugs. Early treatment AD can change the course of the disease and not only ease the symptoms, so today's efforts in the search for drugs are focused on stopping the primary pathological processes in the brain. After AB diagnosis, great efforts must be made to provide the patient and caregiver with a high quality of life, offer activities, offer full assistance from the practical changes in everyday living, the environment and social activation. This is only achieved if all the professional caregivers, relatives and patient "sit around the table" and make a care plan. Today, this is one of the most important mechanisms of non-pharmacological treatment of a dementia patient and lies in the responsibility of the health and social system of the state. In simple words, the patient must be able to "live his life" [37].

Symptomatic therapy

In the short history of symptomatic drugs for AD, the inhibitors of Acetylcholinesterase (AchEI) take the primary role. After discovering that the cholinergic system in the brain is one of the most affected and that it is engaged in memory and attention [38], the development of drugs has led to the first AChEI – Tacrine, which was withdrawn due to the serious side effects. After Tacrine three drugs, donepezil, rivastigmine and galantamine are still widely accepted symptomatic medications. Their application in Croatian healthcare has been de-

layed for 15 years. The main principle of these drugs is to prevent AChE from metabolizing the neurotransmitter substance Acetylcholine, which allows its long life and thus prolongs the effect of improving nerve cell communication. "Saving" acetylcholine makes possible to retain cognitive function over time. Many studies have confirmed the effect of this drug group especially in the first 3-6 months, while long-term therapy leads to stabilization of disease progression and slower deterioration. These effects can be monitored by changes in metabolism using PET- FDG camera or blood circulation using SPECT. These three drugs do not have the same mode of function. Donepezil reversibly inhibits only AChE having half-time degradation for 70 hours, galantamine reversibly inhibits AChE but also modifies nicotine receptors and has half-decay degradation for 7 hours while rivastigmine inhibits irreversibly both AChE and Butyryl ChE and half-time degradation is only 1.5 hours. Each physician who is prescribing these medicines should be familiar with guidelines on how to initiate treatment but also how to monitor the effect of treatment by observing the clinical picture, measuring cognitive testing, heteroanamnestic data, estimating the changes in quality of life (ADL) and in health economics indicators. A few years after the appearance of AChEI, AD medication was enriched with a medicine memantine whose function is to modify glutaminergic neurotransmission in the brain. Memantine is a partial NMDA receptor inhibitor and is licensed for medium to heavy and heavy AB forms in combination with AChEI. Most patients with AChEI after the addition of memantine experienced ADL enhancement as well as reduction of aggressiveness and illusion. The main principle of treatment AD is primary administration of AChEI and only secondary memantine [39]. The same therapeutic principle is applied even in LBD and PDD. For other non-AD neurodegenerative phenotypes including PART, there is now studies or guidelines how to use AChEI or memantine therapy. Based on anecdotal or empirical clinical experiences AChEI are not the first-choice drugs in these conditions.

Treatment of neuropsychiatric symptoms

Neuropsychiatric symptoms (NPS) in AD occur in 80% to 90% of patients and most AD patients will show one or more symptoms during the illness. Symptoms may range from mild (depression, anxiety, drowsiness, and apathy) to severe (agitation, aggression, aberrant vocalization, hallucinations, and disinhibition). These symptoms can be persistent or recurrent during the development of illness and are associated with increased patient and carers anxiety which leads to increase rates of institutionalization and increased mortality. It is therefore important that these symptoms should be treated with pharmacologi-

cal and nonpharmacological therapies based upon the principles of treatment for idiopathic psychiatric disorders. One of the most important general principles of neuropsychiatric symptoms therapy in older patients with AD is to initiate the treatment of a specific symptom with small doses of drugs and to slowly increase the dosage (start low, go slow but treat to target).

For timely and target-related NPS treatment, early recognition of so called Behavioral and Psychiatric symptoms in Dementia (BPSD) in mild cognitive impairment is crucial for the proper understanding of the causal-to-cognitive relationship between cognition and behavior. Understanding the behavior of the brain in a neurobiological sense through the understanding of neurochemistry of neural circuits and cognition enables the proper design, monitoring of therapy and its effect. Progress has been made in the definition of depression, apathy and psychosis in dementia, and has achieved a higher level of consensus in treatment. For example, depression in dementia differs in terms of phenomenology, course of disease, and pharmacological response compared to idiopathic depression. Definitions of agitation and aggression require further work in describing the phenomenon. Non-pharmacological treatments with AD include interventions such as cognitive stimulation, cognitive exercise, behavioral changes, physical exercise, music, and multi-sensory stimulation. Non-pharmacologic treatments and interventions should be targeted patients and care providers [40].

Disease Modifying Therapy

Substances in development (or any future drug) are directed to early treatment of disease in stages of clinical manifestations of mild cognitive impairments before dementia syndromes occur. The main strategy of these "drugs" is to stop the formation and amyloid accumulation in the brain or accelerate amyloid cleansing from the brain. From successful experiments on experimental animals in 1999, almost 20 years have passed to develop biological agents or antibodies to amyloid whose function is to prevent plaque formation but also to clean up existing ones in humans. Several world companies have been working on different types of anti-amyloid antibodies either as passive immunization or as vaccination. After several years in the finding the proper target-related antibodies and proper types of patients entering the study, we have recently got the results of anti-amyloid antibody which in the Phase 1 and 2 stage of development in human, showed an interesting effect of amyloid plaque cleaning from the brain and significant improvement of cognitive function [41]. Other substances directed to the inhibition of the amyloid production enzymes or the inhibition

of tau-aggregation are in developmental stages. Other approaches to treatment such as giving trophic factors, mitochondrial modification, and stimulation of nicotine receptors are still in the early stages of development and testing.

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UDK: 616.892.3
DOI: 10.21857/ygjwrcjzxy
Review article
Received: 1.12.2018.
Accepted: 28.3.2019.

FRONTO-TEMPORAL DEMENTIA: THE ROLE OF INFLAMMATION AND IMMUNITY

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Summary

Frontotemporal Dementia (FTD) is a neurodegenerative disorder which is characterized by behavioural abnormalities, language impairment, and deficits of executive functions. Behavioural variant FTD (bvFTD) and Primary Progressive Aphasias (PPAs) represent the most common phenotypes. The identification of mutations responsible for autosomal dominant inherited disorder, namely *Microtubule Associated Protein Tau (MAPT)*, *Granulin (GRN)* and *chromosome 9 open reading frame 72 (C9orf72)* mutations, contributed to elucidate the molecular pathways involved in brain depositions of either Tau or TAR DNA-binding protein 43 (TDP43) inclusions. In FTD cases associated with pathogenic *MAPT* mutations, Tau accumulation in neurons and glia has been explained in terms of abnormal phosphorylation of the protein, or an altered proportion in the ratio of the 4R and 3R Tau isoforms; conversely, *GRN* mutation haploinsufficiency and *C9orf72* ex- pansion lead to TDP43 aggregation, with a less clear mechanism. However, in the majority of sporadic FTD patients, the molecular pathways triggering Tau or TDP43 protein deposition are still to be uncovered. No risk factors other than genetic background have been recognised in FTD. An immuno-mediated inflammatory hypothesis to neurodegenerative processes has been claimed on the basis of epidemiological studies and genome-wide association analysis (GWAS). Moreover, for some cases of FTD language variants, an autoimmune condition has been suggested. In this review, a brief evaluation of literature data on immune homeostasis in FTD is presented, in order to provide potentially evidence-based approaches for a disease still orphan of any treatment.

Key words: Dementia, Fronto-Temporal Lobar Degeneration, Glutamate Receptors, autoimmunity

Introduction

Frontotemporal Dementia (FTD) is one of the most common neurodegenerative conditions after Alzheimer Disease (AD). Most FTD patients are affected by progressive behavioral abnormalities, language impairment, and deficits of executive functions [1, 2]. The two main pathological hallmarks in FTD are represented by brain depositions of either Tau or TAR DNA-binding protein 43 (TDP43) [3] selectively affecting the frontal and temporal regions. Pathogenic mutations in Microtubule Associated Protein Tau (MAPT), Granulin (GRN) and expansion on chromosome 9 open reading frame 72 (C9orf72) are the main causative genetic factors and the identification of these genes contributed to a major understanding of the disease. Nevertheless it is still unknown whether Tau and TDP43 deposits represent the initial mechanism or simply the result of other unknown environmental, genetic or inflammatory factors [4-9]. At present, though genetic background is still considered the major determinant of the disease [10, 11], evidences from different sources highlighted the role of inflammation in agreement with several discoveries in Autoimmune Encephalitis (AIE) which contributed to modify the paradigm of the Central Nervous System (CNS) as an immune privileged-site [12].

The contribution of GluR3 autoantibodies to FTD etiology

In FTD, different observations argued for an immune system involvement and significant prevalence of autoimmune disorders has been observed [13, 14, 15]. Genome-wide association analysis (GWAS) in FTD found a significant enrichment for elements of the immune system involved in antigen presentation, including the HLA-DR5 locus [16] and granulin has been associated with inflammatory and wound response [17]. Again, in TREM2 T66M knock-in mouse models there is a dysfunction in microglia and aberrant glucose metabolism in the frontal lobes [18]. Recently, our group reported anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies in a significant proportion of patients fulfilling clinical diagnostic criteria for FTD [19, 20, 21]. On the other hand, emerging evidence of frontotemporal areas involvement in autoimmune CNS disorders has been increasingly reported in the past years. More generally, antibody-associated neuronal autoimmune diseases has become a heterogeneous group of syndromes mainly divided into two groups: classic paraneoplastic syndromes (PNS), linked to the presence of a specific systemic cancer, and autoimmune encephalitis (AIE), with antibodies directed towards the extracellular domain of surfaced neuronal proteins, causing direct neuronal

injury [22, 23, 24]. In the absence of neoplasia, the etiopathogenic mechanism underlying autoimmune activity has been less understood. The first auto-antibody to be identified, against GluR3, was in Rasmussen's encephalitis, in 1950s [25, 26]. Moreover, in the autoimmunity CNS disorders spectrum, limbic encephalitis is a well-recognized condition, defined as a subacute onset of short term memory loss, behavioral changes and seizures, mainly involving the temporo-medial lobes and the amygdalae, with variable evidence of CSF inflammation [27]. Different types of neuronal antibodies have been recently identified and, specifically, antibodies directed against voltage-gated potassium channels (VGKC-Abs) are often associated with limbic encephalitis, presenting with seizures, amnesia and medial temporal lobe inflammation [28-29]. Predominantly in young women, another type of auto-antibody, directed against the N-methyl- D-aspartate subtype of ionotropic glutamate receptors (NMDAR) has been identified, which seems to be commonly associated with a prominent movement disorder [30-32]. Dysfunction of glutamatergic signaling can also result in limbic encephalitis when the immune system attacks the AMPA glutamate receptors, which mediate the majority of fast excitatory synaptic transmission in the CNS [33]. Patients affected are usually women older than 50 years old, who present with subacute memory loss, confusion, agitated behavior, and seizures. Remarkably, in the last decade new autoimmune synaptic antibodies have been discovered, namely anti-Leucine-rich glioma inactivated 1 (anti-LGI1), anti-contactin-associated protein-like 2 (anti-Caspr2), and anti- γ-aminobutyric acid class B (anti-GABAB) receptors [29] thus underlining the role of antibody-mediated attack to neuronal structures [33].

Toward an alternative GluR3 autoantibodies dependent etiologic mechanism for FTD

The etiopathogenic mechanisms underlying CNS autoimmunity are still unknown, although an infective trigger has been proposed. Notably, 20% of patients with Herpes simplex virus encephalitis have relapsing symptoms, especially in children, without viral reactivation or response to acyclovir but, in some cases, they show anti-NMDAR antibodies [34] supporting the view that the infectious prodrome, whenever it occurs, represents an inflammatory event associated with CSF lymphocytosis. In fact, it has been proposed that the inflammatory reaction might be responsible for a temporary and/or localized disruption of the BBB, allowing antibodies to gain entry into the CNS [35-35]. Still it is unclear what drives regional vulnerability, but it has been claimed that serum antibodies might find facilitated conditions to penetrate into the brain

of patients through the heavily vascularized nasal mucosa and the olfactory sensory axons, as well as via the trigeminal nerve into the brainstem [37] though there is evidence that the expression of neuronal antigens is region-specific [38]. More importantly, serum IgA/IgM anti-NMDAR occurs in a significant number of patients with undefined dementia, characterized by higher frequency of CSF abnormalities, sub-acute or fluctuating disease progression and immunotherapy response [39]. Besides those reversible syndromes, clearly linked to a monophasic inflammatory immune-mediated reaction, increasing data seem to emphasize the link between inflammation and neurodegenerative processes. In fact, a robust demonstration of an autoimmunity process linked to neuro-degeneration, has been provided by the identification of IgLON5-antibody in patients with sleep disorders, abnormal behavior, movements and brainstem symptoms with a chronic progressive disease course; Tau protein aggregation has been observed in the hypothalamus, thalamus and brainstem in brain autopsy [40-43]. Furthermore, an inflammatory contribution to neurodegenerative disorders pathogenesis has been hypothesized both in AD [12] both in the senile and presenile populations [44]. With regard to FTD, though a substantial genetic component has been reported in around 10-20% of genetic FTD cases [45-47], no substantial risk factors responsible for sporadic dementia have been identified yet. Notably, a genome-wide association study (GWAS) conducted on a large cohort of mainly clinically diagnosed FTD, has identified a significant association with the HLA locus, supporting the claim that neuro-degeneration might be triggered by the immune system [16]. Furthermore, Miller and colleagues have shown a higher prevalence of systemic autoimmune disease in semantic variant PPA (svPPA) patients [13] consistent with similar subsequent findings in FTD patients with C9orf72 expansion [48]. Another recent and substantial evidence of autoimmunity co-existence in neurodegenerative disorders has been proved by the detection of anti-AMPA GluA3 antibody in serum and cerebrospinal fluid (CSF) of a single FTD patient; the extension of the study to a large clinical series of FTD demonstrated a significant proportion positive for anti-GluA3 antibodies in serum as well as in cerebrospinal fluid [19-20]. As a matter of fact, the incubation of rat hippocampal neuronal primary cultures with CSF with anti-GluA3 antibodies led to a decrease of GluA3 subunit synaptic localization of the AMPA receptor (AMPAR) and loss of dendritic spines. The significant reduction of the GluA3 subunit seems to correlate with increased levels of neuronal tau protein [20]. Altogether these findings argue for a potential role exerted by the dysregulation of the immune homeostasis in FTD, even though it has to establish at what stage autoimmunity plays an active role in neurodegenerative process.

