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NEURODEGENERATIVE DISEASES CHALLENGES: EARLY DIAGNOSIS AND PANDEMICS

Editors: Vladimira Vuletić and Daniel Rukavina



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CROATIAN ACADEMY OF SCIENCES AND ARTS
Department of Biomedical Sciences in Rijeka
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Vladimira Vuletić and Daniel Rukavina

EDITORIAL

Neurodegenerative diseases are conditions which primarily affect the neurons in the human brain. They are incurable and 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%. Neurodegenerative diseases will be new pandemics.

It is therefore necessary to educate health professionals at local and global level in early diagnosis and early treatment of neurodegenerative diseases. Early diagnosis will improve neurosciences researchers' work in early phase and possible give us a neuroprotection treatment in near future. The right management and treatment on time will improve life quality not just patients but also caregivers and family members.

Nevertheless, we are facing COVID-19 pandemics and the impact of the COVID-19 pandemic on the lives of particularly affected families, on health systems, the economy, and the world economy. Regardless of the respiratory symptoms, 85% of patients with SARS-CoV-2 had acute, subacute, and long-term symptoms and complications of the peripheral and central nervous systems. There is a new term a post COVID 19 neurological syndrome for persisting of neurological symptoms long time after recovery of COVID 19 infections. Neurological departments are facing with adaptive work, telemedicine, phone consultation, reduction of neurological department capacity and team members in benefit of COVID 19 departments. Fear of this new pandemic situation reduced asking help and coming to hospitals and centers in situation of worsening of neurodegenerative diseases even in life threatening situations. The real consequences will be seen in near future.

In our Clinic of Neurology at the Faculty of Medicine in Rijeka, a few years earlier, 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 centre 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.

In this pandemics time we have organized in out-patients clinic evaluation (clinical, diagnostic), register, and follow up patients with post COVID 19 neurological syndromes. The need of such register was recognized.

Thanks to efforts of our Clinics and in collaboration with the Department of Biomedical Sciences in Rijeka of the Croatian Academy of Sciences 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 po-

int 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 book is a summary of the most representative and updated lectures “a state of art” covering a wide scientific interest area 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 early diagnosis and early treatment in neurodegenerative diseases and postcovid neurological syndromes. 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 in neurodegenerative diseases and postcovid neurological syndromes and will improve day-to-day management of dementias in Croatia.

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ALZHEIMER'S DISEASE AND USE OF CEREBROSPINAL FLUID BIOMARKERS

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Summary

Alzheimer's disease (AD) is the most common cause of dementia. The "amyloid cascade hypothesis" is the prevailing model for the underlying cause of AD and explains how aggregated amyloid- β cause neurotoxic effects in the brain. AD has a long-lasting course and can present as both typical and atypical clinical phenotypes. Cerebrospinal fluid (CSF) analyses for "core AD CSF biomarkers" and synaptic proteins have been thoroughly evaluated in research studies, showing high diagnostic performance, and are today available for routine clinical diagnostics on high-precision fully automated instruments. The current AD therapy is based on two classes of cognition-enhancing drugs acetylcholinesterase inhibitor and NMDA-receptor antagonist where most patients experience a delay of cognitive decline, but disease-modifying drugs in the form of amyloid- β immunotherapy has recently been approved in the US, and are under evaluation at the European Medicines Agency.

Key words: CSF markers, Alzheimer disease, biomarkers

State of Art

Alzheimer's disease (AD) is by far the most common dementia disease; it is estimated that as many as 250,000 people in Sweden (10 milion people) will have

dementia in 2050 [1]. Neuropathologically, AD is characterized by the combination of amyloidosis ($A\beta$ plaques), tau pathology in the form of tangles and neurofibrillary threads, and neurodegeneration (neuron and synapse degradation) [2,3]. There are two forms of plaques in AD, namely "diffuse plaques" which consist only of loosely aggregated $A\beta$, and which are later assumed to be converted into the other form of plaques which have a core of hard aggregated $A\beta$, which are surrounded by damaged nerve cell protrusions and activated glial cells. $A\beta$ aggregates and plaques also affect other proteins and physiological processes, which leads to the normal nerve cell protein tau being phosphorylated and starting to aggregate into tangles [4].

The vast majority of all Alzheimer's cases are sporadic, but there is also a rare (less than 1% of all cases) hereditary form called familial AD. The mutations that lead to familial, autosomal dominant, AD are found in the amyloid precursor protein (APP), or in the presenilin 1 and presenilin 2 (PSEN1, PSEN2) genes.

Familial AD usually begins before the age of 65, but old age is otherwise the biggest risk factor for sporadic AD, the risk of falling ill increases significantly after the age of 65. The most important risk gene is apolipoprotein E (APOE), where a variant called APOE $\epsilon 4$ increases the risk up to 10-12 times for homozygotes, and 3-4 times for heterozygotes [5].

The completely dominant explanatory model for how AD arises is the so-called The "amyloid cascade hypothesis" in which a physiologically normal protein in the brain, amyloid- β ($A\beta$), begins to aggregate, which is thought to impair the function of nerve cells, causing them to begin to degenerate (Fig. 1). The cause of the aggregation of $A\beta$ in sporadic AD is not known, but it is probably not the production of $A\beta$ that is increased, but the degradation or excretion of $A\beta$ from the brain (often called "clearance"), which is decreased [6]. Experimental and clinical observations strongly suggest that it is $A\beta$ that initiates the disease process.

Clinical Picture

The clinical criteria for AD dementia include that there should be a cognitive impairment that affects at least two of the following domains: memory, reasoning and handling of complex tasks, visuospatial abilities, language functions, and personality and behavior. There are two main phenotypes of AD: amnesic (which is most common) and non-amnesic. The most obvious symptoms are impaired learning ability and difficulty reproducing newly acquired information, while other cognitive abilities are less affected in the beginning. AD has a long-term course and the deterioration usually takes

place slowly over several years, but the course is highly variable. In the early stages of the disease, mild cognitive impairment (MCI), patients show only mild memory problems, often accompanied by behavioral changes such as depression and lack of initiative, but without the disturbed influence of activities of daily living (ADL). Later, the symptoms progress to “dementia”, which according to the DSM-IV criteria is defined as a memory disorder in combination with aphasia, apraxia, agnosia or impaired executive ability, to such an extent that it affects social or work ability. The investigation of AD often begins in primary care where a basic investigation is performed. This includes a medical history, computerized tomography (CT) scan of the brain (to rule out for example subdural hematoma), brief cognitive tests such as the Mini Mental State Exam (MMSE) to grade the symptoms, and blood tests such as TSH to rule out diseases that may affect cognitive ability. After this, the patient may be referred (if necessary) to a specialized memory clinic, where more advanced diagnostic methods (MRI, PET scan, EEG, CSF analyzes and neuropsychological testing) are most often used.