Several neuroimaging studies including different autoimmune disease have shed some lights on the multifaced impact of immunomediated neuroinflammation [49-54]. Despite normal findings in NMDAR encephalitis, longitudinal imaging studies showed that severe disease courses can result in hippocampal or mild global atrophy, with functional, volumetric and white matter changes in the hippocampus correlating with memory performance, disease severity and duration [48, 55]. Similarly, AMPAR and LGI1R encephalitis lead to hippocampal atrophy later in their course [56-58]. Among others, the perisylvian region and the insula are the predominant site for signal abnormality and atrophy [31, 59, 60], with evidence of asymmetrical insular and frontal atrophy correlating with epilepsy duration [61]. Similarly, FTD presents with a focal atrophic pattern affecting primarily the frontotemporo- insular structures [62, 63], even though different patterns may be identified, according to the presenting clinical syndrome [64-70]. Interestingly, in addition to white matter hyperintensities [71, 72], several studies have highlighted a common limbic involvement in FTD, even in the very early disease phases [73-76]. In the last years, microglial activation has become a novel target of PET tracers, such as radio-labeled PK11195, which binds to the translocator protein (TSPO). TSPO is localized on the mitochondrial membrane and it is only minimally expressed in the healthy brain, whereas overexpressed in neuroinflammatory disorders [77]. The application of TSPO imaging to neurodegenerative disorders has confirmed the concurrent presence of inflammation in many conditions, usually reflecting the regional distribution of the pathology [78]. With regard to FTLD, microglial activation has been demonstrated both in tauopathies [79, 80], and in TDP43 proteinopathies [81]. Interestingly, microglial activation has been described before the occurrence of overt anatomical changes in MAPT presymptomatic carriers [82] as well as in the less atrophic hemisphere of FTD patients [83]. These data in addition to open a new avenue have the potential of offering a therapeutic strategy for sporadic cases. Indeed, while patients with autoimmune encephalitis (i.e. anti-NMDA or anti-AMPA receptor encephalitis) are often seriously affected, these disorders have been shown to be responsive to immunomodulatory therapies [35, 84-87]. In the context of FTD, few case reports of antibody–associated encephalopathies (i.e. anti-VGKC, anti-NMDA and anti-AMPA-mGluR3) presenting as frontotemporal dementia–like syndromes have also shown initial beneficial responses after intravenous immunoglobulins, steroid infusions, or rituximab treatment [88-90]. Overall these findings contribute to expand the notion of possible therapeutic perspectives in the treatment of autoimmune related neurodegeneration, in which immunomodulating treatments could potentially reduce or revert the

intracellular accumulation of pathological protein aggregates. It has to acknowledge that the very few available data may anticipate a new pathogenesis and treatment in FTLD for selected cases in whom an early diagnosis "autoimmune FTD" and a prompt treatment could be critical to prevent irreversible neuronal damage and reduce possible neurological sequelae.

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UDK: 616.892.3
DOI: 10.21857/ydkx2crex9
Review article
Received: 17.12.2018.
Accepted: 28.3.2019.

DEMENTIA IN PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL SYNDROME

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Summary

In the article, clinical syndromes of Corticobasal degeneration (CBD) and Progressive supranuclear palsy (PSP) are outlined, both in the context of early single-entity perspective, but also later several-entities perspective. In particular, cognitive, mood and behavioral impairments are described. Although these largely overlap in the two conditions (particularly across the frontal lobe symptoms), there are also noticeable differences in the cognitive, behavioural and mood profile between the two syndromes – reflecting predominantly subcortical pathology of PSP and subcortico-cortical pathology of CBD. While PSP patients exhibit particularly apathy, the most distinctive cognitive and higher brain function impairment in CBD are apraxia, alien limb phenomena, and cortical sensory loss.

Key words: progressive supranuclear palsy, corticobasal degeneration, dementia, cognition, tauopathy

History

Both, Progressive supranuclear palsy (PSP) and Corticobasal degeneration (CBD) were described in the sixties of the last century; both were initially believed to be a specific, unitary entity and both subsequently were broken into several disease entities. PSP was first described as a distinct disorder in 1964 by Steele, Richardson and Olszewski [1] and it is still sometimes referred to as Steele-Richardson-Olszewski syndrome. "Corticodentatonigral degeneration with neuronal achromasia" was first described in 1967 in three patients of Irish decent with asymmetric, akinetic-rigid and cortical neurodegenerative

syndrome. [2] Later it was found that cerebellum is not affected and the entity was, particularly in European literature, renamed as corticobasal degeneration (CBD). [3]

Demographics

Progressive supranuclear palsy (PSP) is estimated to affect about six people in every 100,000 people worldwide and CBD five people per 100,000 in the general population. [4] Symptoms of PSP begin on average after age 60 and prevalence is higher in men than in women. Symptoms of CBD begin between the ages of 50-70 and prevalence is higher in women than in men.

Etiology & Pathophysiology & Pathology

The exact cause of both PSP and CBD is unknown. Both are tauopathies, along with Alzheimer's disease, Pick disease, Niemann-Pick disease type C and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).

Pathology of CBD and PSP largely overlap, with accumulation and spreading of abnormal deposits of the insoluble tau enriched in the four-repeat (4R tau) isoform through the nervous system, particularly in the white matter.

However, there are also distinguishing features between CBD and PSP:

- difference in the distribution of tau pathology - CBD has greater cortical tau pathology, and PSP has greater subcortical tau pathology [5];
- difference in astrocytic lesions - astrocytic plaques in CBD and tufted astrocytes in PSP.

In patients presenting as CBS the underlying tau pathology include CBD in 55%, PSP pathology in 20%, Pick's disease in 7%, and non tau pathology in the remaining. [6] Corticobasal degeneration (CBD) cases with tau pathology had differing densities of tau pathology in different neuroanatomical regions that correlated with the clinical presentation (e.g. greater tau burden in the primary motor and somatosensory cortices in CBD and greater tau burden in limbic and hindbrain structures in PSPS).

Many regard corticobasal degeneration and progressive supranuclear palsy as different loci on a disease spectrum. They are usually sporadic; in very few cases they results from mutations in the MAPT gene.

How tauopathies evolve remains unknown. They may be triggered by

- an unconventional infectious prion-like agent;
- by a random genetic mutations;

- by an unknown toxin in the food or environment;
- by a dysfunctional body's built-in mechanisms for clearing free radicals;
- by a combination of these mechanisms.

Signs and Symptoms

Both, Progressive supranuclear palsy (PSP) and Corticobasal degeneration (CBD were initially described as a well defined, unitary entities. However, later studies revealed that both disorders encompass several phenotypic variants.

The first definitive diagnostic clinical clues of PSP are impairment of balance, postural instability with unexplained falls and blurring of vision due to slowness of eye movements, inability to voluntarily shift gaze vertically (supranuclear gaze palsy) and levodopa unresponsive parkinsonism. In the course of the disease, other signs & symptoms occur: trouble controlling eyelids and difficulty in opening the eyes, dysphagia, dysarthria, mask-like facial expression, cognitive dysfunction, apathy and mood disorder.

Currently PSP is divided into several clinical phenotypes:

- classical variant (Richardson syndrome, PSP-RS);
- variant with progressive gait freezing (PSP-PGF);
- variant with predominant parkinsonism (PSP-P);
- variant with predominant frontal presentation (PSP-F).

To a certain degree, these clinical phenotypes differ also pathologically; PSP-P has less tau pathology than PSP-RS and the mean 4R tau/3R tau ratio was significantly higher in PSP-RS compared to PSP-P.

Similarly, CBD was initially described as a progressive markedly asymmetric movement disorder presenting with a combination of levodopa unresponsive focal rigidity and bradykinesia, dystonia, myoclonus, apraxia, higher cortical impairment, and alien-limb phenomena. However, later studies revealed several distinctive clinical presentations [7]:

- corticobasal syndrome (CBS): asymmetric rigidity and apraxia, cortical sensory deficits, dystonia and myoclonus;
- frontal behavioural-spatial (FBS),
- nonfluent/agrammatic variant of primary progressive aphasia (naPPA),
- progressive supranuclear palsy syndrome (PSPS, also called Richardson's syndrome): postural instability, early unexplained falls, vertical supranuclear gaze palsy, symmetric motor disability and dysphagia

Cognition

The first articles heralded an approach to CBD and PSP that focused on movement rather than cognition, although European researchers often categorized similar patients as 'Pick's disease type 2'.

Actually, in both, PSP and CBD, alterations of cognition, mood and behavior develop early and represent an important and constituent part of the diagnosis. In particular, both may show 'frontal' signs: changes in judgment, problem solving, 'emotional incontinence' and loss of insight, particularly a peculiar form of impaired anticipatory awareness. Abnormalities in antisaccades (difficulties looking in the direction opposite to the visual stimulus) reveal a dysfunction of the dorsolateral prefrontal cortex.

Although there is quite an overlap, noticeable differences in the cognitive, behavioural and mood profile between CBD and PSP have been also described.

In the original article, Steele et al. [1] reported that mild dementia was present already in early stages. While short-term memory is – similarly to Huntington's and Parkinson's disease - relatively preserved, cognitive slowing, frontal signs and signs of subcortical dementia are typically present in patients with PSP. PSP patients exhibit particularly apathy (91%), with or without depression, dysinhibition (36%), dysphoria (18%) and anxiety (18%), but rarely (<9%) irritability, abnormal motor behaviors, or agitation. [8] Apathy in PSP is significantly associated with executive dysfunction. Speech in PSP is more dysarthric, not aphasic as in CBD: characterized by spastic, hypernasal, flat, monotonous, low-pitched articulation. And later in the disease palilalia and stuttering or almost continuous involuntary vocalizations (groaning, grunting, moaning, humming) may occur.

Nowadays, many believe that dementia is the most common sign of CBD. [9,10] Interestingly, in a strive for high diagnostic specificity, the 2000 clinical criteria of CBD excluded "early dementia". [11] Semantic memory is usually well preserved. The most distinctive cognitive and higher brain function impairment in CBD are apraxia, alien limb phenomena, and cortical sensory loss. Behavioral and personal changes, aphasia, visual neglect and mood disorders (depression) also develop in the course of the disease.

Apraxia is most commonly ideo-motor by nature (not knowing "how to do" as opposed to "what to do") and localized in limbs and in oro-buccal area. Apraxia may be improved by using the tool or with tactile stimulation. So-called apraxia of eyelid opening is not a true apraxia, but a form of pretarsal dystonia. Alien limb phenomenon develops in about one third of the CBD cases and includes several semiologies, e.g. a complex unintentional limb movements inter-

fering with normal task, levitation, sensation that a limb is foreign or that it has a will of its own. It is typically an 'anterior' or 'motor' alien hand as opposed to the 'posterior' or 'sensory' alien hand syndrome due to the lesion of the thalamus, splenium of the corpus callosum or occipito-temporal lobe. Language and speech disturbances most commonly present as primary progressive aphasia (PPA), progressive aphasia, progressive nonfluent aphasia, apraxia of speech and may progress to mutism.

Frontal lobe syndrome and behavioral variant frontotemporal dementia (FTD) are also common in CBD, presenting as a spectrum from executive dysfunction, apathy, to severe behavioural and personality changes, such as bizarre or antisocial behavior, irritability, disinhibition, hypersexuality.

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UDK: 616.892.3
DOI: 10.21857/m8vqrtzwv9
Review article
Received: 29.1.2019.
Accepted: 10.5.2019.

DEMENTIA WITH LEWY BODIES AND PARKINSON'S DISEASE DEMENTIA

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Summary

Dementia is a frequent but often unrecognized problem in advanced stages of Parkinson's disease (PD). The point prevalence of dementia in PD patients is around 30% and around 10% of a PD population will develop dementia per year. Risk factors and different biomarkers have been studied trying to predict pre-dementia stages of cognitive impairment in PD and finding neuroprotective treatments. Dementia with Lewy bodies (DLB) is also an often-unrecognized neurodegenerative disease. It is the second most common neurodegenerative dementia after Alzheimer's disease. Incidence of Lewy body dementias is 5.9 cases per 100,000 person-years. It shares some clinical, genetic, neurochemical, morphological and pathological features with Parkinson's disease (PD), Parkinson's disease dementia (PDD) and has unknown etiology. Nevertheless, they differ in timing of cognitive, behavioral and motor symptoms, medications response, and neuropathological contributions. Despite new diagnostic criteria, both dementias are often misdiagnosed and untreated. In this article, we review the current knowledge regarding cognitive impairment and understanding of dementia and overlapping symptoms in PDD and DLB

Key words: Dementia with Lewy bodies, Parkinson's disease dementia, overlapping and controversies

Parkinson's disease dementia (PDD)

Dementia is a frequent but often unrecognized problem in advanced stages of Parkinson's disease (PD). Usually, PD is considered as mostly a motor disease with known cardinal symptoms (*tremor*, *bradykinesia/akinesia*, and *rigidity*), but non-motor symptoms are influencing the quality of life and earlier institutionalization of PD patients [1]. The point prevalence of dementia in PD patients is around 30% and around 10% of a PD population will develop dementia per year what is four to six times greater than in subjects without PD [2]. In a general dementia population, 3 to 4% of cases are due to Parkinson's disease dementia **(**PDD) [3]. It is known that the longitudinal development of dementia is: progressive rates of 26% at 3 years, 28% at 5 years, and 48% at 15 years [4] and an 8-year cumulative prevalence of PDD in elderly PD patients is of 78% [5]. Although cognitive impairment can exist at time of diagnosis, the mean duration of PD before dementia develops is approximately 10 years [5,6].

Risk factors for PDD studied so far are: higher age, more severe parkinsonism, in particular rigidity, postural instability and gait disturbance, and mild cognitive impairment at baseline; and also, male gender, education, depression, visual hallucinations can influence on that [7]. Cognitive impairment in PD can vary from subjective cognitive decline, mild cognitive impairment to PDD and includes attentional, executive, visuospatial, and memory dysfunctions. Cognitive problems and dementia are more common in PD patients with akinetic/rigidity type [5]. A task force of the Movement Disorder Society developed diagnostic criteria for PD dementia that includes demonstrable slow progressive impairment in more than one above-mentioned cognitive domain and with at least one behavioral symptom (apathy, depression/anxious mood, hallucinations, delusions or excessive daytime sleepiness) [8].

Most neuropathological studies indicate that the presence of cortical and limbic Lewy bodies and Alzheimer's disease (AD) pathology (neurofibrillary and amyloid-β plaque) correlates with the severity of cognitive impairment [9,10]. The Braak hypothesis of a caudal to rostral progression of the disease, including the involvement of the cortex is well-known [11]. Several neurotransmitters including dopamine, acetylcholine, noradrenaline, and serotonin may contribute to PD cognitive impairment in accordance to marked loss of limbic and cortically projecting dopamine, noradrenaline, acetylcholine and serotonin neurons. [10].

There are many different biomarker studies and efforts (from laboratory to novel structural and functional imaging techniques) trying to find biomarkers of pre-dementia stages of cognitive impairment in PD, when we can try with re-

searching of some neuroprotective treatments. However, no biomarker has yet been validated. Nevertheless, low levels of epidermal and insulin-like growth factors or uric acid in plasma/serum and of Aß in CSF, reduction of cerebral cholinergic innervation and glucose metabolism measured by FDG- PET mainly in posterior areas, and hippocampal atrophy in MRI might be indicative for risk of dementia in PD patients [12].

There are known role of the APOE*ε4 allele, Glucocerebrosidase (GBA) mutations and mutation in gene encoding for α-syn (SCNA) and triplications in cognitive decline in PD, whereas the findings are mixed for Microtubule-associated protein tau (MAPT) polymorphisms [13]. Dementia can be seen in familial forms of PD in the Parkin gene mutations, PARK1 and PARK8 and is rare in PARK2, PARK6, and PARK7 [14]. In every-day practice, we are using published criteria and tests to identify cognitive deficits in PD [15]. An increase in low frequency (delta and theta) EEG spectral power distinguishes PDD from PD and AD [16].

There is still a lack of effective treatment of PDD. Only rivastigmine has got the approvement of Food and Drug Administration. Other cognitive enhancing medications have some mild effect in PD dementia. A cognitive training, physical excersize and neurostimulation have some promising results [17-20].

Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease and the most common neurocognitive disorder with Lewy bodies, but often passed unrecognized. Nevertheless, DLB is often missed and misdiagnosed with AD and PDD so appropriate treatment is late and distressing side effects, due to inappropriate drug prescription, can be caused.

It accounts for 25% of all dementias [21]. Incidence of Lewy body dementias is 5.9 cases per 100,000 person-years and prevalence very from 3 to 26.3% over the age of 65 years. In addition, in a population-based study, 7. 6% of dementia cases were diagnosed as dementia with Lewy bodies. Life expectancy after disease onset is 5-7 years [21]. Risk factors of (DLB) include advanced age, hypertension, hyperlipidemia, and carriers of one or more APOE ε4 alleles. However, presence of APOE ε4 may be an important predictor of more rapid decline [22]. Neuropathological characteristics are deposition of α-synuclein in Lewy bodies, Lewy neurites and Lewy dots, loss of tegmental dopamine neurons and basal forebrain cholinergic neurons but also in 25-50% of cases full blown Alzheimer pathology (β-amyloid deposits and tau neurofibrillary tangles) is present. There

are also deficits of GABA and serotonin neurotransmission [22]. The new consensus of DLB diagnosis points clinical signs and symptoms as core or supportive and biomarkers as indicative or supportive [23].

Progressive cognitive problems in DLB have features of cortical and subcortical dementia that interferes with normal social or occupational functions, or with usual daily activities. Mostly the initial clinical features of DLB include confusion, memory disorders, and impaired judgment. Patients with DLB have more prominent impairment of attention, executive functioning, visuospatial problems, more difficulties in clock drawing or figure copying as compared to patients with Alzheimer's disease who have more prominent memory changes on Mini Mental State Examination [24]. **The essential feature** for diagnose of DLB is dementia. **Other core** characteristics are early hallucinations (mostly visual and well formed), fluctuating attention and alertness (delirium-like), extrapyramidal signs (Parkinsonism- one or more cardinal features like bradykinesia, rigidity or resting tremor) and Rapid Eye Movement (REM) sleep behavior disorder (RBD) which usually precede cognitive problems and is present in 76% DLB patients [23]. Sometimes, parkinsonism is an initial symptom and then the 1-year rule is very important to distinct DLB from PDD. However, parkinsonism is very common core symptom in over 85% DLB patients [23]. Documentation of only one of the cardinal features, bradykinesia, resting tremor, or rigidity, is required for DLB, while at least two are required to diagnose PD.

Supportive clinical features in the new criteria are: severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression. In new criteria, a severe antipsychotic sensitivity is named as supportive, because reduced prescribing of D2 receptor blocking antipsychotics in DLB limits its diagnostic usefulness [25].

The indicative biomarkers are: a) visualization of reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging using a ligand that binds to presynaptic dopamine transporters N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) DAT-Scan. b) abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy and c) polysomnographic confirmation of REM sleep without atonia.

The supportive biomarkers in new criteria are: a) relative preservation of medial temporal lobe structures on CT/MRI scan, b) generalized low uptake on SPECT or FDG-PET perfusion and metabolism scan, respectively, with reduced occipital activity called the cingulate island sign on FDG-PET imaging

and c) prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range are named as supportive biomarkers [26].

In addition, importance of EEG specific abnormalities in posterior derivations is pointed in new criteria due to a predictive value of 90% for the diagnosis of DLB compared with AD and correlate positively with the severity of clinically observed cognitive fluctuations [27].

Amyloid PET imaging shows increased amyloid β brain deposition in 50% of patients with DLB, but presence of tau and medial temporal lobe atrophy are key indicators of coexisting AD pathology in DLB, known predictor of clinical phenotype and progression [28,29]. Two assessment toolkits are built to improve the diagnosis of DLB [30]. In management of LBD patients, knowing disease's specificities and multidisciplinary approach are very important. Due to frequent sensitivity to some medications, it is recommended to start cautiously at low dose tracking the most troublesome problems. There are no medications approved especially for DLB and no disease-modifying agents. A treatment is still symptomatic and include pharmacological and nonpharmacological treatment mostly for cognitive, neuropsychiatric, motor and sleep disturbances. Rivastigmin more than donepezil is preferred for cognition, quetiapine, risperidon and clozapine for visual hallucinations. For depression mirtazapine is more preferred than selective serotonin or serotonin-norepinephrine reuptake inhibitors, due to the side effects of later ones. For parkinsonism, levodopa in lower doses is better than dopamine agonists, and clozapine and melatonin for RBD. Memantine is suggested to be add on dopamine medication. Orthostatic hypotension can be treated with non-pharmacological approach: hydration, salt tablets, compression stockings, avoidance of exacerbating medications, and in hard cases pharmacologicaly with fludrocortisone and midodrine. It is very important that dosing and medication selection are individualized considering degree of functional impact of symptoms being targeted and side effect thresholds. Occupational therapy, physical therapy, speech therapy such as Lee Silverman Voice Therapy, cognitive training, exercise, active social life and other lifestyle changes are very important in all neurodegenerative diseases [31].

DLB/PD/PDD: CURRENT CONCEPTS OF OVERLAPPING AND CONTROVERSIES

Parkinson's disease (PD), Parkinson's disease dementia (PDD), Dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and peripheral autonomic failure (PAF) share pathological markers of abnormal α-synuclein aggregation and that group of diseases is called synucleinopathies.

However, DLB and PDD are considered as major neurocognitive disorders with Lewy body pathology, although there are some scientists discussing that they are the same disease [32] the clinical picture differe these two clinical entities. So far, we know that both entities share clinical, genetic, neurochemical, morphological and pathological features, but a comprehensive distinction between them is still missing.

We only have an arbitrary distinction considering the time of onset of motor and cognitive symptoms: dementia often preceding parkinsonism in DLB and onset of cognitive impairment after onset of motor symptoms in PDD (1-year rule) [33]. Dementia occurring in a patient with a pre-existing clinical diagnosis of PD should be referred to as PDD. A cognitive impairment is an early sign in DLB while extrapyramidal motor features are often mild or absent, at least until the late stages. An early and prominent extrapyramidal motor features required for PD diagnosis is a typical characteristic of PDD, with neuropsychiatric and cognitive symptoms occurring later. It is widely accepted that the difference between these two distinct clinical syndromes of DLB and PD/PDD shareing underlying pathomechanisms, could be a different propagation patterns of α-syn pathology across different neuronal pathways. A concomitant AD pathology is more common in DLB as compared to PD/PDD.

It is suggested that they are subtypes of an α-synuclein-associated disease spectrum (Lewy body diseases), which include incidental Lewy body disease, non-demented Parkinson's disease, PDD, DLB, and DLB with Alzheimer's disease [34]. Previous studies have shown more pronounced cortical atrophy, elevated cortical and limbic Lewy pathologies (with APOE ε4), apart from higher prevalence of Alzheimer pathology in DLB than PDD [33]. It can be the cause of an earlier onset, greater severity of cognitive defects, more often attentional fluctuations in DLB. The main clinical overlaps are: rigidity, akinesia, cognitive impairments, frontal executive dysfunction, visual-constructive impairment, mild language impairment, hallucinations (visual), delusions (less frequent), mood disturbances (depression, anxiety), RBD and neuroleptic sensitivity. Known dissimilarities in clinical pictures are: some cognitive dysfunctions: deficiencies of attention greater, episodic verbal memory tasks lower in DLB, tremor significantly less frequent in DLB, motor performance: slower walk and poorer balance in DLB, hallucinations more frequent in DLB, relative timing of dementia and parkinsonism (1 year rule), onset of dementia later in PDD, orthostatic hypotension more frequent in DLB, frontal/temporal-associated cognitive subsets more severe in DLB, cognitive decline is faster in DLB/DLB + AD than in PDD, delusions, attentional fluctuation and visual hallucinations more frequent in DLB,

visual hallucinations: spontaneous in DLB; after L-dopa therapy in PDD, but also in drug-naive patient. Known laboratory overlaps are: decreased DAT-Scan binding in putamen, reduced cardiac MIBG binding, medial temporal lobe relatively preserved (CT, MRI), occipital hypoperfusion in FDG-PET, similar EEG abnormalities, similar metabolic decrease in cerebral cortex, larger width of 3rd ventricle and frontal horns and GBA mutations. Known laboratory dissimilarities discussed lately are: Grey matter cortical atrophy more frequent and more severe in DLB, White matter hypointensities in temporal lobe more severe and more frequent in DLB, Different functional connectivity corticostriatal disruption: PDD: frontal cortical disruption; DLB: parietal and occipital disruption, More severe Aβ brain deposition (PiB uptake) in DLB, Tau-PET imaging more severe in DLB, Several genetic differences (APOE ε4, mitochondrial transcription factor A (TFAM)), Low DAT uptake in caudate related to functional impairment in DLB, not in PDD, SN sonography (size, asymmetry), CSF AD profile more common in DLB and CSF αSyn oligomers increased in PDD. Morphological overlaps are: mixture of cortical and subcortical LB/αSyn and AD-related pathologies, similar Braak LB stages (4–6) and Braak neuritic stages (5 or 6), relation between pαSyn and tau aggregation to Aβ deposition in cortex, initial αSyn aggregation in pre-synapses inducing neurodegeneration via interference with axonal transport, postsynaptic protein downregulation. Known morphological dissimilarities are: higher Aβ load in cortex and striatum in DLB, Aβ phases and neuritic plaque scores higher in DLB, higher cortical LB load in temporal & parietal cortex in DLB, increased tau loads in cortex and striatum in DLB, more frequent and severe αSyn load in hippocampal subareas CA2 in DLB, minor deviations in severity and lesion pattern in SNc, pedunculopontine cholinergic cell loss in hallucinating PDD, but not in DLB, higher 5-HT1A receptor binding in cerebral cortex in DLB [33].

Conclusion

In conclusion, although these disorders overlap in many aspects of their presentations and pathophysiology they differ in other elements such as timing of cognitive behavioral and motor symptoms, medications response, and neuropathological contributions. It is very important to recognize DLB early and to provide the best possible treatment and adequate information to patients and their relatives. In this article, we review the status of knowledge regarding cognitive impairment and current understanding of dementia and overlapping symptoms in PDD and DLB. This should help clinicians to diagnose DLB and PDD at an earlier stage and provide better patient care. Further studies in synu-

cleinopathies are needed for elucidation which patients and when will develop cognitive problems or extrapyramidal symptoms and what are the biological factors that could determine that. That is a prerqusite, towards the sussesful development and implementation of personalized medicine and disease-modifying therapy.

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UDK: 616.8-003.8
DOI: 10.21857/90836cwj3y
Review article
Received: 29.12.2018.
Accepted: 28.3.2019.

MULTIPLE SCLEROSIS AND COGNITIVE IMPAIRMENT: WHERE DO WE STAND?

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Summary

Multiple sclerosis is a progressive and chronic disorder of the central nervous system that is characterized by widespread plaques and inflammatory damage in the brain and spinal cord. Pathophysiology in MS encompasses both grey and white matter of the brain through inflammation mediated neuronal, synaptic and axonal damage. The symptomatology of MS encompasses motor, cognitive and neuropsychiatric problems, with great differences in scope from patient to patient. It is now widely accepted that cognitive impairment is present in the majority of patients with MS, with a prevalence of 45 to 65%. Routine examinations of patients with MS are not sufficiently sensitive to detect cognitive impairment, which can cause neurologists to neglect this part of the disease, even though it affects patient quality of life significantly. There is a general variability in the cognitive domains that are affected by MS, however the most common are memory, information processing speed, attention, and verbal fluency. Assessing cognitive deficits is a challenge, however there are a few well validated neuropsychological series of tests available that can be incorporated in routine examinations. Treating cognitive impairment in MS patient can have three main strategies: using disease modifying therapies, symptomatic therapy and cognitive rehabilitation. Unfortunately, there is limited evidence that current strategies are effective in tackling the problem. High-quality studies with adequate methodologies are needed for establishing unified guidelines for treatment. Even though current therapeutic measures are limited, there is hope that advances in pharmacotherapy and neuroimaging will bring about the necessary guidelines to improve the quality of life of these patients.

Key words: multiple sclerosis, cognitive impairment, neuropsychological assessment, neuroimaging

Introduction

Multiple sclerosis (MS) is a progressive and chronic disorder of the central nervous system (CNS) that is characterized by widespread plaques in the brain and spinal cord. These plaques, or lesions, refer to an area of damage to the myelin sheath of neurons in the CNS [1]. A direct cause for the disease has not been discovered yet, however it is thought to be a combination of environmental, genetic, immunological and viral factors [2]. There is broad range of symptoms present in MS, due to the various locations where lesions occur. The symptomatology of MS encompasses motor, cognitive and neuropsychiatric problems, with great differences in scope from patient to patient [3]. The most common symptoms in the start of the disease include blurred vision, numbness, tingling and discoordination. The progressive nature of the disease causes a steady loss of function, severe fatigue, motor difficulties and varying cognitive dysfunction [4].

It is now widely accepted that cognitive impairment is present in the majority of patients with MS, with a prevalence of 45 to 65% [5]. It can affect the patients from the beginning to the later stages in the disease [6], and even occur regardless of the physical symptoms [4]. Routine examinations of patients with MS are not sufficiently sensitive to detect cognitive impairment, which can cause neurologists to neglect this part of the disease, even though it affects the patients quality of life significantly [7]. The same can be said of research in this part of the field, as MS research has exponentially increased in the last few decades, while cognition-related MS research is lagging behind [8]. We will first review the current knowledge about pathophysiology behind the cognitive impairments in MS, followed by the hallmarks of cognitive dysfunction in MS. Finally, we will provide information on how to diagnose the cognitive deficits, along with known treatment options to manage them.

Pathophysiology of cognitive impairment in MS

For many years, MS was wrongly thought to be a disease that affected only the white matter, while cognition used to be attributed solely to the cortex and grey matter [9]. This disconnect led to a lack of studies focused on cognitive impairments in MS. However, advancements in the fields of neuroscience and neuroimaging have changed the way we perceive physiology and pathophysiology of the brain. Modern neuroimaging has revealed the complexity of cortical and subcortical networks, which pave the way for understanding the diverse MS symptomatology. In essence, MS is an inflammatory disease with white and grey matter lesions in the CNS that result in demyelination, axonal damage and

neurological dysfunction [10]. The course of the disease in most patients is relapse-remitting MS (RRMS), characterized by periods of symptom exacerbation and periods of full recovery. The progressive nature of the disease leads to a state where most patients gradually become worse with minor remissions, which is called secondary-progressive MS (SPMS). The most severe clinical course of MS is primary-progressive (PPMS), which has a continuous and gradual worsening of symptoms [11].