The clinical picture in AD is variable and often difficult to distinguish from other neurodegenerative diseases, not least early in the course. After a long (several decades) preclinical phase in which the pathology builds up, the disease usually debuts with impaired episodic memory [7], but non-amnesic forms of the disease also occur. As the neurodegenerative process spreads from the medial parts of the temporal lobe over the posterior temporoparietal cortex to the entire cerebral cortex [8], symptoms typically develop in the form of impaired thinking, language disorders, impaired spatial perception, impaired practical ability, and impaired perception.

The diagnostic difficulties are greatest in the late-onset (> 65 years) form of the disease. The reason for this is that most patients not only have amyloid and tau pathology in the brain, but have combinations of Alzheimer's changes together with e.g. Lewy bodies, TDP-43 aggregates, cerebrovascular disease and hippocampal sclerosis [9]. Based on cerebrospinal fluid and PET biomarkers, which can detect Alzheimer's pathology in living patients (see below for more information), the National Institute on Aging and the Alzheimer's Association (NIA-AA) recently presented a new definition of AD, based on identifying the pathology with biomarkers according to the A/T/N classification where A stands for amyloidosis, T stands for tau pathology, and N stands for neurodegeneration [10]. Detection of Alzheimer's pathology is done using biomarkers, while cognitive symptoms are only used to grade the severity of the disease.

CSF Analysis for AD

Cerebrospinal fluid assays for so-called “core AD CSF biomarkers” have been available for clinical diagnosis for several years. These biomarkers follow the so-called A/T/N classification and include A β (A β 42, and the A β 42/40 ratio), phosphorylated tau (P-tau), and “total tau” (T-tau), where the combination lowered A β 42 and the A β 42/40 ratio together with increased T-tau and P-tau are often referred to as the typical 'Alzheimer's profile' [11].

Pathophysiology and cerebrospinal fluid analyses

β -amyloid (A β 42) is the predominant form in the amyloid plaques that form in the brain at AD (6). Decreased A β 42 in cerebrospinal fluid strongly correlates with the degree of binding of amyloid ligands measured by PET technique [12], suggesting that decreased A β 42 in AD is caused by the peptide getting stuck in the plaques in the brain tissue, leading to lower cerebrospinal fluid levels [13]. Consistency with amyloid PET is even better if the A β 42/40 ratio is used instead [14-16], probably because A β 40, which is unchanged at AD [17], normalizes the A β 42 concentration between people with constitutionally low or high total A β production. A plaque-induced relative decrease in A β 42 concentration can thus be detected with greater accuracy [18].

Tau is a neuronal protein localized to axons and the cerebrospinal fluid level of T-tau is seen as a marker of the intensity of neurodegeneration in AD, an interpretation that is mainly based on how the level of T-tau changes in other neurodegenerative diseases. For example, there is a very pronounced increase in Creutzfeldt-Jakob disease, where there is a very rapidly progressing neurodegeneration, but also that T-tau predicts the rate of progression of the disease in different phases of AD. The liquid level of P-tau is linked to the degree of phosphorylation of tau, and thus probably also to the development of tau pathology in AD. Unlike T-tau, P-tau does not change either in acute brain injury or in other diseases with tau pathology, and P-tau therefore appears to be a specific marker for AD. Both T-tau and P-tau concentrations are usually normal in other tauopathies, such as in various forms of frontal lobe dementia and progressive supranuclear paralysis.

A very large number of studies have consistently shown a high diagnostic accuracy of A β 42, T-tau and P-tau in cerebrospinal fluid for AD [17]. This also applies to MCI, where patients seek for memory impairment or in some cases other mild cognitive symptoms. A summary of how well these cerebrospinal fluid tests predict neuropathological diagnosis, based on over 750 individu-

als, showed that A β 42 in cerebrospinal fluid, either alone or in combination with T-tau and P-tau, had a very high concordance with a neuropathological diagnosis of AD, with a ROC AUC value of 0.92 [19]. The cerebrospinal fluid analyzes (low A β 42 together with high T-tau or P-tau) were able to predict which MCI patients had prodromal AD with 95% certainty [20], a finding that could be verified shortly afterwards in several large studies [21-23]. The level of A β 42 begins to decline even before the first symptoms appear [24], while the increase in T-tau and P-tau comes somewhat later in the course of the disease in closer connection with the onset of clinical disease [25]. In addition to massive clinical validation, these CSF analyses have undergone technical developments, from early manual ELISA methods to those currently available on automated instruments, which has resulted in high precision, also between different clinical laboratories [26].

Recently, the Alzheimer's Association has presented recommendations, so-called Appropriate Use Criteria (AUC), for the use of cerebrospinal fluid analyzes (A β 42, T-tau and P-tau) in the clinical investigation and diagnosis of suspected Alzheimer's disease [19]. These recommendations are divided into a number of indications for cerebrospinal fluid analyzes (Table 1) and are intended to guide the clinician and obtain a more consistent and evidence-based use of these diagnostic tests.

Table 1. Clinical indications for appropriate use of lumbar puncture (LP) and cerebrospinal fluid testing in the diagnosis of AD

No.	Indication	Ratings
1	Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD or expressed concern about developing AD	Inappropriate
2	Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history	Inappropriate
3	Patients with SCD (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD	Appropriate
4	Patients with SCD (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD	Inappropriate
5	MCI that is persistent, progressing, and unexplained	Appropriate
6	Patients with symptoms that suggest possible AD	Appropriate
7	MCI or dementia with an onset at an early age (<65)	Appropriate
8	Meeting core clinical criteria for probable AD with typical age of onset	Appropriate
9	Symptoms of REM sleep behavior disorder	Inappropriate
10	Patients whose dominant symptom is a change in behavior (e.g., Capgras Syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where AD diagnosis is being considered	Appropriate
11	Use to determine disease severity in patients having already received a diagnosis of AD	Inappropriate
12	Individuals who are apolipoprotein E (APOE) $\epsilon 4$ carriers with no cognitive impairment	Inappropriate
13	Use of LP in lieu of genotyping for suspected ADAD mutation carriers	Inappropriate
14	ADAD mutation carriers, with or without symptoms	Inappropriate

Abbreviations: AD, Alzheimer’s disease; LP, lumbar puncture; REM, rapid eye movement; SCD, subjective cognitive decline; ADAD, autosomal dominant Alzheimer’s disease; MCI, mild cognitive impairment. (from ref. 19)

Synaptic markers for Alzheimer's Disease

Synapse degeneration is an important component in the development of symptoms in AD [27 - 29]. Synapse proteins, such as the presynaptic SNAP-25 and the dendritic protein neurogranin, are secreted into cerebrospinal fluid [30,31]. The level of neurogranin in cerebrospinal fluid is increased in AD [32]. High neurogranin is seen early in the course of the disease and predicts progression of cognitive symptoms [33]. An interesting and important finding is that increased neurogranin appears to be specific for AD; it is not seen in other neurodegenerative diseases such as frontal lobe dementia or Lewy body dementia [34, 35], which may have a value in differential diagnosis.