Each relapse of the disease causes a progressive loss of axons and myelin, which impairs conduction of signals between different parts of the brain. The explanation to how this damage happens is becoming increasingly complex. Although the trigger is still not known, the pathogenetic cascade of MS comprises immune cell infiltration to the CNS, thought to be a consequence of immunological interactions between an underlying degenerative disorder and an aberrant immune response [12]. The damage lymphocytes cause activates the microglia cells, which can contribute to the neurodegeneration through myeloperoxidase release and subsequent mitochondrial dysfunction [13]. Furthermore, the constant activated state of microglia and oligodendrocytes causes an increase in glutamate production, which is known to be excitotoxic and cause neuronal and axonal damage [14]. This occurs in both the white and grey matter of the brain, and it is becoming increasingly clear that white matter lesion assessment is insufficient to evaluate the occurrence of cognitive impairment in MS [15]. It is important to note that demyelination and axonal damage is not the only damage that is present in MS. Recent studies of brain autopsies have shown that neuronal spine loss is present in numerous normal-appearing grey matter without demyelination, which indicates a synaptic pathology present throughout the brain grey matter. [16]

Grey matter or cortical lesions appear from the beginning of MS and even evolve faster than white matter lesions [17]. The inflammation and demyelination in these lesions differ in several aspects to those found in the white matter, with the critical role in these lesions being played by microglia, and not infiltrating lymphocytes [18]. More importantly, recent MRI studies have shown that grey matter volume loss correlate better with cognitive impairment in MS than the white matter volume loss [19]. Unfortunately, it seems that the grey matter volume loss increases exponentially with the disease stage, from 3.4-fold normal in early relapse-remitting MS to 14-fold normal in secondary-progressive MS, indicating a severe increase in both motor and cognitive symptoms. [20]

Another pathophysiological aspect that could contribute to cognitive impairment in MS is the progressive volume loss and atrophy of the corpus callosum.

In a longitudinal study done by Granberg et al, progressive corpus callosum atrophy was present in all patients at different time points. Importantly, the progression of the atrophy correlated with the cognitive impairment, indicating an increasing difficulty in performing connectivity-demanding cognitive tasks in patients as the disease progressed [21]. These findings taken together support a neurodegenerative disease process, which encompasses the whole brain tissue through inflammation mediated neuronal, synaptic and axonal damage.

Hallmarks of cognitive impairment in MS

Cognitive deficits are prevalent in 45-65% of MS patients [5], however severe dementia is relatively uncommon and can occur in 20-30% of patients in the final stages of the disease [22]. The cognitive symptomatology can appear in the earliest stages of the disease, even as first symptoms of MS. [23] There are relatively few long-term longitudinal follow-up studies studying the evolution of cognitive impairment in MS. Current research indicates that the cognitive decline develops in a linear fashion on a group level, with the proportion of MS patients without cognitive impairment declining as the duration since diagnosis increases [21, 24, 25].

There is a general variability in the cognitive domains that are affected by MS, however the most common are memory, information processing speed, attention, and verbal fluency [26]. Impaired memory is considered to be the most common impaired cognitive function in MS [27], however the nature of the impairments is under some debate. It has been thought that long-term and working memories are most commonly affected [22], while more recent studies indicate that MS patients have difficulties with encoding and information storing and not the retrieval of long-term memory [11]. Memory impairment appears to be unrelated to physical disability, disease duration or depression, and starts with information retrieval in verbal episodic memory and progresses to encoding difficulties in time [28]

One of the common complaints patients with MS have is that they feel everything takes a longer time to do. Reduced information processing speed is connected to impairments in working memory and executive functions, and often appears in the same timeframe as other cognitive deficits [29]. A recent study by Van Schependom et al. indicated that reduced information processing speed is often the first cognitive deficit in MS [30]. It is thought that this manifests due to decreased neuronal conduction speed as a consequence of demyelination, which impacts the patients ability to complete even basic tasks, let alone demanding work [31]. Furthermore, reduced information processing

speed appears to be related to the grey matter damage in the posterior lobules of the cerebellum [32]

Another important cognitive domain commonly affected in MS is attention, a complex cognitive function that encompasses processes such as alertness, vigilance, concentration and multi-tasking [27]. Up to 25% of MS patients have impaired attention, with mostly complex functions such as selective and divided attention affected, especially in patients with reduced cortical activity in prefrontal and parietal areas [33]. However, recently the thalamus has also been designated as a key grey matter structure for attention performance [34]

Interestingly, cognitive impairments can also be found in clinically isolated syndrome (CIS), which is the first clinical onset of potential MS [36]. The prevalence of cognitive impairment in CIS is from 50-60% with deficits similar to confirmed MS, mostly in memory, information processing, executive functions and verbal fluency [36,37] These studies signify the importance of cognitive deficits in MS, as well as their presence from the very beginning of the disease.

How to diagnose and assess cognitive impairment in MS?

It has been mentioned before that neurologists often neglect cognitive impairment in MS, while it is known that routine examinations are not sufficient to detect the nuances of cognitive deficits [7]. Therefore, it is clear that timely diagnosis and assessment of cognitive impairment is essential in MS patients. The first step is to have a suspicion of cognitive decline, which can manifest in various ways due to the diverse symptomatology in MS. Some of the "red flags" for clinicians include difficulties in providing coherent history and following instructions during examination, unexplained difficulties at work, missed visits and a depression that does not respond to antidepressants [26]. The patient's family can be of great help in diagnosing cognitive problems as they have the best knowledge of a patient's general cognitive capacity [26]. Neuroimaging can also be a great asset, as a significant cortical atrophy on an MRI scan is indicative of structural damage, which predisposes individuals to cognitive impairment [38]. It is outside of the scope of this paper to review the extensive advances in the field of MS neuroimaging, however it is important to point out that also thalamic, hippocampal and cerebellar atrophy and decreased connectivity can be present and have strong effects on cognition in MS [39]

There are several cognitive batteries available in assessing cognitive impairment in MS patients. The Brief International Cognitive Assessment for MS (BICAMS) is a simple tool that is easy to administer in routine clinical examinations. It consists of the Symbol Digit Modality Test (SDMT), the California Verbal

Learning Test-II (CVLT-II) and the Brief Visuospatial Memory Test-Revised (BVMTR). In total the time to complete the test is approximately 15 minutes per patient [40]. Its simplicity and short time for completion makes it ideal for small centers without dedicated neuropsychologists and can be incorporated into routine examinations. It was also found to be a useful screening tool in predicting actual functioning everyday performance in patients with MS [41], as well as a valuable tool in evaluating the effect of disease-modifying therapies (DMTs) on cognitive performance [42]. Another benefit of BICAMS is easy facilitation for international use, with many translations and validations performed already [43]. Unfortunately, this hasn't been completed in Croatia as of writing this review and should be a goal for future studies.

There are two more cognitive batteries relevant and validated in MS, and are widely used in clinical practice and research: the Brief Repeatable Battery of Neuropsychological tests (BRBN) [43] and the Minimal Assessment of Cognitive Function in MS (MACFIMS) [44]. In general, both tests contain more cognitive domains than the BICAMS, and can be used to assess cognitive impairment more thoroughly. BRBN contains the Selective reminding test (SRT; auditory and episodic verbal memory), the 10/36 spatial recall test (10/36; visual and spatial episodic memory), the Word list generation task (COWAT; verbal fluency and executive functioning), the Paced auditory serial addition task (PASAT; auditory processing speed and working memory) and the Symbol digit modalities test (SDMT; visual processing speed) [45]. The BRBN usually takes 20-45 minutes to complete and has excellent specificity (94%) and good sensitivity (71%) for detecting cognitive impairment in MS.

MACFIMS is an even more thorough neuropsychological battery, containing a multitude of tests that cover most cognitive domains. The test includes SDMT, PASAT and COWAT like the BRBN, but includes CVLT-II and BVMTR that are also present in BICAMS. It also includes the Delis-Kaplan Executive Function System (D-KEFS; executive functioning) and Judgement of line orientation test (JLO; spatial processing) [45]. The MACFIMS in an undoubtedly well-designed neuropsychological battery that gives the most accurate assessment cognitive problems in MS patients, however it is also the lengthiest series of tests (90 minutes) and requires a large amount of experience and expertise to interpret the results. [46]

Further important factors when assessing patients are the concomitant states that are often present in MS patients, namely depression and fatigue, as both can significantly affect the assessment results. Several studies have shown that there is an increased lifetime prevalence of depression in MS patients compared to

the general population [47]. Moreover, a recent study by Nunnari et al. revealed that the presence of depression in MS patients has a significant impact on cognitive impairment when compared to non-depressed MS patients [48]. Fatigue, on the other hand, affects up to 90% of patients [49]. However, recent studies have shown that it is important to distinguish motor and cognitive fatigue. It has been found that cognitive fatigue is not independently related to objective cognitive impairment, whereas depression may influence cognitive function in impaired patients when it is severe. [50]

How to treat cognitive impairment in MS?

Treating cognitive impairment in MS patient can have three main strategies: using DMTs, symptomatic therapy and cognitive rehabilitation. DMTs are drugs that alter the disease course of MS. Unfortunately, most largest clinical trials of DMTs did not include cognitive parameters in primary outcomes or had varied assessments that prevents their comparability [51]. In recent times, the number of studies covering DMT effectiveness in treating cognitive impairment has increased. Currently, the greatest benefit of DMTs on cognitive impairment was found in treatment with IFN β-1a and IFN β-1b. It has been found that IFN β-1a can stabilize or delay cognitive deficits in most patients with mild RRMS during a 5-year period [52]. IFN β-1b was also found to be beneficial in stabilizing cognitive deficits long-term over a 16-year period [53], as well when given early in patients with CIS in the BENEFIT (Betaseron/Betaferon in Newly Emerging MS For Initial Treatment) study [54, 55]. A recent study by Mokhber et al. demonstrated that IFN β-1a has better outcomes with treating cognitive impairment than IFN β-1b [56]. Studies with glatiramer acetate have shown that patients have stable cognitive performance, however it is not certain if that is a direct consequence of treatment and further studies are needed [57, 58]. The same can be said of fingolimod, which was found to be an effective treatment for MS, but no concrete conclusions have yet been made regarding its effect on cognitive impairment [59]

The effect of natalizumab, a potent drug in MS treatment, has also been studies in relation to cognitive functioning in MS patients. A large, randomized controlled study AFFIRM (Natalizumab Safety and Efficacy in Relapse-Remitting Multiple Sclerosis) has shown a positive effect on cognition in MS patients. The same was not observed in the SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) [60]. It cannot be clearly said if natalizumab has a beneficial effect on cognitive performance as even the smaller studies have different conclusions,

while it appears that the effectiveness depends on the individual and perhaps the localization and extent of the disease [61, 62]. Discontinuing natalizumab treatment should be done with care, as a worsening of cognitive function is possible, which goes in parallel with the reactivation of disease noted in clinical examinations and neuroimaging [63]

In general, using symptomatic treatment for cognitive impairment in MS patients has not been proven effective in controlled studies, though the overall quality of studies has been low so far. [64] Most of the studies so far have methodological limitations and therefore limit the possible conclusions. Treating brain activation and memory issues in cognitively impaired patients with symptomatic treatment was not effective with rivastigmine [65], donepezil [66] and memantine [67]. On the other hand, neurostimulants have uncertain results. Problems with study design persist in this group of drugs as well, and there are significant differences in-between studies. There appears to be some limited advantages in using neurostimulants (e.g. modafinil) to improve both physical and cognitive performance, however higher quality of studies are needed to make any firm conclusions [45, 68]

Cognitive rehabilitation can be useful in restoring select domains in cognitive functioning to improve the quality of life. A Cochrane study performed in 2015 concludes that there is some low-level evidence to support the effectiveness of cognitive rehabilitation, mostly in memory function and quality of life [69]. Unfortunately, that is based on limited evidence, as the available studies are lacking in methodological quality. Interestingly, a recent neuroimaging study evaluated the effects of cognitive rehabilitation on neuroplasticity in the brain and found promising results [70]. Additional research in this field could provide a way to validate the most effective rehabilitation interventions in these patients.

To summarize, there is a lack of treatment options of cognitive impairment in MS. Performing studies with better methodologies is needed for establishing unified guidelines for treatment. Even though current therapeutic measures are limited, there is hope that advances pharmacotherapy and neuroimaging will bring about the necessary guidelines to improve the quality of life of these patients. Novel technologies could help broaden therapeutic possibilites, such as repetitive transcranial magnetic stimulation (rTMS), whose effectiveness in treating cognitive impairment in MS is being researched with some promising early results [71]

Conclusion

Cognitive impairment in MS affects up to two thirds of patients and is a great burden on the quality of life, even from the very beginning of the disease onset. It is an important topic of debate among many different medical disciplines and after years of neglect, has seen a steady increase in number of research projects and studies. High-quality studies concerning both pharmacological and cognitive rehabilitation are sorely needed, as it is necessary to form unified guidelines for treatment. Unfortunately, current therapeutic options are limited, but there is hope that increased awareness of the issue will bring about novel therapeutic measures to improve the quality of life in these patients.

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UDK: 616.892.3
DOI: 10.21857/9e31lhne3m
Review article
Received: 14.1.2019.
Accepted: 10.5.2019.

PRION ASSOCIATED DEMENTIA

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Summary

Prions are small protein aggregates exhibiting a self-replicating feature and have been recognized as the causative factor in several neurological diseases. Human prion diseases are characterized by progressive neurodegeneration coupled with spongiform change of the neuropil and deposition of disease-associated proteins. Although much attention has been given to the transmissible form of the disease, majority of the cases are sporadic in nature, with a proportion of cases exhibiting a clear genetic background. Prion diseases are a known cause of dementia, especially in younger patients, marked by a swift cognitive and somatic decline, usually leading to a lethal outcome in a short period of time after initial diagnosis is established. Current body of knowledge shows that, although studies in humans and animal models show cell–to-cell transmission of disease-associated proteins in several neurodegenerative disorders leading to dissemination of pathological protein aggregates, prions remain the only proven proteinaceous agents to directly cause neurodegenerative pathological changes

Key words: prion diseases, Creutzfeldt–Jakob disease, rapidly progessive dementia, prion protein gene

Prion diseases

Prion diseases belong to a group of rare neurodegenerative disorders, which show a range of clinical and epidemiological features. The pathophysiological background of the diseases is based on the spreading of specific protein pathologies associated with the so-called " proteinaceous infectious particles" or

prions - protein structures without nucleic acids. The prion protein consists of approximately 250 amino acids encoded by the gene located on the short arm of the chromosome 20 and is normally present in the cell in its cellular conformation (PrPC), while the disease is present in the post-translationally modified form (PrPSc) which is protease resistant and responsible for protein buildup and progression of specific pathology. [1] The common neuropathological features of prion diseases are spongiform changes in the gray matter, neuronal loss, reactive gliosis and accumulation of an abnormal form of prion protein in the brain. Prion diseases demonstrate a variety of epidemiological features and can occur in a sporadic, acquired or genetic form. It is actually the acquired form that can be transmitted in a iatrogenic fashion, as a result of surgical procedures, or cannibalistic ingestion of CNS tissue of diseased individuals, which has caused considerable interest due to its putative public health implications. The fact that exposure of individuals who later develop prion disease to the tissues of animals infected with the bovine spongiform encephalopathy has garnered much public health and regulatory activities. The incidence and mortality of prion diseases is approximately 1-1.5 million per year [2], but increased interest and improvement in diagnostic options have led to an increased number of diagnosed patients. There is significant variability in reported incidence among individual countries, which may be due to different levels of available medical services.

Epidemiologically, prion diseases can be divided into sporadic, genetic and acquired forms. The sporadic form is characterized by the absence of a clear infective cause or heredity, with rapidly progressive dementia, myoclonus and ataxia. It is most commonly caused by sporadic Creutzfeldt-Jakob's disease, but rarer causes include sporadic fatal insomnia or variably protease-sensitive prionopathy. Genetic forms include familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome, and Fatal familial insomnia. The acquired forms of prion diseases include variant CJD which is spread through the consumption of infected bovine tissue, iatrogenic CJD, and Kuru disease resulting from cannibalistic consumption of infected human tissue.