Blood tests for Alzheimer's Disease

Analytical advances have made it possible to measure several of the Alzheimer's markers in standard blood samples. Several articles have presented promising results for plasma concentration determination of A β 42 and A β 42 using Single Molecule Array (Simoa) technology [36] and immunoprecipitation combined with mass spectrometry [37, 38], where a lower A β 42/40 ratio showed good agreement with amyloid-PET. The axonal protein neurofilament light (NFL) can also be measured in blood samples with Simoa technology [39], and studies on AD show an increased level of NFL in plasma, as well as a good agreement with NFL concentrations in CSF samples [40]. In this context, however, it should be emphasized that the NFL is a general marker for neurodegeneration and other nerve cell damage regardless of genesis [41]. It is thus not specific to any particular neurodegenerative disease. A future application for plasma NFL could be as a first screening test in the clinical evaluation of patients with suspected cognitive impairment or symptoms of other nerve cell damaging processes. Very promising data have recently been published which show that P-tau in plasma can with great certainty distinguish between AD and other neurodegenerative diseases, as well as demonstrate the amount of tau pathology in the brain in AD [42].

Pharmacological treatment of Alzheimer's Disease

Many types of neurotransmitter abnormalities occur in AD, affecting cholinergic, monoaminergic and glutamatergic systems [43]. Two classes of cognition-enhancing drugs have been approved for use in the disease - cholinesterase inhibitors (AChEI) and N-methyl-d aspartate (NMDA) receptor antagonist - memantine. AChEI reduces the perisynaptic metabolism of acetylcholine and

thus increases the availability of acetylcholine, which in turn improves the postsynaptic stimulation. AChEI includes donepezil, rivastigmine and galantamine. Donepezil and galantamine only inhibit acetylcholinesterase, while rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. AChEI is often combined with memantine, which acts on the glutamatergic system by antagonizing the NMDA receptor and normalizing glutamatergic neurotransmission [44]. Combination therapy with AChEI and memantine is common [45], but a meta-study showed no additive benefits [46]. A majority of patients develop improved cognitive ability after starting treatment [47]. Long-term studies indicate continued benefit of therapy despite cognitive impairment over time, with less impairment observed in treatment groups than in those who did not receive treatment. Recently, a meta-analysis has suggested individualization of AChEI therapy in relation to gender, APOE genotype and age in patients [48]. Discontinuation of therapy is usually determined when the patient has reached a level of deterioration where cognitive-enhancing therapy no longer has a positive impact on quality of life, but exactly how to determine this is debated. A restrictive approach should be taken with regard to anticholinergic drugs, such as urinary spasmolytics, older antihistamines, neuroleptics, certain antiparkinsonian drugs and tricyclic antidepressants.

Importantly drug developments have given immunotherapies, such as the A β antibody aducanumab, for which target engagement in the form of dose-dependent reductions in amyloid PET measures have been demonstrated (PMID: 27582220), which also recently was approved by the FDA (PMID: 34320283). Also other amyloid immunotherapies such as the A β antibody donanemab have been shown to give marked reductions in brain amyloid load (PMID: 33720637). The promise of such disease-modifying drugs further strengthens the need of blood biomarkers for AD for use in primary care screening of patients with memory problems, and for high precision CSF tests for diagnostic use in memory clinics.

Conflicts of Interest

NB is serving as DSMB member for potential drug compound from Green Valley. Leader of the DSMB for potential drug compound from Kirin-Kiowa Company

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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References

- [1] Socialstyrelsen nationella riktlinjer - Alzheimer Sjukdom 2017. <https://roi.socialstyrelsen.se/riktlinjer/nationella-riktlinjer-for-var-d-och-omsorg-vid-demenssjukdom/1>
- [2] Kaj Blennow K, de Leon MJ and Zetterberg H. Alzheimer's Disease, *Lancet* 2006.368:387-403.
- [3] Bogdanovic N. Alzheimer's disease: Towards a multifaceted approach in neuropathological diagnosis (dissertation) Stockholm, Karolinska Institutet, 1998
- [4] Hardy J and Selkoe D. The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. *Science* 2002. 297: 353–56.
- [5] Fratiglioni L et al. In: Denning T, Thomas A, eds. *Oxford textbook of old age psychiatry*, 2nd edn. Oxford: Oxford University Press, 2013. 389–413.
- [6] Masters CL, Bateman R, Blennow K et al. Alzheimer's Disease. *Nature Reviews Disease Primers* 2015. 1:15059.
- [7] Dubois B, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 2014. 13:614–629.
- [8] Braak H, Thal D, Ghebremedhin E et al. Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. *J Neuropathol Exp Neurol* 2011. 70:960–9.
- [9] Kovacs GG, Milenkovic I, Wohrer A, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol*. 2013. 126(3):365-84.

- [10] Jack CR Jr, Bennett DA, Blennow K et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018. 14(4):535-62.
- [11] Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med*. 2018;284(6):643-63
- [12] Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann Neurol*. 2006. 59(3):512-9..
- [13] Andreasen N, Hesse C, Davidsson P et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch Neurol*. 1999. 56(6):673-80.
- [14] Janelidze S, Zetterberg H, Mattsson N et al. CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. *Ann Clin Transl Neurol*. 2016. 3(3):154-65.
- [15] Lewczuk P, Matzen A, Blennow K et al. Cerebrospinal Fluid Abeta42/40 Corresponds Better than Abeta42 to Amyloid PET in Alzheimer's Disease. *J Alzheimers Dis*. 2017. 55(2):813-22.
- [16] Pannee J, Gobom J, Shaw LM et al. Round robin test on quantification of amyloid-beta 1-42 in cerebrospinal fluid by mass spectrometry. *Alzheimers Dement*. 2016. 12(1):55-9
- [17] Olsson B, Lautner R, Andreasson U et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*. 2016;15(7):673-84.
- [18] Lewczuk P, Matzen A, Blennow K et al. Cerebrospinal Fluid Abeta42/40 Corresponds Better than Abeta42 to Amyloid PET in Alzheimer's Disease. *J Alzheimers Dis*. 2017. 55(2):813-22.
- [19] Shaw LM, Arias J, Blennow K, Galasko D, Molinuevo JL, Salloway S, Schindler S, Carrillo MC, Hendrix JA, Ross A, Illes J, Ramus C, Fifer S. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. *Alzheimers Dement* 2018;14(11):1505-1521
- [20] Hansson O, Zetterberg H, Buchhave P et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol*. 2006. 5(3):228-34.
- [21] Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol*. 2009. 8(7):619-27.
- [22] Shaw LM, Vanderstichele H, Knapik-Czajka M et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Annals of Neurology*. 2009. 65(4):403-13.
- [23] Mattsson N, Zetterberg H, Hansson O et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *Jama*. 2009. 302(4):385-93.