Human prion diseases

Sporadic (idiopathic) prion disease:

Sporadic Creutzfeldt-Jakob disease (sCJD)
Sporadic fatal insomnia (sFI)
Variably protease-sensitive prionopathy (VPSPr)

Acquired (infected) prion disease

Human origin
- Iatrogenic CJD (due to medical procedures)
- Kuru

Bovine origin
- Variant CJD (vCJD)

Familial (inherited or genetic) prion disease

Genetic CJD
Gerstmann-Sträussler-Scheinker syndrome (GSS)
Fatal familial insomnia (FFI)

The typical human prion disease is sporadic Creutzfeldt–Jakob disease (sCJD), first identified in 1920 [3, 4] initially thought of as a rare, atypical form of dementia until it was shown that it can be transmitted to primates by intracerebral inoculation [5]. CJD is a rapidly progressive dementia associated with cerebellar ataxia, diffuse myoclonus, and various other neurological disorders. More than 90% of patients with prion disease suffer from CJD. According to the cause, the disease can occur in four forms: sporadic, familial, iatrogenic and variant.

The disease occurs worldwide, without specific seasonal prevalence, with an annual incidence of 1-1.5 per million. The incidence is higher in Israelis and Libyans, North-African immigrants to France, as well as Afro-Americans in the United States. Disease affects equally men and women, and the incidence is increased in the middle-aged individuals.

The hereditary forms comprise 10 to 15% of cases, and are most often caused by mutations in the PrP gene [1].

Pathogenesis of the disease

Prion protein is normally found in the cell and is most abundant in nerve cells where it is believed to be involved in cellular communication and signal transduction. The increased expression of proteins in nerve cells clarifies the perceived preference for the transmission of diseases primarily through the nerve tissue, namely, brain and dural tissue, but also corneas. The appearance of familial forms suggests genetic susceptibility to the illness, although the possibility of a common exposure to the infectious agent cannot be ruled out.

The only clearly demonstrated method of disease spreading is iatrogenic and has been proved in several cases after corneal and dural transplantation

harvested from infected individuals or after implantation of infected electrodes, as well as from the administration of growth hormone and gonadotropin derived from cadaveric tissues [6].

Prion proteins are extremely resistant to the effects of nucleases, proteases, ultraviolet and X radiation. Also, according to their sequence, they are evolutionarily conserved, which is why it is believed that transmission of infected animal tissue, such as sheep or cow, is possible, which results in the variant form of the disease.

A great deal of attention was dedicated to the epidemic of prion disease in cows (mad cow disease) that began in 1985. The patients were younger (average 27 years) than those with typical CJD (65 years). The first symptoms of illness manifested themself with unusual psychological and sensory symptoms. The EEG's findings did not show any typical changes for advanced stages of the disease. It is assumed that the mode of transmission of the disease was the ingestion of infected cow's flesh and tissues.

Pathology of the disease

Creutzfeldt–Jakob disease (CJD) mainly affects the cerebral and cerebellar cortex. However, in some cases almost exclusively occiptoparietal regions can be affected, while in others cerebellum is primarily affected. The degeneration and disappearance of neurons is associated with marked astrophilic proliferation; ultrastructural studies show microscopic vacuoles that give the tissue a typical spongy appearance and are located within cytoplasmic extensions of glial cells and neuronal dendrites. Neuropathologic findings of CJD are characterized by spongiform changes in gray matter, gliosis—particularly in hypertrophic astrocytosis—neuropil rarefaction, neuron loss and PrP deposition. [7]. In general, the cerebral neocortex is the most severely affected region in sCJD pathology, and the severity of damage is associated with total disease duration. [8, 9]. The pathological findings can be staged based on the spongiform changes and strocytosis, with VI stages describing the progression of the diseases: Stage I, spongiform change; Stage II, hypertrophic astrocytosis; Stage III, neuropil rarefaction; Stage IV, neuron loss; Stage V, status spongiosus; and Stage VI, large cavity formation (Table 1) [10].

Table 1. Pathological characteristic and staging of sporadic Creutzfeldt-Jakob disease (adapted from Iwasaki, 2017.)

Cortical pathologic staging	Characteristic pathology	Simple staging classification	Pathological findings
Stage 0	No abnormality	None	no pathologic abnormality by HE staining
Stage 0.5	PrP deposition		only PrP deposition is observed by immunostaining
Stage I	Spongiform change	Mild	mild spongiform changes in the neuropil
Stage II	Hypertrophic astrocytosis		gliosis with hypertrophic astrocytosis apparent in the neuropil
Stage III	Neuropil rarefaction	Moderate	neurons mildly decreased in number, hypertrophic astrocytosis
Stage IV	Neuron loss		neurons moderately decreased in number, severe hypertrophic astrocytosis
Stage V	Status spongiosus	Severe	neuropil shows severe rarefaction and severe neuron loss with fibrous gliosis
Stage VI	Large cavity formation		large-sized cystic cavitations observed with macrophages in the cavities

Genetics of Creutzfeldt–Jakob disease (CJD)

The prion protein gene (PRNP) is located on chromosome 20p13 and is composed of two exons. The primary protein sequence of the PrP consists of 253 amino acids before posttranslational modification. The normal, cellular form of PrP is often referred to as PrPC, in which "C" stands for cellular. The misfolded, disease-causing, form of the PrP, called the prion, is commonly referred to as PrPSc, in which "Sc" stands for scrapie. In 1989, mutations in PRNP were first shown to cause the genetic form of the disease [11, 12, 13]. Although most PRNP mutations causing the genetic form are missense, several insertions, a few nonsense and at least one deletion mutation have also been identified [14, 15].

The heterogeneity of clinical presentation is linked to variations in the PRNP genotype at codon 129 of the and the type of prion protein deposited in the brain. The division of sCJD into six subtypes based on these variables (codon 129 genotypes [MM, MV, and VV] and prion protein types 1 and 2) largely correlates with variations in phenotype, including age at onset of symptoms (Table 2) [16]. The MM1 form presents with the classical phenotype and a median age at onset of 66 years, whereas the other forms have atypical clinical features and an earlier age at onset, notably the VV1 subtype.

Table 2. Diagnostic procedures in CJD (adapted from Annus et al 2016)

	Type	Sensitivity	Specificity
Clinical symptoms			
EEG	sCJD	64%	91%
MRI	sCJD	96%	93%
CSF 14-3-3 protein measurement	probable sCJD gCJD	43–100%	47–97%
PRNP analysis	gCJD		
CSF PrPsc detection by RT-QuIC	sCJD	96%	100%
Nasal brushing—PrPsc detection in the olfactory epithelium by RT-QuIC	sCJD gCJD	97%	100%
Urinary PrPsc detection by PMCA and Western blotting	vCJD	93%	*100%*

Clinical Symptoms of Creutzfeldt–Jakob disease (CJD)

The most important clinical manifestation of the disease is progressively rapid cognitive and motor decay during several weeks or months. In a third of the patients, prodromal symptoms are nonspecific and include fatigue, sleep disorder, loss of body weight, depression, anxiety and personality changes. In the earlier stages of the disease, there is a characteristic heterogeneity of the symptoms, but the most common are changes in behavior and emotional response, intellectual functions, coupled with ataxia and visual disturbances, as described by distortion of shape or "leveling of the object", but there is sometimes a real impairment of visual abilities. Early stages of illness are often dominated by the symptoms of confusion, with hallucinations, delusions and agitation. In some patients there is cerebellar ataxia (Brownel-Oppenheimer's variant) or visual disorders (Heidenhain's variant) that are preceded by mental changes which may be dominant over several months. Sometimes headaches, vertigo and sensory symptoms appear, but these symptoms are quickly replaced by dementia and mutism [17].

As a rule, the disease progresses rapidly in the way that clear deterioration can be seen from week to week, even day to day. Sooner or later, in almost all cases, myoclonic contractions of different muscle groups appear, sometimes unilateral, which soon become generalized. Myoclonisms are associated with a pronounced "startle" response, especially upon loud noise. They can usually

be triggered by any kind of sensory stimulation. Dizziness and ataxia are also pronounced during the first few weeks of the disease. These changes gradually give way to mutism, stupor, and coma. Signs of degeneration of the pyramidal tract, convergence or upward gaze paresis and extrapyramidal signs appear in a small number of patients, most often as the disease progresses. The disease ends lethally, usually within less than a year of symptom onset. In about 10% of patients, the disease progresses extremely fast, within a few weeks or months. In only small proportion of cases the disease may last up to 2 to 10 years. Such long-term illnesses are seen usually in the iatrogenic form of the disease.

Typical clinical course of Creutzfeldt–Jakob disease (CJD)

First stage: nonspecific symptoms such as fatigue, unsteadiness, dizziness, decrease in activity, anxiety, depression, visual disorder and memory disturbance; DWI MRI (DWI) shows hyperintensity in the cerebral cortex and striatum

Second stage: cognitive dysfunction worsens rapidly, myoclonus appears, gait disturbance progresses, patient becomes bedridden, motor paralysis, aphasia, apraxia, sensory disturbance, brisk deep tendon reflex, appearance of pathological reflex, cerebellar ataxia, muscle rigidity, dystonia, startle reaction; PSWCs are observed

Third stage: disease progresses to the akinetic mutism state, patient subsequently presents with decorticate rigidity or tetraplegia in flexion with contracture; myoclonus, PSWCs on EEG, and hyperintensity regions on DWI gradually diminish

Clinical subtypes of Creutzfeldt–Jakob disease (CJD)

Classic type / myoclonic type: acute progressive cognitive dysfunction, akinetic mutism state within several months after onset, PSWCs on EEG in the early disease stages

Heidenhain variant: visual symptoms (visus defigurata, defective color vision, cortical blindness), subsequently acute cognitive dysfunction with myoclonus, PSWCs at the occipital lobe.

Brownwell-Oppenheimer variant / ataxic variant: onset of cerebellar symptoms, dementia progresses subsequently, frequently no PSWCs

Thalamic degeneration / sporadic fatal insomnia: characterized by psychiatric symptoms, autonomic dysfunction and sleep disorders, slowing of basic rhythm, PSWCs are not present

Amyotrophic form: extremely rare, characterized by remarkable muscle atrophy

Diagnostic procedures

Clinical diagnosis is based on the recognition of the typical symptoms, especially the unique presentation of the dementia syndrome with marked progression, not rivaled by any usual neurodegenerative diseases, and is associated with stimulus-sensitive myoclonus and the characteristic EEG changes that occur in most patients.

Brain MRI with T2-weighted, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences often reveals abnormalities in the cortical gray matter (cortical ribboning) (Figure 1) and deep nuclei (Figure 2) in CJD [17, 18]. High signal intensities in the caudate nucleus and putamen or in at least two cortical regions (temporal-parietal-occipital) in the FLAIR or DWI sequences are included in the the MRI diagnostic criteria for sCJD [19, 20]. When MRI includes sequences assessing for reduced diffusion such DWI (with or without ADC), it has sensitivity and specificity for sCJD of 91–96% and 92–94%, respectively [21].

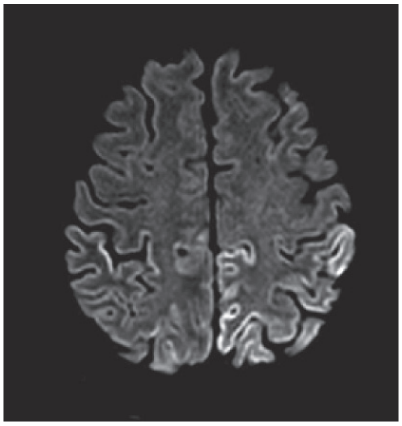

Figure 1. Magnetic resonance imaging of the brain-FLAIR showing cortical ribboning

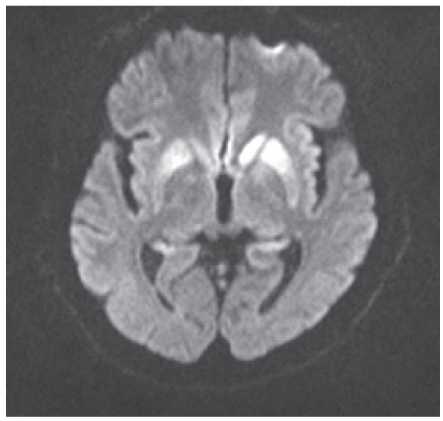

Figure 2. Magnetic resonance imaging of the brain FLAIR. Hyperintense signal changes in the basal ganglia.

The electroencephalogram (EEG) may support the diagnosis, but the EEG findings alone are not specific for CJD. Frontal intermittentnon-peaked rhythmical delta activity is generally seen in the early phase of sCJD [22]. Periodic synchronous bi- or triphasic sharp-wave complexes are found in the terminal stage of sCJD, with asensitivity of 64% and a specificity of 91% [23].

Elevated levels of the 14-3-3 protein in the cerebrospinal fluid (CSF) have been utilized as a biomarker for CJD, but they are generally indicator of neuronal damage Increased levels of total Tau protein with normal phosphorylated Tau levels can also be found in CJD patients, but findings are not specific to prion disease. In general, standard CSF protein biomarkers, including 14-3-3 protein, total tau (t-tau), and neuron-specific enolase (NSE) have been used as biomarkers for CJD diagnosis, although their clinical utility is quite controversial [24]. CSF 14-3-3 generally has been reported to have approximate sensitivity of 92% and specificity of 80% [25], whereas CSF t-tau typically has reported sensitivity and specificity higher than 90%, for sCJD [26]. These three proteins likely are markers for rapid neuronal injury, however, and thus not specific for CJD [27]. (Table 2)

An ideal biomarker in hPrD would involve detection of prions. Techniques such as protein misfolding cyclic amplification (PMCA) and real-time quaking-induced conversion (RT-QuIC) have been used to detect PrPSc forms in a patient's sample due to their ability to convert PrPC into aggregated protein isoforms that are resistant to protease activity [28]). A few studies have demonstrated modest sensitivity (>80%) but high specificity (98%) of CSF RT-QuIC for sCJD [29, 30] Therefore, RT-QuIC with CSF is more specific than 14-3-3 and probably NSE and t-tau. The latest Centers for Disease Control and Prevention (CDC) criteria for diagnosis of CJD list RT-QuIC in CSF and other fluids as the main biomarker for probable CJD (https://www.cdc.gov/prions/cjd/diagnostic-criteria.html).

Pathohistological methods such as the analysis of brain tissue of patients with variant CJD utilizing antibodies against the abnormal prion protein are also in use, but this technique is not suitable for early diagnosis of the sporadic form of disease. Genetic testing can only be used if there is a suspicion of familial CJD. Testing is performed from peripheral blood cells and the assay covers polymorphisms and mutations in the PRPN gene.

Therapy

There is no specific treatment of subacute CJD and antiviral drugs have been proven ineffective. With regard to the transmission of disease in iatrogenic patients, it is important to undertake precautions in medical procedures and handling of materials from patients with CJD. Special isolation rooms are not necessary and the family of patients and staff can be relieved by the fact that normal contact does not carry the risk of transmission. Prions are resistant to boiling, processing with formalin and alcohol and ultraviolet radiation, but can be inactivated by autoclaving at 132 ° C for at least an hour or by immersion in

5% Na-hypochlorite for one hour. Needles and electrodes require cautious disposal through incineration, or can be autoclaved or immersed in disinfectant. Performing brain biopsies or autopsy also requires special procedures. Needless to say, CJD patients as well as other dementia patients cannot be organ donors.

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UDK: 616.892.3
DOI: 10.21857/mzvkptz479
Review article
Received: 10.8.2018.
Accepted: 10.5.2019.