- [24] Skoog I, Davidsson P, Aevvarsson O et al. Cerebrospinal fluid beta-amyloid 42 is reduced before the onset of sporadic dementia: a population-based study in 85-year-olds. *Dement Geriatr Cogn Disord*. 2003. 15(3):169-76.
- [25] Stomrud E, Hansson O, Blennow K et al. Cerebrospinal fluid biomarkers predict decline in subjective cognitive function over 3 years in healthy elderly. *Dement Geriatr Cogn Disord*. 2007. 24(2):118-24.
- [26] Bittner T, Zetterberg H, Teunissen CE et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-26.
- [27] DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol*. 1990. 27(5):457-64.
- [28] Blennow K, Bogdanovic N, Alafuzoff I et al. Synaptic pathology in Alzheimer's disease: relation to severity of dementia, but not to senile plaques, neurofibrillary tangles, or the ApoE4 allele. *J Neural Transm*. 1996. 103(5):603-18.
- [29] Sze CI, Troncoso JC, Kawas C et al. J. Loss of the presynaptic vesicle protein synaptophysin in hippocampus correlates with cognitive decline in Alzheimer disease. *Journal of neuropathology and experimental neurology*. 1997. 56(8):933-44.
- [30] Davidsson P, Jahn R, Bergquist J et al. Synaptotagmin, a synaptic vesicle protein, is present in human cerebrospinal fluid: a new biochemical marker for synaptic pathology in Alzheimer disease? *Mol Chem Neuropathol*. 1996. 27(2):195-210.
- [31] Davidsson P, Puchades M, Blennow K. Identification of synaptic vesicle, pre- and post-synaptic proteins in human cerebrospinal fluid using liquid-phase isoelectric focusing. *Electrophoresis*. 1999. 20(3):431-7.
- [32] Thorsell A, Bjerke M, Gobom J et al. Neurogranin in cerebrospinal fluid as a marker of synaptic degeneration in Alzheimer's disease. *Brain research*. 2010. 1362:13-22
- [33] Kvartsberg H, Duits FH, Ingelsson M et al. Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. *Alzheimers Dement*. 2015. 11(10):1180-90.
- [34] Portelius E, Olsson B, Högglund K et al. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology. *Acta Neuropathol*. 2018. 136(3):363-76.
- [35] Wellington H, Paterson RW, Portelius E et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. *Neurology*. 2016. 86(9):829-35.
- [36] Janelidze S, Stomrud E, Palmqvist S et al. Plasma beta-amyloid in Alzheimer's disease and vascular disease. *Sci Rep*. 2016. 6:26801
- [37] Nakamura A, Kaneko N, Villemagne VL et al. High performance plasma amyloid-beta biomarkers for Alzheimer's disease. *Nature*. 2018. 554(7691):249-54
- [38] Ovod V, Ramsey KN, Mawuenyega KG et al. Amyloid beta concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement*. 2017. 13(8):841-9

- [39] Gisslen M, Price RW, Andreasson U et al. Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study. *EBioMedicine*. 2016. 3:135-40.
- [40] Mattsson N, Andreasson U, Zetterberg H et al. Alzheimer's Disease Neuroimaging I. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. *JAMA Neurology*. 2017. 74(5):557-566
- [41] Rohrer JD, Woollacott IO, Dick KM et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. *Neurology*. 2016. 87(13):1329-36.
- [42] Janelidze N, Palmqvist S, Smith R, Beach TG, Serrano G.E, Chai X, Proctor NK, Eichenlaub U, Zetterberg H, Blennow K, Reiman EM, Stomrud E, Dage JL, Hansson O. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nature Medicine*, 2020. 26, 379-386.
- [43] Noetzli, M. & Eap, C. B. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin. Pharmacokinet*. 2013. 52, 225–241.
- [44] Parsons, C. G., Danysz, W., Dekundy, A. et al. Memantine and cholinesterase inhibitors: complementary mechanisms in the treatment of Alzheimer's disease. *Neurotox. Res*. 2013. 24, 358–369.
- [45] Tariot PN, Farlow MR, Grossberg GT et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004. 291, 317–324.
- [46] Tsoi KKF, Chan JYC, Chan FCH, Hirai HW, Kwok TCY and Wong SYS. Monotherapy Is Good Enough for Patients with Mild-to-Moderate Alzheimer's Disease: A Network Meta-analysis of 76 Randomized Controlled Trials. *Clin Pharm Therap* (2019) 105: 121-130.
- [47] Di Santo, S. G., Prinelli, F., Adorni, F et al. A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. *J. Alzheimers Dis*. 2013, 35, 349–361.
- [48] Lane RM and Darreh-Shori, T. Understanding the Beneficial and Detrimental Effects of Donepezil and Rivastigmine to Improve their Therapeutic Value *Journal of Alzheimer's Disease* 44 (2015) 1039–1062.

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BIOMARKERS OF EARLY PARKINSON'S DISEASE

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Summary

Parkinson's disease (PD) is the second most common chronic age-related, progressive neurodegenerative disorders. The hallmark symptoms of PD include motor features (bradykinesia, postural disturbances, rigidity or tremor or both) and non-motor features (hyposmia, sleep disorders, autonomic, neuropsychiatric and sensory symptoms). The diagnosis of PD depends mostly on clinical motor findings (cardinal symptoms) which appear when 60-80% of the substantia nigra (SN) dopamine neurons are lost. PD is, therefore, often diagnosed clinically when disease progression is already advanced. But a long latency between the first damage to dopaminergic cells and the onset of clinical symptoms is known and this is a time where we can do something to stop the disease. Therefore, it is very important to find reliable biomarkers that can distinguish PD in an early phase, to let interventions at the onset of disease and to monitor the progress of therapeutic interventions that may slow or stop the course of the disease. Identifying a successful biomarker depends inevitably on fully understanding the pathophysiology underlying the disease. In this manuscript will be explored the recent advances in PD biomarker research for disease diagnosis and disease surveillance from a variety of clinical, biochemical, genetic and neuroimaging perspectives.

Key words: Parkinson's disease; biomarkers; early phase

Introduction

Parkinson's disease (PD) is the second most common chronic age-related, progressive neurodegenerative disorders. The hallmark symptoms of PD include motor features (bradykinesia, postural disturbances, rigidity, or tremor or both) and nonmotor features (hyposmia, sleep disorders, autonomic, neuropsychiatric, and sensory symptoms). The diagnosis of PD depends mostly on

clinical motor findings (cardinal symptoms) which appear when 60-80% of the substantia nigra (SN) dopamine neurons are lost [1]. Unfortunately, PD is, often diagnosed clinically when disease progression is already advanced. But a long latency between the first damage to dopaminergic cells and the onset of clinical symptoms is known and many studies are trying to find out if the disease can be stopped in that long period. Therefore, it is very important to find reliable biomarkers that can distinguish PD in an early phase. If we will be able to do that, we could try interventions at the onset of disease and monitor the progress of therapeutic interventions. In that way we could find treatment that may slow or stop the course of the disease. In PD, despite remarkable advances in our insight into the responsible mechanisms, the etiology remains unknown. The key neuropathology in PD is Lewy body deposition (abnormal aggregates of a misfolded protein called α -synuclein) and consequently neuronal dysfunction, involving many other brain areas and neurotransmitter systems [1]. In their early research, Brack et al. proposed a staging scheme based on rostral-caudal pathological progression. In their work they suggested that in the earliest stages, PD damage is confined to non-dopaminergic structures in the lower brainstem, the olfactory bulb or perhaps the peripheral autonomic nervous system, accounting for the early appearance of non-motor symptoms [2]. So far, we have only symptomatic treatments existing and used for PD [3].

Clinical diagnosis of PD is challenging (especially in the early stages of the disease), due to high misdiagnosis rate (10-30 % for early stages), as symptoms show fluctuating clinical syndrome over time [4]. In addition, there are numerous overlapping symptoms with other morbidities (e.g., such as essential tremor, multiple system atrophy, and progressive supranuclear palsy). Research in recent years, prompted by epidemiological data on risk factors and prodromal biomarkers, has proposed diagnostic criteria based upon the likelihood of prodromal disease (with 80% certainty) [5]. This has been recently changed especially parts with gut microbiome in patients who have REM sleep behavior disorder (RBD) or Parkinson disease, REM sleep behavior disorder and later genetic and autonomic cohorts, olfactory loss, substantia nigra hyperechogenicity, neurogenic and symptomatic orthostatic hypotension, and age-related penetrance (6). Also, the new biomarkers that were added are: diabetes, global cognitive deficit, physical inactivity, and low plasma urate levels in men [6].

PD biomarkers can be subdivided into four main types: clinical, imaging, biochemical and genetic. It is also important to be aware of potential risk factors like environmental toxins, drugs, pesticides, brain micro trauma, focal cerebrovascular damage, and genomic defects. Recently suggested innovative approaches with combination of prodromal symptoms and imaging or biochemical

biomarkers to identify individuals at high risk of developing motor-PD are very useful especially in very early stages [7]. Some of them combines the presence of mood symptoms and/or RBD with results from smell testing, genotyping, and keyboard-tapping tasks. We hope that this would help us more to identify a population at significant risk of PD or find PD patients in preclinical phase. The new insight in early PD divides it into 3 stages: preclinical, prodromal, and clinical stage [8].

For better PD management it is very important get early diagnosis not only for early treatment and counseling, but to identify a potential population for clinical trials of disease-modifying agents. The development of appropriate biomarkers or combination will help us in getting the early diagnosis, detecting disease progression and the discovery of new treatments for PD.

In this manuscript will be presented and discussed known PD biomarkers for early diagnosis of PD, what includes different clinical, biochemical, genetic and neuroimaging groups of biomarkers.

Clinical biomarkers

Clinical biomarkers are mostly detectable in prodromal and clinical phase. Slight motor signs with possible somnolence are barely noticeable but non-motor symptoms like REM sleep behavior disorder, autonomic dysfunction, olfactory dysfunction, depression are usually prominent in prodromal phase. But, as we know, in preclinical stage the neurodegeneration has started, but symptoms are absent. Diagnosis of preclinical stage consequently requires better biomarkers (for example, cerebrospinal fluid or imaging markers) which will help us find patients in very early stage. We still don't have validated biomarkers for that stage, but we know some risk factors like genetic markers, some environmental factors, some personality features, substantia nigra hyper-echogenicity on ultrasound exam etc. When we recognize these risk factors, we can look for possible neurodegeneration.

We must be aware that in prodromal stage PD patients do not have clinical PD as defined by current diagnostic criteria, but, as studies have shown, clinical symptoms or signs of neurodegeneration are evident. Experts in movement disorders are trained to recognize this early prodromal stage. Clinical stage is defined as the presence of full parkinsonism: progressive bradykinesia plus either rest tremor, rigidity, or both. As we know, bradykinesia has the best correlation with the well-known pathological features of PD (nigrostriatal dopaminergic loss). Existing of cognitive problems or dementia should be looked in the end of prodromal stage due to many markers of prodromal PD are equally predictive of DLB [9].

RBD, olfactory dysfunction, depression, and bowel dysfunction often precede by many years the cardinal motor features of PD. RBD is also associated with a higher risk for development of parkinsonism. In very early stage of PD studies have shown the importance of noticing symptoms like depression, personality traits, and reduced interest in new experiences. Hyposmia is present in over 90% of PD patients and it is also in connection with greater risk for PD [8]. Constipation is also very important factor in prediction of conversion to PD. Beside this prodromal non-motor symptoms, for early diagnosis and prediction are important dopaminergic imaging and subtle motor parkinsonism. The period between the appearance of a marker and conversion to PD is variable, ranging from 5 years for impaired motor performance to >20 years for autonomic symptoms. Some diagnostic tests for prodromal symptoms are cheap like questionnaires and some expensive like some imaging methods.

Biochemical biomarkers

Biochemical biomarkers are very important and usually very easy to get. In relatively noninvasive way, some body fluids and tissues are taken and studied for some important proteins' levels and other molecules specific to the disease. Different biomarkers in blood, saliva, cerebrospinal fluid (CSF) and biopsies are evaluated for years in many investigations. The identification of proteins associated with PD has been improved by advances in genetics. A direct link between α -synuclein (α -Syn) and PD is strongly supported by the discovery that point mutations or multiplications of the gene cause parkinsonism. α -Syn can be detected in PD patient's CSF, saliva, serum, urine, and in the gastrointestinal tract [10] [11]. Beside studies of α -Syn as a biomarker, there are a lot of research with main goal finding a potential of α -synuclein as a therapeutic target. Amyloid- β 1-42, tau protein, neurofilament light chain, uric acid, neuroinflammation markers like β 2-microglobulin, interleukin-1 β and interleukin-8 are also biomarker with high potential but still inconsistent. Several blood and cerebrospinal fluid markers have been tested in clinical PD, but evidence for fluid markers of early stage or prodromal PD is extremely limited. Also, no blood or CSF biomarker has yet reached a sufficient sensitivity or specificity even to be widely accepted as a diagnostic marker of clinical PD. For now, they might be used as risk markers [12].