VASCULAR DEMENTIA

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Summary

Vascular dementia is one of the most common causes of dementia after Alzheimer's disease, causing around 15% of cases. Vascular dementia is the most severe form of vascular cognitive impairment that by definition compromise alterations in cognition, ranging from subtle deficits to full-blown dementia, attributable to cerebrovascular causes. Advanced age is a powerful risk factor for vascular cognitive impairment, and the prevalence and incidence of cognitive impairment increases exponentially after age 65. After advanced age recurrent stroke is second the strongest predictors of dementia onset. Vascular cognitive impairment stem from a wide variety of cardiovascular and cerebrovascular pathologies and it is generally thought that cognitive impairment results from the brain dysfunction caused by cumulative tissue damage. Despite the fact that vascular dementia is often encountered there is still a lot of uncertainties over disease classification and diagnostic criteria, controversy over the exact nature of the relation between cerebrovascular pathology and cognitive impairment, and the paucity of identifiable tractable treatment targets although recent work has led to a substantially improved understanding on how vascular brain injury affects cognition. Preventing vascular injury remains a promising approach to reduce the global burden of dementia, but additional efforts are needed to define the optimal strategy for prevention and develop efficient symptomatic treatments.

Key words: vascular dementia, vascular cognitive impairment, therapy, prevention

Introduction

Dementia have been recognized by the World Health Organization as the major threat to the modern society. The World Health Organization estimates that 35.6 million people live with dementia, a number that is anticipated to triple by 2050. Every year 7.7 million new cases of dementia are diagnosed, imposing an enormous burden on caregivers, and financial cost to society. Although recent data suggest a decline in prevalence, dementia still remains a devastating and costly disease. The realization of its paramount public health impact has led nations to develop national plans to cope with dementia and attempt to reduce its devastating effects. [1] Vascular dementia (VaD) is one of the most common causes of dementia after Alzheimer's disease (AD), causing around 15% of cases. It compromise a heterogeneous group of brain disorders in which cognitive impairment is attributable to cerebrovascular pathologies.

The prevalence of vascular cognitive impairment (VCI), which includes milder forms of cognitive impairment, is strongly age related. In subjects aged 65 to 84 years, the prevalence of mild forms of VCI not qualifying for dementia is higher than that of VaD. Rates of conversion to dementia, institutionalization, and mortality are significantly increased in these patients, identifying patients with VCI as an important target population for prevention [2].

Risk factors for vascular cognitive impairment and vascular dementia

Prevalence and incidence of cognitive impairment increases exponentially after age 65 stressing advanced age as powerful risk factor for VCI and VaD. Vascular risk factors, including hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and hyperhomocystinemia are also implicated as risks factors for dementia independently of the associated increase in stroke risk. After advanced age recurrent stroke is one of the strongest predictors of dementia onset. Furthermore, the metabolic syndrome, including insulin resistance, hypertension and dyslipidemia, has been associated with lower cognitive performance [3].

Several genetic mutations are associated with VCI. The most common of these is the CADASIL syndrome caused by a frame shift mutation of *Notch-3* that either creates or eliminates a cysteine residue [4].

Mechanisms of cognitive impairment

Cognitive dysfunction is most often associated with more subtle vascular alterations targeting predominantly the deep hemispheric white matter but se-

vere ischemia resulting from arterial occlusion can lead to brain damage and VCI, e.g., multi-infarct dementia. Despite the diversity of the underlying brain pathology, the vascular alterations have a similar pathogenic bases, resulting from hypoperfusion, oxidative stress and inflammation, which in turn lead to endothelial damage, brain blood barrier breakdown, activation of innate immunity and disruption of trophic coupling between vascular and brain cells. The hemispheric white matter, which is particularly susceptible to the deleterious effects of vascular risk factors, is a major target of vascular pathology. The resulting demyelination and axonal loss plays a role in the broad functional brain changes underlying cognitive impairment and in the associated cerebral atrophy. Brain atrophy is among the strongest predictors of cognitive impairment in patients with pure vascular disease, and a growing body of evidence suggests that the effects of subcortical ischemic lesions on cognitive functioning are mediated by the ensuing loss of cortical gray matter. There are several mechanism that can cause cognitive deficit n VCI and VaD such as silent brain infarcts, cerebral microinfarcts and microbleeds.

Silent brain infarcts refers to infarcts without attributable acute neurological symptoms They are common in elderly people with prevalence that increases from 10% to 40% in subjects aged 65 and 90 years, respectively, and the prevalence is even higher in patients with vascular risk factors. Most silent brain infarcts are lacunes. In the Framingham Offspring study, the presence of silent brain infarcts at baseline doubled the risk of dementia, showing association between the presence of silent brain infarcts and performance on cognitive testing as well as a steeper decline in cognitive function [5]. Cerebral microinfarcts are small ischemic lesions not visible to the naked eye (typically <1 mm) but detected microscopically during pathological examination. These lesions represent the most widespread form of brain infarction and may be located in cortical or subcortical regions and are particularly common in patients with VCI. However, they are also frequent in AD patients and in unselected elderly people. Quantifying cerebral microinfarcts in vivo remains a challenge: they are best detected on ultrahigh-field MRI at 7 T, but may occasionally be seen on conventional 3T scans [6]. Microbleeds are small, round, well-defined foci of MRI signal void appearing black on gradient echo T2*-weighted scans. Microbleeds are detected in 10% to 15% of elderly subjects and in ≤80% of patients with VaD disrupting structural connectivity and, hence, network function [7].

Therapy of vascular dementia

There are no licensed treatments for VCI and VaD. General management principles for VCI include the treatment of comorbidities, including psychological and behavioral symptoms, providing information and support to the patient and caregivers and maximizing independence. The pathological evidence for a cholinergic deficit in VCI has prompted randomized controlled trials with acetylcholine inhibitors (AcHI) choline esterase inhibitors and memantine in patients with VaD. Recent systematic review and meta-analysis of the effectiveness of AcHI inhibitors and memantine has showed a modest effect versus control on MMSE scores for patients with VaD (0.91 MMSE points at 6 months) [8]. In clinical practice AcHI and memantine are widely used for patients with VaD although these drugs are only licensed for use in AD or PDD.

Prevention

Increasing evidence indicates that the risk of VCI and VaD can be reduced by preventive measures. Interventions include lifestyle modifications, the control of vascular risk factors, treatment of concomitant vascular disease, and established strategies for stroke prevention.

Lifestyle Factors

The most convincing evidence for an influence of diet on VCI and VaD risk comes from studies on vitamin E, acting as an antioxidant, fish, n-3 fatty acids, polyunsaturated fats, B12 vitamin, and folates, that is, components found in Mediterranean diet. Several prospective observational studies have shown that adherence to such a diet is associated with a lower risk of AD and cognitive decline. However, there are few specific data for VCI [9]. Physical activity has beneficial effects on synaptogenesis, neurogenesis, and vascular health and might, therefore, reduce the risk of cognitive impairment. Indeed, observational studies suggest a beneficial influence on risk of cognitive decline, VaD, AD, and dementia in general [10].

Vascular Risk Factors and Concomitant Vascular Disease

A study in the UK population suggests that the prevalence of dementia may be decreasing by controlling blood pressure and other risk factors. Rigorous blood pressure control reduces white matter damage and staves off cognitive decline. Countless studies show that use of antihypertensive medications can

reduce the risk of VaD. In addition, the patient's coronary artery disease, atrial fibrillation, and ischemic heart disease have to be appropriately managed [11].

Conclusions

VCI and VaD are major contributors to age-relate dementing illnesses and comprise a heterogeneous group of cognitive disorders attributable to vascular causes. Despite the fact that VCI and VaD is often encountered there is still a lot of uncertainties over disease classification and diagnostic criteria, controversy over the exact nature of the relation between cerebrovascular pathology and cognitive impairment, and the paucity of identifiable tractable treatment targets.

Multiple vascular disorders occur in the aging human brain, which may induce various types of cerebral tissue lesions like hemorrhage, infarction, hippocampal sclerosis, and white matter lesions. Any of these changes can result in cognitive decline and dementia. In addition vascular cells play critical role in the maintenance of the health of neurons, glia and myelin and vascular pathology is also an integral part of AD, and play a defining role in the expression of the cognitive dysfunction. Therefor vascular contributions to cognitive impairment are receiving heightened attention as potentially modifiable factors for dementias of later life since in the absence of effective therapies, promoting and maintaining vascular health seems critical to prevent both the vascular and neurodegenerative components of the disease and is probably the best possible course of action at the present.

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UDK: 616-079:616.892.3
DOI: 10.21857/9xn31cr48y
Review article
Received: 9.9.2018.
Accepted: 10.5.2019.

POSITRON EMISSION TOMOGRAPHY AND SINGLE PHOTON EMISSION TOMOGRAPHY IN NEURODEGENERATIVE DISEASES, ESPECIALLY DEMENTIAS

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Summary

Functional brain imaging with Single Photon Emission Tomography and Positron Emission Tomography using various radio-ligands can improve the clinician's diagnostic accuracy of neurodegenerative brain disorders and help us understand the underlying pathological processes as well as follow the response to treatments.

The metabolic brain changes that occur in the process of neurodegeneration can be detected earlier then with the structural brain imaging. Similarly, the depositions of pathological amyloid and tau proteins can be detected already in the preclinical phase of the neurodegenerative brain diseases.

Key words: Single Photon Emission Tomography (SPECT), Positron Emission Tomography (PET), dementias, neurodegenerative diseases

SINGLE PHOTON EMISSION TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET) are both emission tomographic techniques, meaning that the source of radioactivity is within the patient. Gamma rays are emitted from radiopharmaceuticals, which are most often intravenously administered to subjects.

PET offers a more accurate detection of the distribution of activity in the tissue and a better spatial resolution comparing to SPECT. However, the half-lives of PET tracers are shorter compared to the SPECT ones. For example, Fluorine-18 (18F) is a fluorine radioisotope, which is an important source of positrons and is most frequently used in clinical practice. Its half-life is 109.8 minutes compared to many hours to days for the SPECT tracers. Using SPECT and PET techniques we can image/measure regional cerebral blood flow with perfusion SPECT, regional glucose consumption with fluorodeoxyglucose PET (FDG PET), various neurotransmission, activity of numerous cerebral enzymes, neural inflammation and deposition of abnormal proteins in brain tissues. Blood perfusion and glucose consumption studies are highly correlated to the local intensity of glutamatergic synaptic activity. As approximately 90% of brain synapses are glutamatergic, the activity measured by perfusion SPECT and FDG PET is called a "brain activity" [2].

Nowadays, diagnostic performance of PET is much better than SPECT, and PET studies are getting more widely available, therefore PET has become the instrument of choice in nuclear medicine to evaluate cognitive disorders [3,4].

Fluorodeoxyglucose Positron Emission Tomography (FDG PET)

Results of FDG PET imaging directly reflect the tissue state by depicting regional anomalies at the synaptic level even if they are only dysfunctional without an actual loss [5]. Glucose metabolic reductions could reflect: reductions in the density or activity of dendrites or perisynaptic glial cells, a metabolic dysfunction in neurons or glial cells, or a combination of them [4,6]. Hypometabolism is therefore observed in various neurodegenerative disorders.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with an insidious onset and is characterized by a severe decline in episodic memory and other cognitive functions. In AD, a typical pattern of metabolic reduction is involving parietotemporal regions and the precuneus/posterior cingulate complex (PCC) (Fig. 1) [5,7] AD variants such as the "language variant" (logopenic variant primary progressive aphasia - lvPPA), the "behavioral/dysexecutive variant", and the "visual variant" (posterior cortical atrophy - PCA) show a distinct patterns of focal hypometabolism reflecting the specific dysfunctions: left-sided posterior temporal anomalies in lvPPA, sparing of the PCC and frontal lobes in "frontal variant" and bilateral occipital regions hypometabolism in PCA. [8,9,10]

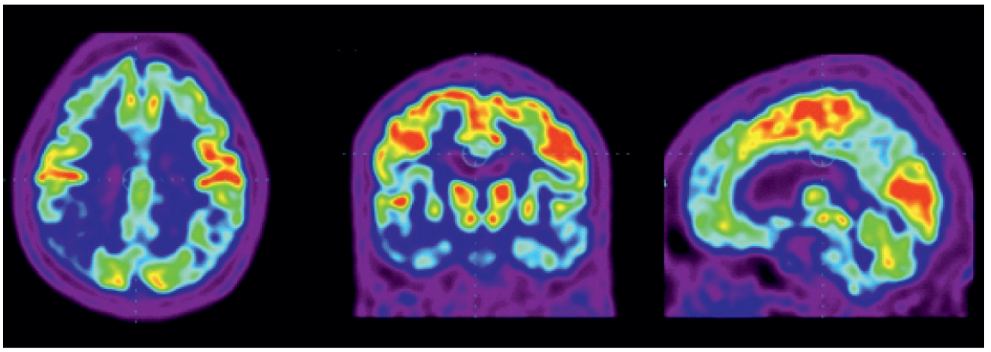

Figure 1. FDG PET image in patient with Alzheimer's disease (hypoactivity is observed in parietal and temporal cortices)

Dementia with Lewy bodies often presents with parietal hypometabolism reminiscent of AD, with sparing of the PCC (also known as the "posterior cingulate island sign") and occipital involvement (Fig. 2) [11,12].

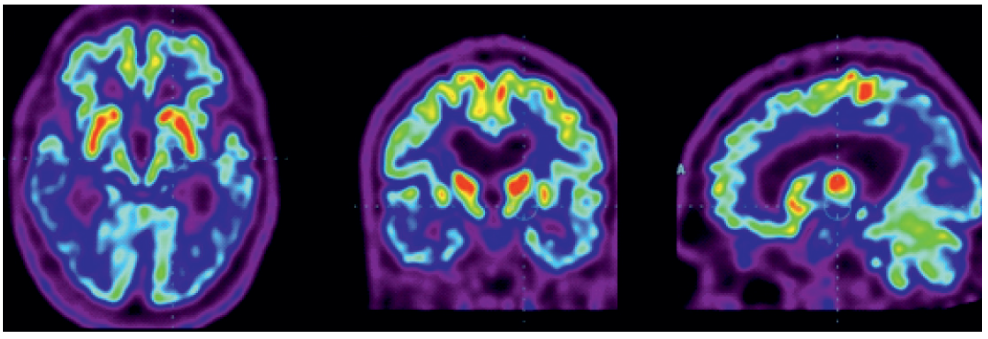

Figure 2. FDG PET image in patient with dementia with Lewy bodies (hypoactivity is observed in parietal and occipital cortices)

Classic behavior type of **frontotemporal dementia** (bvFTD) shows hypometabolism in frontal and anterior temporal regions (Fig. 3), whereas semantic variant primary progressive aphasia is associated with bilateral but usually quite asymmetric (left dominant) anterior temporal lobe hypometabolism. Progressive nonfluent aphasia (nonfluent variant of primary progressive aphasia (nfvPPA) typically targets the left dorsolateral and dorsomedial prefrontal cortex.