However, studies investigating markers of α -synuclein in different tissues like skin, gut mucosa, the salivary glands have promising results, but still have not enough strength to be in everyday practice. People with prodromal PD were more likely to exhibit deposition of phosphorylated α -synuclein in different tissues. Nevertheless, more research in future is needed to understand, for ex-

ample, whether gastrointestinal biopsies are helpful in the detection of prodromal PD. The predictive value of pathological markers taken invasively must be clearly established before this method becomes part of routine diagnosis of early prodromal PD [12]. Also, all procedures from collecting biochemical biomarkers to their storage and analyze must be standardized.

Genetic biomarkers

The most often genetic mutations leading to PD are α -syn (SNCA), Parkin, PTEN-induced kinase 1 (PINK1), DJ-1, and Leucine-rich repeat kinase 2 (LRRK2), and account for 2-3% of all cases with classical parkinsonism [13] [14]. GBA (glucocerebrosidase) is present in 5-10% of PD patients, and it is the most important risk factor for PD [15]. Genetic studies helped us to elucidate the pathophysiological mechanism and pathways contributing to clinical diagnosis. Also, they are very important to identify populations at risk. These factors are present in preclinical stage, decades prior to any development of symptoms. It is very important to find that individuals with such "gene positive at-risk" and maybe follow them and study biomarker efficacy in reflecting disorder progression from asymptomatic to end-stage disease. Nevertheless, known proteins associated with disease pathophysiology and connected with genes mutation (DJ-1, parkin, ubiquitin, Apo A1, etc.) are studied and identified as good biomarkers.

Neuroimaging biomarkers

Single photon emission tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI) and transcranial sonography (TCS) allow non-invasive tracking of molecular targets important for PD [16]. MRI and TCS can monitor structural changes in the brain that may suggest increased risk for PD [17]. The importance of that early slight changes on imaging is that they are detectable in risk phase and preclinical phase of PD years before symptoms. Nevertheless, PET and SPECT are reliable in assessing function, getting diagnosis and monitor disease severity and progression. PD is associated with nigral degeneration and striatal dopamine deficiency, so the neuroimaging of the dopamine system is very useful. Transcranial sonography (TCS) can detect a hyperechogenicity in midbrain with good accuracy in PD, even in early preclinical phase of disease. TCS is available, cost-effective method and could be very helpful as a possible imaging biomarker in PD, but its accuracy is very dependent on operator skill and good temporal window [18]. Voxel-based morphometry techniques are used mostly for differentiating between PD and other motor disorders in the early stages [19].

Conclusions

Early PD can now be identified by combining a variety of nonmotor markers, motor measures and biomarker testing. With advancing knowledge on the specificity of markers, value of marker combinations and lead time, the field is very promising. But standardization is very important. The main goal is to find good biomarkers of early phase for investigation neuroprotective treatments. With all extensive investigations and novel technologies we will soon be ready to start those trials with disease modifying treatments. With a focused effort, a future, in which we can modulate progression of PD and possibly even prevent clinical PD, might be possible very soon.

References

- [1] Berg D, Lang AE, Postuma RB, Maetzler W, Deuschl G, Gasser T, Siderowf A, Schapira AH, Oertel W, Obeso JA, Olanow CW, Poewe W, Stern M. Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. *Lancet Neurol*. 2013 May;12(5):514-24.
- [2] Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003 Mar-Apr;24(2):197-211.
- [3] Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA*. 2020;323(6):548–560.
- [4] Adams WR. High-accuracy detection of early Parkinson's Disease using multiple characteristics of finger movement while typing. *PLoS One*. 2017;12(11).
- [5] Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Haliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2015;30(12):1600-1.
- [6] Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB; MDS Task Force on the Definition of Parkinson's Disease. Update of the MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2019;34(10):1464-1470.
- [7] Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al PREDICT-PD: Identifying risk of Parkinson's disease in the community: methods and baseline results *Journal of Neurology, Neurosurgery & Psychiatry* 2014;85:31-37.
- [8] Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nat Rev Neurol*. 2016 Oct 27;12(11):622-634.

- [9] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* 2015 Oct;30(12):1591-601.
- [10] N. Malek, D. Swallow, K.A. Grosset, O. Anichtchik, M. Spillantini, D.G. Grosset, Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease - a systematic review, *Acta Neurol. Scand* 2014;130:59e72.
- [11] B. Mollenhauer, O.M. El-Agnaf, K. Marcus, C. Trenkwalder, M.G. Schlossmacher, Quantification of alpha-synuclein in cerebrospinal fluid as a biomarker candidate: review of the literature and considerations for future studies, *Biomark. Med.* 4 (2010) 683e699.
- [12] Delenclos M, Jones DR, McLean PJ, Uitti RJ. Biomarkers in Parkinson's disease: Advances and strategies. *Parkinsonism Relat Disord.* 2016 Jan;22 Suppl 1(Suppl 1):S106-10.
- [13] Klein, M.G. Schlossmacher, Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder, *Neurology* 2007;69: e2093-e2104.
- [14] H. Houlden, A.B. Singleton, The genetics and neuropathology of Parkinson's disease, *Acta Neuropathol* 2012;124:e325-e338.
- [15] M. Beavan, A. McNeill, C. Proukakis, D.A. Hughes, A. Mehta, A.H. Schapira, Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort, *JAMA Neurol* 2015;72: e201e208.
- [16] N. Pavese, D.J. Brooks, Imaging neurodegeneration in Parkinson's disease, *Biochim. Biophys. Acta* 2009;1792:e722-e729.
- [17] D. Berg, S. Behnke, K. Seppi, J. Godau, S. Lerche, P. Mahlke, et al., Enlarged hyperchogenic substantia nigra as a risk marker for Parkinson's disease, *Mov. Disord* 2013;28:e216-e219.
- [18] Poewe W, Mahlke P. Combined assessment of midbrain hyperchogenicity, hypsmia and motor asymmetry improves diagnostic accuracy in early Parkinson's disease. *Expert Rev Neurother.* 2012; 12:911-4.
- [19] Shao N, Yang J, Li J, Shang HF, Ross GW, Poewe W. Voxelwise meta-analysis of gray matter anomalies in progressive supranuclear palsy and Parkinson's disease using anatomic likelihood estimation. *Front Hum Neurosci.* 2014; 8:63.

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WHAT CAN WE LEARN FROM THE NEUROPATHOLOGICAL STUDY OF PRECLINICAL AND EARLY NEURODEGENERATIVE DISEASES?

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Summary

Understanding patterns of neuropathological progression in neurodegenerative diseases is of paramount importance with implications on our understanding how such diseases evolve clinically. As a consequence, such knowledge can contribute to establishing appropriate biomarkers allowing early clinical diagnosis and ultimately early therapeutical interventions.