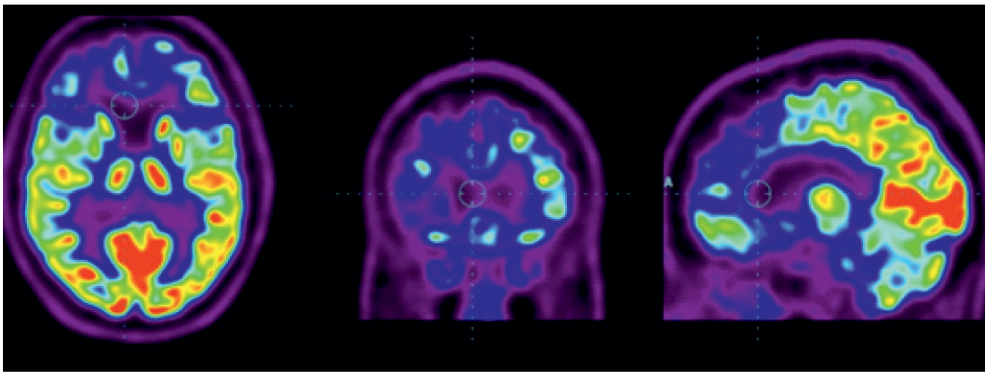

Figure 3. FDG PET image in patient with behavioral variant of frontotemporal dementia (hypoactivity is observed in frontal cortices)

Corticobasal degeneration (CBD) is a very heterogeneous neuropathology and can generate a number of clinical phenotypes. FDG PET findings in CBD often show asymmetric dorsal frontal and anterior parietal metabolic reduction with common ipsilateral, striatal, and thalamic involvement.

A growing body of evidence supports the value of FDG PET in the diagnosis of patients with atypical/unclear conditions [4,5,13] FDGPET can significantly improve diagnostic accuracy and lead to earlier treatment, better planning for future care, and less suffering for patients and their families.

A retrospective memory clinic study evaluating the value of FDG PET in mild cognitive impairment (MCI): showed that the addition of FDG PET to the routine memory clinic workup significantly lowered the number of unclear diagnoses from 39% to 16% [14] FDG PET was also associated with a change in diagnosis in 29% of patients and a 64% increase in the use of cholinesterase inhibitors.

In another study, FDG PET changed the clinical diagnosis in 35%, altered the use of acetylcholine-esterase inhibitor medication in 17%, and reduced uncertain diagnoses from 30% to 18% [15].

Recent European Federation of the Neurological Societies (EFNS) guidelines [16] recommend the use of FDG PET for degenerative diseases showing atypical features and diagnostic uncertainty. However, in a number of cases, equivocal or incongruent FDG PET results may leave clinicians in an even greater dilemma. Repeat FDG after a year [17] reduced the number of unclear diagnosis from 80% to 34% and led to diagnostic change in 24% of cases and treatment modification in 22% of patients.

FDG PET is an effective and safe modality to identify diagnostic patterns of glucose hypometabolism in neurodegenerative dementias and is an effective and useful adjunct to other diagnostic information in the assessment of patients with progressive cognitive impairment [4, 18].

AMYLOID PET

Amyloid PET ligands enable the detection and quantification of amyloid neuritic plaques in the living human brain. The first tracer with specific binding to amyloid-beta (Ab) applied in human studies was ^{11}C-labeled Pittsburgh Compound B (PiB) [19] There are currently three FDA and EMEA approved ^{18}F labeled tracers available for clinical use: florbetapir, flutemetamol and florbetaben. All these tracers have been validated prospectively by comparing the PET signal with AD neuropathological changes and have shown high correlations between *in vivo* tracer retention and postmortem measures of fibrillar Ab [1].

The pattern of Ab deposition across AD patients is very similar, even in atypical clinical phenotypes such as PCA, lvPPA, and behavioral/ dysexecutive AD [1, 20] Additionally, it has been discovered that the extent and the distribution of Ab PET correlates only moderately with patterns of neurodegeneration and with cognitive deficits [21, 22]. This has led to the suggestion that deposition of Ab is the trigger of a cascade of neuropathological events in the development of AD, rather than the driver of neurodegeneration and clinical disease progression. Using amyloid PET for research purposes has led to improved models of disease pathogenesis and understanding a long preclinical disease phase in AD as well as better subject selection for clinical trials.

Frontotemporal lobar degeneration form a spectrum of clinical syndromes: behavioral variant FTD, FTD with motor-neuron disease, semantic variant primary progressive aphasia, and non-fluent variant PPA. FTLD and AD are the leading causes of early age-of-onset dementia, occurring with similar frequency in patients presenting younger than the age of 65 years. [23] Clinically distinguishing the two during life, can be challenging because of clinical and anatomic overlap, and misdiagnosis rates of 10% to 40% are reported even in expert centers (24].

Differentiating AD from FTLD is an important clinical use for amyloid PET because Ab plaques are not present in FTLD pathologic spectrum. Differentiating AD and FTLD was the focus of one of the largest studies on the diagnostic use of amyloid PET published to date [25] PiB visual reads had a higher sensitivity for AD than FDG- PET (89.5% vs. 77.5%), with similar specificity (83% vs. 84%). When scans were classified quantitatively, PiB had higher sensitivity (89%

vs. 73%), whereas FDG had higher specificity (83% vs. 98%). PiB outperformed FDG in classifying 12 patients with known histopathology (97% vs. 87% overall accuracy).

Amyloid PET has undoubtedly a great potential as a diagnostic tool [19] Similar to FDG PET, it is now an established technique with data incorporated in the most recent consensus guidelines for the diagnosis of AD and predementia AD-related conditions [26, 27].

Tau Protein Positron Emission Tomography (TAU PET)

It is well known that tau pathology has devastating effects on synaptic function. [28] Since there is no beneficial anti-Ab treatment available for AD, the development of PET tracers that bind to protein tau aggregated NFTs was warmly expected.

Tau imaging is bringing new applications. From recapitulating the pathological studies of Braak and Braak to early and differential diagnosis of AD and non-AD tauopathies. Additionally, the tau imaging elucidated the underlying pathology in subjects with neurodegeneration but absence of Ab deposition "suspected nonamyloid pathology" [SNAP] and in "primary age-related tauopathy" [PART] [1].

Tau distribution correlates strongly with the clinical evolution of AD, and postmortem tau aggregates are closely associated with cognitive performance during life [29].

However, tau imaging has its own limitations and challenges. Tau is found in brain at lower concentrations than Ab and is characterized by different isoforms. Thauopathies present with a mixture of various isoforms. Off-target binding to neuromelanin and melanin-containing cells to brain hemorrhagic lesions, in the striatum and choroid plexus has to be taken into account while interpreting the scans [30].

Tau PET imaging has shown a minimal cortical and subcortical uptake in cognitively intact young adults. In cognitively intact and Ab-negative older adults increased uptakes of tracer was found in medial temporal lobe regions (mostly entorhinal cortex and parahippocampal gyrus). In cognitively intact Ab-positive older adults uptake of tracer extended to inferior and lateral temporal lobe regions. AD patients showed additional and more diffuse tracer in neocortical areas, involving temporal, parietal, and frontal lobes. [31]. These findings suggest that the presence of NFTs in the inferior temporal gyrus is an early sign of subsequent cognitive impairment and conversion to AD dementia. [1] Neuropathological studies and animal studies of AD have showed a robust associa-

tion between tau deposits, decreased cognitive function, and neurodegenerative changes [28].

The distribution of tau is different from Ab distribution in the brain. Tau accumulates in focal targeted areas of the mesial temporal cortex, whereas amyloid highly diffuses in the brain. Medial temporal tau depositions may be present before Ab, but once amyloid starts to accumulate, the degenerative cascade becomes faster and irreversible [31, 32].

Multimodal imaging

Using multimodal imaging, we may nowadays detect and longitudinally observe all three pathophysiological processes in AD: amyloid and tau pathology as well as neurodegeneration. FDG and amyloid PET both better predict conversion from mild cognitive impairment to AD than structural MRI, as has been shown in multi modal studies [33] and in a meta-analysis [34]. Studies comparing FDG with amyloid PET imaging suggest that they have similar predictive accuracy. Amyloid PET shows higher sensitivity than FDG, whereas FDG PET shows higher specificity and greater short-term predictive value [35]. Whereas amyloid load increases up to 25 years before the onset of cognitive symptoms (in familial AD mutations) but then plateaus in later disease stages, FDG-PET shows a more linear correlation with disease progression [36]. Additionally, in clinical variants of AD (AD memory, lvPPA, and PCA), clinical syndromes correlate to patterns of glucose metabolism, whereas amyloid PiB-PET binding is similar across clinical phenotypes [37]. FDG and PiB jointly improve the classification of one variant from others, but the added effect of joint FDG-PiB versus FDG alone has shown to be small. Nowadays, integrative algorithms for clinicians working in memory clinics to deal with complex/atypical cases with unclear diagnoses are being proposed [1].

Conclusion

The clinical diagnosis of neurodegenerative dementia has only moderate sensitivity and specificity when compared with the pathological findings. Misdiagnosis rates are even higher in atypical patients with an uncertain diagnosis, close to 30% [38]. The practical clinical use of amyloid and FDG PET imaging has recently been evaluated in the diagnostic process of patients with an uncertain diagnosis [39] as well as its effect on clinicians' decision making [40]. The use of amyloid PET in the differential diagnosis of atypical cases has even shown to have a beneficial impact on caregivers, by reducing their uncertainty, reduc-

ing anxiety and depressive symptomatology [41]. Currently, brain imaging techniques can detect more than medicine can treat and ethical dilemmas are common. Patient should be offered a comprehensive diagnostic workup including clinical evaluation and imaging that is evidence based. Informing patients and their family members comprehensively about the possible effects of the imaging results on patients' further management is mandatory before the evaluation [42].

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UDK: 616.8-009
DOI: 10.21857/m3v76t6ply
Review article
Received: 13.12.2018.
Accepted: 28.3.2019.

CLINICAL UPDATES AND MANAGING OF RETT SYNDROME

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Summary

Rett syndrome is a neurological disorder caused by a defective protein involved in the transcription of methylated DNA. It affects almost exclusively girls. The causative gene is the methyl CpG-binding protein2-gene (MECP2) located on the X-chromosome. The diagnosis is made clinically, based on internationally accepted criteria that were last revised in 2010. More than 95% of the MECP2 mutations occur de novo. Over 95% mutation detection rate occurs in individuals with typical Rett syndrome when standard techniques are used to analyze the coding region and through complementing MLPA analysis for large deletions and gross rearrangements in the gene. Early diagnosis and comprehensive life-long management of Rett syndrome can significantly improve the health and longevity of affected individuals. Management is optimized by the involvement of a multidisciplinary team consisting of many different medical and paramedical specialists and an individualized approach at every age. Parents are an integral part of this team, as they become the greatest experts concerning their affected child's history, behavior, and needs.

Key words: Rett syndrome, methyl CpG-binding protein2-gene (MECP2), multidisciplinary team

Introduction

The prevalence of the classic syndrome is estimated to be 1 in 10,000 females [1] but varies according to countries from 1/8000 – 1/15.000. Current understanding of the typical and atypical forms suggests that the overall prevalence is probably much higher. It is the third most common cause of intellectual disability in females next to chromosomal anomalies (e.g. Down syndrome) and the X-linked familial intellectual disability (e.g. Fragile X syndrome in 20% of the female carriers).

Rett syndrome was thought to be an X-linked dominant condition with lethality in hemizygous males for a long time. Rett syndrome in boys with a normal 46, XY karyotype is very rare. Typical RTT, like in girls, can only occur in a boy with an additional X chromosome (carrying the MECP2 mutation) in all cells (47, XXY or Klinefelter syndrome) or in only part of the body cells (somatic mosaic). On the other hand, there are the MECP2 mutations that cause the typical syndrome in girls and where the mother is a healthy skewing carrier. These mutations will lead to intrauterine death or early infantile epileptic encephalopathy with early death before or around the first year of life. In addition, there are the more sporadically occurring variants in MECP2 in males who are hardly seen in RTT girls and whose disease-causing properties are not immediately clear, certainly not when such a case has never been described before. Often these variants in MECP2 are compatible with a long survival. The clinic is then very different without meeting the necessary criteria for the diagnosis of typical or atypical RTT: non-specific intellectual disability; intellectual disability with motor deficits (speech and writing difficulties and / or neurological problems with coordination in motor skills); severe intellectual disability with spasticity with symptoms similar to RTT (scoliosis, hyperventilation, intense visual interaction); intellectual disability with psychiatric disorders (bipolar disorder or juvenile schizophrenia) and tremors; intellectual disability with psychosis, spasticity and macro-orchidism (PPM-X syndrome).The current advances in DNA diagnostics are now more common with MECP2 mutation in males. One estimates the frequency of MECP2 mutation between 1.3 and 1.7% of the male population with intellectual impairment. The clinic in boys is not unequivocal as described in the girls. It is therefore referred to as MECP2 related disorders in males because the clinical phenotype does not meet the diagnostic criteria for RTT (Table 1). In addition, MECP2 duplication syndrome, FOXG1 syndrome and CDKL5 syndrome are considered separate entities, although with many intersections.

Table 1. MECP2 related Sex-associated Syndromes and Symptoms

MECP2	Female	Male
Loss of function	Typical RTT	Infantile epileptic encephalopathy
	Atypical RTT	Typical RTT (47, XXY or somatic mosaic)
	ID with seizures	ID with motor deficits
	Mild ID	Bipolar disease, ID and tremors
	Learning difficulties	Juvenile onset schizophrenia, ID and tremors
	Autism	ID, psychosis, pyramidal signs, macroorchidism (PPMX syndrome)
	Normal carrier	
Overexpression	Preserved speech	Severe ID and RTT features
		Non specific XLMR

The MECP2 duplication syndrome occurs in both sexes with severe intellectual disability in the male and preserved speech in the female, recurrent infections and motor impairment in combination with features similar as in RTT (epilepsy, hyperventilation, autonomic disturbance, etc.) or as a non-specific form of intellectual impairment with or without autistic features. The clinical severity is mainly determined by the extent of the duplication and whether or not other important genes are involved in this duplication.

The pathology of Rett syndrome differs from other disorders with mental retardation in that the pattern of dendritic changes in the brain is unique [2,3]. Brain weight is reduced in girls with Rett syndrome but does not diminish with age. The defined cause of this arrest in brain development and how this results in altered neurophysiology is not yet well understood. There is evident failure of dendritic arborization in specific sites of the brain, correlating with the cortical localization of some of the significant motor and behavioral symptoms. In relation to the peculiar movement disorder in Rett syndrome, the substantia nigra,

basal ganglia, cerebellum, and spinal cord have been found to show specific alterations (Table 2). Various neurotransmitter systems have also been studied with varied and inconclusive results apart from the demonstration of monoaminergic dysfunction. [4].

The disturbances in autonomic function have been studied and related to immaturity of brainstem autonomic centers resulting in hypersensitivity to sympathetic stimuli with insufficient parasympathetic control. This is the so-called sympathicovagal imbalance which is unique in Rett syndrome. [5,6]. New insights into the brainstem phenomena have led to the neurophysiologic delineation of cardiorespiratory phenotypes, such as "forceful breathers," "feeble breathers," and "apneustic breathers." Each of these cardio-respiratory phenotypes has a specific therapeutic approach that will be discussed later.

Table 2. The six (6) cardinal features of RTT in relation to pathology

Affected Part	Reported Pathology	Clinical Observations
Cortical	Decreased dendritic arborization and smaller than normal brain	Severe mental retardation
Cortical	Epilepsy	Seizures
Extrapyramidal	Monoaminergic dysfunction	Dystonia, incoordination of motor activities, orthopedic deformities, and secondary muscle wasting with contractures
Brainstem	Monoaminergic dysfunction	Dyspraxia, agitation, and sleep disturbances
Brainstem	Immaturity with incompetence of inhibitory neuronal networks	Abnormal breathing rhythms and lack of integrative inhibitions, which are likely causes of sudden deaths
Brainstem	Dysautonomia	Cold and blue extremities and sympatho-vagal imbalance

Manifestation and management

Early intervention and comprehensive lifelong management can have a significant impact on the health and longevity of affected individuals. Good management requires the involvement of a multidisciplinary team consisting of many medical and paramedical specialists and the development of an individualized approach. Parents are critical members of the team, as they become the greatest experts concerning their own child's history, behavior, and needs. Many of the suggestions and recommendations described below are the result of over 35 years of personal experience together with review of international scientific expertise.