In the past over nearly three decades, it has become clear that from the earliest disease stages neuropathological progression takes place in an anatomically stereotypical manner. As a general rule neuropathology is thought to start in well-defined, circumscribed anatomical areas of the central nervous system from where it progresses in a predictable manner to additional cerebral regions via pre-existing neural networks.

The significant body of data that is relevant for understanding disease progression has essentially emerged by studying large cohorts of preclinical cases with early pathological changes, together with cases with intermediate level of clinical presentation and neuropathological changes and also end-stage cases with fully developed clinical presentation and neuropathology. The best studied examples include Alzheimer's disease (AD) and Parkinson's disease (PD). In the former both the amyloid- ($A\beta$) and tau (neurofibrillary tangle) pathologies while in the second the Lewy (-synuclein) pathology have been shown to progress in anatomically determined, stereotypical manner in distinct stages.

In this chapter, patterns of progression of a number of neurodegenerative diseases is briefly discussed, including AD, Parkinson's disease PD, corticobasal

degeneration (CBD) and progressive supranuclear palsy (PSP). It is emphasised that understanding the neuropathological changes which characterise the early disease phases including the preclinical stage of diseases, is of paramount significance as this information help also to understand clinical progression.

Key words: CBD, neuropathology studies, early phase of neurodegenerative diseases

Introduction to understanding aspects of neurodegeneration

Neurodegenerative diseases represent a major group of neurological conditions, characterised by relentless clinical progression, which is closely associated with a gradual topographical expansion and an increase in the severity of the underlying pathological changes affecting distinct groups of neurons, neuronal networks. Some of the conditions in this group, such as AD and PD, are of paramount public health importance while others, such as frontotemporal dementia (FTD), motor neuron disease/amyotrophic lateral sclerosis (MND/ALS), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and Huntington's disease (HD), although have significantly lower general population prevalence rates, are relatively frequently seen in specialist clinics.

The neurodegenerative diseases which are in the focus of this chapter are characterised by misfolding, abnormal aggregation and accumulation of specific diseaseproteins, hence they belong to the wider group of proteinopathies or proteopathies [29]. Although the initial trigger of the pathological process that leads to protein aggregation is not fully understood, several genetic mechanisms and post-translational modifications of disease proteins have been shown to be able to destabilise the normal secondary structure of proteins [24].

In the majority of neurodegenerative conditions one of four disease proteins form intracellular or extracellular inclusions/deposits, while in AD two pathological proteins deposit. 1.) The A β peptide, which is the main component of the extracellular senile/neuritic plaques and the vascular amyloid of cerebral amyloid angiopathy also seen in the majority of AD cases [10]. 2.) The microtubule-associated protein, tau, which forms the filaments of the neurofibrillary tangles (NFTs) in AD and other tauopathies. Tau is also the disease protein of other neuronal inclusion types such as the Pick bodies and astrocytic as well as oligodendroglial inclusions in the different tauopathies [26]. 3.) The α -synuclein protein, which is the major component of the neuronal Lewy bodies in PD as well as dementia with Lewy bodies (DLB) and the glial (oligodendroglial) cytoplasmic inclusions in multiple system atrophy [27] and finally 4.) the TAR DNA-binding protein, 43kDa (TDP43), which is the major disease protein composing

intraneuronal inclusions in a significant proportion of frontotemporal lobar degenerations and in the majority of sporadic MND/ALS [21, 22].

Understanding the neuropathological changes underlying preclinical and early disease stages is a precondition to early clinical diagnosis

Relentless clinical deterioration is a hallmark feature of neurodegenerative diseases, which is determined by a continuous anatomical progression of the underlying pathology specific for a given disease. Since the early 1990s, the patterns of neuropathological progression of a number of neurodegenerative diseases have been studied and clarified. These include AD [2, 3], PD [4], argyrophilic grain disease [25], MND/ALS [7], behavioural variant of FTD [6], Pick's disease [14], PSP [18, 30] and CBD [19, 20]. These studies provided evidence that neurodegenerative diseases are not static, but dynamic, constantly evolving conditions also implicating that pathology appears in clinically asymptomatic individuals (preclinical phase) and that after the preclinical phase, due to progression of the underlying pathology, patients enter initially into a phase characterised by mild clinical symptoms/signs and finally into a phase with full blown clinical picture [5, 15, 20]. Working with this hypothesis, neuropathological studies of some of the conditions led to the identification of the groups of neurons and neuronal networks that are first affected by a given neurodegenerative disease process and also the structures which are affected in subsequent disease stages. In the following section the early neuropathological changes in AD, PD, PSP and CBD will be briefly discussed (Table 1).

Table 1. Representative areas affected in different stages of disease progression in four neurodegenerative diseases

Neuropathological stage	Alzheimer's disease pathologies		Parkinson's disease (α-synuclein pathology)[1]	Corticobasal degeneration (tau pathology)[20]	Progressive supranuclear palsy (neurofibrillary tau pathology)[18]
	Tau (neurofibrillary tangles)[2]	Aβ (plaques)[28]			
1*	Pontine structures Transentorhinal cortex	Neocortex	Dorsal IX/X motor nucleus and/or intermediate reticular zone	Basal ganglia circuitry (mainly astroglial)	Globus pallidus, subthalamic nucleus, substantia nigra
2*	Entorhinal region Hippocampus	Hippocampus	Raphe nuclei, gigantocellular reticular nucleus, coeruleus—subcoeruleus complex	Dorsolateral prefrontal cortex	Midbrain tegmentum, medulla oblongata, pontine base
3*	Fusiform and lingual gyri	Diencephalon	Pars compacta of the substantia nigra	Posterior cortex	Amygdala, striatum, dentate nucleus
4*	Neocortical association areas	Brainstem	Temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus)	?	Frontal lobe
5*	Extensive neocortical involvement (including the peristriate cortex)	Cerebellum	High order sensory association areas of the neocortex and prefrontal neocortex	?	Parietal lobe, temporal lobe
6*	Secondary and primary neocortical areas (including primary visual cortex)		First order sensory association areas of the neocortex and premotor areas.	?	Occipital lobe

Rows marked 'yellow' signifies preclinical pathology. Although, this has not been determined in progressive supranuclear palsy, it is likely that stages 1 and 2 represent preclinical stages

- Neurofibrillary tangle (tau) stages in Alzheimer's disease are indicated with Roman numbers (I-VI)