Growth and feeding

Physical growth retardation and feeding problems are common features of Rett syndrome. The mechanisms causing this growth failure are poorly understood and the role of MeCP2 in physical growth is yet to be investigated. Both nutritional and no nutritional factors are thought to contribute. Height, weight for height, and head circumference are important parameters to follow at each physician visit. Assessment of daily caloric intake by a dietician is important in poor feeders. The influence of involuntary movement activity, abnormal breathing patterns and epilepsy on the balance between nutritional intake and energy expenditure should be considered. Consider the increased likelihood of gastroesophageal regurgitation if food aversion is obvious, and evaluate this in a standard way. Caloric supplements can be added when caloric intake is insufficient and oromotor problems are minimal. A gastrostomy-button should be placed when the child is not able to eat comfortably and without risk of aspiration, to assure sufficient nutritional and caloric intake. Treatment of gastroesophageal regurgitation is standard.

Development and Behavior

Communication

All girls with Rett syndrome have intellectual disability. The absence of speech in most affected girls, the dyspraxia, and the short attention span with lack of interest in play make developmental testing a difficult task. Girls with Rett syndrome are able to make choices and take causally related action. Therefore, parents and caregivers should be aware that the time they require to show what is wanted or to produce their answer to a specific situation is prolonged.

The intense eye contact behavior is further accentuated in older affected females in a typical eye-pointing behavior, which expresses wishes and remains present even in the most severely affected female. Teachers can use this behavior to develop eye communication in habilitation programs, in training emerging literacy and in augmentative communication through eye gaze computer technology. Some girls with Rett syndrome have preservation of speech or use words and sentences in a meaningful way. Many of them continue to learn new words and names far into stage III and into adulthood. This intense eye contact and eye-pointing behavior is very distinct and separates Rett syndrome from other conditions with severe intellectual disability and/or autism.

Intense Hand Stereotypies

These stereotypies disturb communicative interaction through distraction and agitation. They cause difficulty in concentration on objects for a long time. By forcing the girls to stop the arm and hand movements by gently fixing the elbows or by bracing them during sessions of interaction, the child will appear more quiet and concentrated. In this way, some girls will be more cooperative in sessions with the occupational therapist.

Screaming Spells

Some teens and adults experience periodic sudden violent screaming spells. They are often associated with extreme pain though no specific organ pathology is present and thorough examination does not reveal any somatic abnormality. This is not an epileptic phenomenon but rather is defined as "brain-pain-crying," and can last for hours. Others are abnormally prone to agitation and scream when they do not feel safe for whatever reason. The situation returns to normal when moments of rest and peace are given.

Sleep Abnormalities

These are more or less pronounced, and are a constant feature of Rett syndrome. Night laughter, prolonged wakefulness or early morning waking causes great concern for parents, especially in young preschool girls. These problems may persist into adult life. Night laughter clearly does not disturb the child. The fact that affected children and adults are prone to short periods of daytime sleeping is seen as a need for recovery. The mechanism behind this disruptive night awakening and daytime sleeping is not yet well understood. It might be related to the other autonomic dysfunctions that are associated with midbrain

and brainstem immaturity. Melatonin appeared to improve total sleep time and sleep efficiency in the girls with the worst baseline sleep quality. [7,8]. Pipamperon can be used as a regulator of circadian rhythm with little hypnotic side effects (personal experience). It mainly acts as a serotonin-antagonist, with less adrenolytic and anti-dopaminergic action. It is particularly useful when the girl is abnormally prone to agitation. Pipamperon is not available in the United States as of this writing. The use of eye gaze computer is recommended early after clinical diagnosis in order to obtain more information about speech & language development.

Treatment

Augmentative communication methods should be used to capitalize on the intense visual communicative ability. Guidelines for communication in Rett syndrome are to be published in 2018 by an expert group of speech therapists. During therapy sessions, agitation and distraction should be avoided as much as possible, and gently immobilizing the hands may contribute to the quality of the interaction. To establish visual contact behavior, the examiner's face should be brought closely in front of the subject with avoidance of distraction and agitation as much as possible. Bracing the elbows may help with dominant and intense hand stereotypies. Braces in soft but resisting materials can be used. Allow the child daytime periods without them. Evaluate the effect of bracing on behavior. In case of agitation, bracing should be abandoned. In the presence of agitation, moments of private rest and peace should be granted, according to individual needs. Identification of the trigger and its avoidance is the first line treatment. The use of time-out in sensory deprivation can be tried if this fails. Drugs of choice are resperidone (Risperidal®) or pipamperon (Dipiperon®). Regulation of circadian rhythm can be useful. Melatonin and l-tryptophan are useful in initiating sleep; pipamperon, if available, can be used in low normal dosage when agitation is present. Music therapy is recommended in Rett syndrome as affected people seem to enjoy it and perform better. [9].

Neurologic symptoms

Seizures

Epilepsy is present in up to 80% of affected girls at some time in their lives. [10,11]. It usually starts after age 4 years and tends to diminish in severity in adulthood. Many become seizure. The most common seizure types are partial complex, tonic-clonic, tonic, and myoclonic seizures. Although about 50% of sei-

zures can be controlled by medication, intractable epilepsy occurs significantly more frequently in girls with obvious deceleration of head growth. The electroencephalogram is usually abnormal in Rett syndrome, but there is no diagnostic pattern. Electroencephalogram patterns frequently seen in Rett syndrome include generalized slowing, monorhythmic theta waves, and focal and generalized spikes and sharp waves. Neurophysiologists can use an EEG staging system according to the presence or absence of sleep characteristics like K-spindles and reversed vertex waves, slow wave activity and the intensity of generalized spikes and sharp waves. [12]. These EEG stages do not always coincide with the clinical stage.

The age of onset of seizures is later than usually found in severe mental handicap in general. It is surprising that most children with Rett syndrome, although severely impaired, only experience the onset of epilepsy in stages III and IV and not in the rapid regression stage II. Rarely, infantile seizures, variant infantile spasms or other intractable seizures are present before the appearance of classical Rett syndrome features. In spite of this early and severe onset of epilepsy, no negative effect on the long-term course and prognosis of Rett syndrome has been identified. Status epilepticus does not occur more often than in severely mentally retarded children in general. The probability of death associated with epilepsy is estimated at 9%.

Brainstem events may be confused with seizures or are difficult to interpret as such by parents and care takers. Signs of abnormal brainstem activity include blinking of the eyes, facial twitching, vacant spells with no associated epileptiform activity, and hypocapneic attacks with tetany and cyanosis. Classifying these clinical events requires simultaneous neurophysiological monitoring of brainstem and cortical functions and correlation with behavior. Facial twitching with or without sudden changes in attention and eye deviation should not be *a priori* interpreted as epileptic paroxysms in a young child. This reflects more the ongoing process of immature brainstem activity and is not influenced by antiepileptic drugs. Immature brainstem activity also accounts for the screaming spells, laughing spells, prolonged staring, and so on.

Autonomic Cardiorespiratory Manifestations

Irregular breathing in the waking state associated with nonepileptic vacant spells is the most distressing feature in Rett syndrome. It reflects the immaturity of the brainstem and may contribute to sudden death. Low resting cardiac vagal tone and weak vagal response to hyperventilation and breath-holding suggest inadequate parasympathetic control. Neurophysiological studies have

shown that these baseline brainstem functions are affected in Rett syndrome, whereas the baseline sympathetic tone remains at a neonatal level. Insight into these phenomena has introduced new terminology such as "brainstem storm" and "brainstem epilepsy" as phenomena of abnormal spontaneous brainstem activation (ASBA) associated with altered breathing patterns. [5].Evaluating the brainstem functions in Rett syndrome requires detailed neurophysiology. [6]. The primary pathophysiology is related to a defective control mechanism of carbon dioxide exhalation causing respiratory alkalosis or acidosis. Three cardiorespiratory phenotypes are described, each demanding a specific approach [6]. Forceful breathers usually have fixed low levels of pCO_2 (chronic respiratory alkalosis); feeble breathers usually have fixed high levels of pCO_2 (chronic respiratory acidosis) due to weak respiration; apneustic breathers accumulate carbon dioxide due to delayed and inadequate expirations. Agitation in individuals with Rett syndrome is associated with unrestrained sympathetic activity.

Treatment

There is no general rule for the anti-epileptic treatment in Rett syndrome. Each case should be assessed individually. The most commonly used anti-epileptic drugs are sodiumvalproate, lamotrigine, and carbamazepine. Monotherapy is successful in 50%. Polypharmacy should be avoided as much as possible. Individuals with Rett syndrome are sensitive to anti-epileptic drugs and have a tendency to be easily over-sedated, cognitively depressed, and confused. Feeble breathers and apneustic breathers are very sensitive to opiates and benzodiazepines. These drugs should be avoided in them. Gradual withdrawal of anti-epileptic medication should be considered when individuals become seizure-free.

Treatment of brainstem dysfunctions is extremely difficult and hazardous. There is little experience with medication. Vagal nerve stimulation, as in intractable epilepsy, is under debate. To interrupt an episode of forceful breathing, we recommend first short periods of re-breathing in a total face mask, allowing for surrounding air to flow in, connected with a tube between 40 and 60 cm long as dead space. Long-term weaning from the chronic respiratory alkalosis requires Carbogen treatment (5% CO_2 in oxygen mixture) to move the pCO_2 toward normal (39–44 mm Hg). The use of a mixture with 60% oxygen/40% carbon dioxide given by nasal prongs and under medical surveillance is recommended to lift the low pCO_2 to about 40 mm Hg. [13]. In feeble breathers, oral theophylline is the first choice of drug for respiratory stimulation but its clinical tolerance is very poor. Physical activity during person-to-person contact can stimulate breathing but is short-lived. Continuous positive airway pressure (CPAP) can

be used at night. The end point of treatment is to establish normal breathing rhythm at normal or near normal pCO_2. Feeble breathers have great sensitivity to opiates and benzodiazepines. Weaning from artificial ventilation in intensive care is difficult. In apneustic breathers, oral buspirone is the drug of choice because of its effect on apneusis. [14]. Treatment end point and risks are otherwise similar to feeble breathers.

In general, if one considers the sympathicovagal imbalance in RTT, more parasympathetic feedback can easily be offered through the following means: watching favorite video, vibroacoutic stimulation and/or music [9]., bathing and playing with water, personal physical body contact, horseback riding, walking in open air and physical activity in general, frequent small meals. Parents and care givers should keep in mind that a minimum of 2x60 minutes of movement a day can be easily reached through the moments of individual care, nursing and interactions that may be allowed to last longer.

Cardiovascular symptoms

Females with Rett syndrome have a higher incidence of prolonged QT interval, and heart rate variability is diminished. These abnormalities likely result from impairment of autonomic nervous system control, reducing the electrical stability of the heart and precipitating sudden dysrhythmia's. Imbalance between preserved sympathetic tone and insufficient parasympathetic control is known to cause cardiac arrhythmia. Individuals with prolonged QT interval associated with abnormal breathing pattern are particularly at risk for cardiac arrhythmia, especially the forceful breathers. Of the deaths reported to the International Rett syndrome Association in individuals less than 23 years of age, 22% have been sudden, unexpected death, in comparison with 2.3% in the general population up to the same age. [15].

Cold extremities caused by poor perfusion because of altered autonomic control are common. This is more related to the central abnormalities than to vascular conditions. In the long term, it leads to abiotrophic changes.

Musculoskeletal symptoms

Scoliosis

Scoliosis develops in early school age with various degrees of severity. Sometimes progression is very rapid, depending on asymmetry in muscle tone and the degree of dystonia and muscle wasting. In ambulatory girls, scoliosis appears unpredictable—it may never be present or may only develop to a small

extent. In nonambulatory girls with typical Rett syndrome stage IVB scoliosis develops in spite of preventive measures. Most commonly a double curve develops with a longer upper part (most frequently dextro convex) and a shorter lower part (sinistro convex). When there is no neurologic asymmetry, the spine deformity is usually much more benign.

Kyphosis occurs more in ambulatory girls. It may be related to the degree of extension in the ankle muscles. Tiptoe walking in girls with Rett syndrome, in contrast to other circumstances with neurologic deficit, is related to uncertainty and anxiety about falling. Girls gain support and stability by bending forward on stiff legs, giving them more balance against gravity. When sitting and drowsy, girls tend to drop their heads forward causing more bending of the cervical and high thoracic vertebral column. A high kyphosis is not uncommon in the many milder or variant forms of Rett syndrome and can progress by age.

Foot Deformities

The foot deformities most common in Rett syndrome are equinus and equinovalgus/varus positions. As long as the Achilles tendon can be flexed over 90° with the knee in extension, normal walking remains possible. Further shortening of the Achilles tendons is then compensated for by an "escape" in the valgus or varus position. Young girls do not suffer from this and continue to develop walking ability. If there is hyperextension of the ankles, the need for compensation rises to the knees, the hips and the spine, threatening loss of balance and making walking very difficult if not impossible. Affected girls develop a preference for one leg, putting it forward in every step and using the other leg as support and balance. Direction is chosen through the preferential leg. Sometimes the other leg is placed more to the side causing a girl to walk in circles; sometimes the girl tilts it high up and then forward simulating an involuntary movement.

With careful follow-up of muscle tone and posture, especially of the spine and feet, and with timely corrective measures, walking can be preserved for a long time. Abnormal muscle tone in the flexor/adductor muscles of the hip can lead to dislocation especially in non-walking girls. If orthopedic surgery is considered, an evaluation of feeding, epilepsy, skin problems, and behavior should be carried out before hospitalization. The approach to orthopedic deformities in Rett syndrome requires input from parents, therapists, pediatrician, orthopedic surgeon, and a rehabilitation specialist to find a treatment goal related to the individual's level of function in daily life activities. Good sitting and sleeping positions are important. Botox treatment of spasticity can be used in Rett syndrome

as in spasticity in general, but should be done in consultation with the rehabilitation specialists and orthopedic surgeons. [16] Results depend on good advance selection of affected individuals. The effect, however, is limited in time. Braces or orthoses are used for the spine, the foot and the ankle to prevent further deformation and/or to support walking. Severe tonic-clonic seizures should be well controlled by medication before spinal surgery. Early casting of the trunk as a conservative treatment will not prevent surgical intervention in progressive cases. Kyphosis rarely needs surgical correction.

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Proceedings of the 2nd Rijeka Forum on Neurodegenerative Diseases
held on 17th October 2018 in Rijeka, Croatia

Nakladnik / Publisher
HRVATSKA AKADEMIJA ZNANOSTI I UMJETNOSTI
Trg Nikole Šubića Zrinskog 11, 10000 Zagreb

Za nakladnika / For the Publisher
Dario Vretenar, glavni tajnik / Secretary-General

Grafička urednica / Layout editior
Nina Ivanović

UDK / UDC
Nataša Daničić

Naklada / Copies
200

Tisak / Print
Tiskara Zelina d.d.

Rujan / September 2019

ISBN 978-953-347-283-6

105,00 kn