By investigating large cohorts of preclinical cases and cases with full-blown disease, the pioneering and highly influential studies by Heiko Braak and his colleagues demonstrated patterns of disease progression in the two, most common neurodegenerative diseases AD [2, 3, 28] and PD [4]. Their initial study of AD suggested that the neurofibrillary tangle/tau pathology starts in anterior mesial temporal lobe structures from where it progresses stereotypically in a predictable manner, which they divided into six distinct stages (Braak stages) [2, 3]. A more recent revision of the scheme indicates that tau deposition is likely to start in brainstem neurons with diffuse projections to the cerebral cortical areas. This initial tau deposition is followed by a caudorostral progression leading to involvement of anterior mesial temporal lobe structures in Braak neurofibrillary tangle pathology stages I and II (transentorhinal and entorhinal cortices, hippocampal formation), followed by involvement of basal temporal cortical (fusiform gyrus), insular and basal frontal areas (Braak stages III and IV) and finally neocortical areas such as the prefrontal cortex as well as the high-order sensory association neocortex in Braak stages V and the premotor and primary motor areas as well as sensory first-order association areas and primary fields in Braak stage VI [2, 5]. In contrast to the tau pathology, progression of the A β pathology takes place in a rostro-caudal direction as described by the so-called Thal phases [28]. Accordingly, A β deposition starts in the neocortex followed by involvement of structures such as the hippocampus and parahippocampal gyrus in Thal phase 2, the diencephalon in

Thal phase 3, the brainstem in Thal phase 4 and finally the cerebellum in Thal phase 5 [28].

Progression of the Lewy pathology In PD also shows a stereotypic, anatomical progression pattern with the Lewy pathology appearing in the nuclei of the IX/Xth cranial nerves and the intermediate reticular zone of the medulla and also in the olfactory bulb in clinically asymptomatic individuals years before clinical disease onset [4] (Braak Lewy body stage 1). From here the Lewy/a-synuclein pathology shows a caudorostral propagation with pontine structures, including the locus coeruleus-subcoeruleus complex being affected in Braak stage 2. The pars compacta of the substantia nigra and magnocellular nuclei of the basal forebrain become involved in Braak stage 3, the anteromedial temporal mesocortex (transentorhinal cortex) and allocortex (CA2-plexus) in Braak stage 4, and finally Lewy pathology appears in neocortical areas in Braak stages 5 and 6 [4]. Compared to cases with clinically manifest PD, the Lewy pathology is variable in incidental Lewy body cases (preclinical PD). The Lewy pathology may correspond to Braak stages 1, 2 or 3 (without significant loss of pars compacta dopaminergic neurons) or it may be similar to, but less severe than that seen in PD cases [1, 4, 9].

Data regarding disease progression in PSP are rather scant. In 2007 our research group published a study, in which we applied a scoring system for the assessment of the tau pathology in cases with typical PSP (PSP-Richardson syndrome or PSP-RS) or PSP-parkinsonism (PSP-P). The scoring system we developed, took into consideration the severity and anatomical distribution of the PSP tau pathology [30]. Our study [30] and a recent one [18], have found evidence that tau pathology initially is likely to appear in basal ganglia structures from where it propagates towards the neocortex on one hand and towards brainstem structures and cerebellum on the other.

In two recent studies our research group has demonstrated that in clinically asymptomatic individuals, basal ganglia structures are affected initially by tau pathology in CBD from where, via corticostriatal networks, it propagates towards the dorsolateral prefrontal cortex [19, 20] and, with further disease progression with an anterior-posterior gradient of the tau pathological changes to more posterior frontal and ultimately to other cortical areas and also towards the brainstem. We also showed that in the earliest phases of the CBD disease process in clinically asymptomatic individuals, the astrocytic tau pathology is predominant with neuronal tau pathology becoming more apparent in cases with advanced disease [19, 20]. A scientific commentary was commissioned by the Editor of Brain [17] to accompany our publication, which emphasised the significance of identifying structures affected in preclinical CBD as this information may become helpful for the diagnosis of early CBD by *in vivo* tau imaging.

It is a major research goal that the mechanisms of clinical and pathological disease progression are clarified. In recent years, a significant body of data have emerged from both experimental investigations and human studies indicating that major disease proteins including tau, -synuclein and A β mimic the behaviour of disease-associated prion protein [8, 12, 16]. This would indicate that disease proteins can show 1.) self-amplification via the process of 'permissive templating' [13], 2.) a propensity for cell-to-cell propagation explaining disease spread [12] and 3.) an ability to form different protein conformers, 'strains' which are responsible for the different disease types such as e.g. PSP or CBD within the larger group of tauopathies [11] or for PD and MSA within -synucleinopathies [23].

Conclusions

In this brief chapter I wished to emphasise that several neurodegenerative diseases have been shown to have an often lengthy, preclinical phase, associated with early stages of neuropathological changes. Understanding the neuropathological changes characterising such preclinical stages is of paramount impor-

tance as this information may facilitate the design of appropriate biomarkers and application of refined imaging techniques to aid the clinicians to make an early diagnosis. The knowledge thus obtained may also help early application of appropriate disease -modifying therapeutical approaches once they have become available.

References

- [1] Arizona Parkinson's Disease Consortium, Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White CL III, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG (2010) Multiorgan distribution of phosphorylated α -synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathol* 119:689–702.
- [2] Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol* 112:389–404.
- [3] Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 82:239–259.
- [4] Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *NBA* 24:197–211.
- [5] Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol* 70:960–969.
- [6] Brettschneider J, Del Tredici K, Irwin DJ, Grossman M, Robinson JL, Toledo JB, Fang L, Van Deerlin VM, Ludolph AC, Lee VMY, Braak H, Trojanowski JQ (2014) Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). *Acta Neuropathol* 127:423–439.
- [7] Brettschneider J, Del Tredici K, Toledo JB, Robinson JL, Irwin DJ, Grossman M, Suh E, Van Deerlin VM, Wood EM, Baek Y, Kwong L, Lee EB, Elman L, McCluskey L, Fang L, Feldengut S, Ludolph AC, Lee VMY, Braak H, Trojanowski JQ (2013) Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Ann Neurol* 74:20–38.
- [8] Brundin P, Li J-Y, Holton JL, Lindvall O, Revesz T (2008) Research in motion: the enigma of Parkinson's disease pathology spread. *Nat Rev Neurosci* 9:741–745.
- [9] Dickson DW, Fujishiro H, DelleDonne A, Menke J, Ahmed Z, Klos KJ, Josephs KA, Frigiero R, Burnett M, Parisi JE, Ahlskog JE (2008) Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. *Acta Neuropathol* 115:437–444.
- [10] Glenner GG, Wong CW (1984) Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochem Biophys Res Commun* 122:1131–1135.

- [11] Goedert M, Eisenberg DS, Crowther RA (2017) Propagation of Tau Aggregates and Neurodegeneration. *Annu Rev Neurosci* 40:189–210.
- [12] Guo JL, Lee VMY (2014) Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. *Nat Med* 20:130–138.
- [13] Hardy J (2005) Expression of normal sequence pathogenic proteins for neurodegenerative disease contributes to disease risk: “permissive templating” as a general mechanism underlying neurodegeneration. *Biochem Soc Trans* 33:578–581.
- [14] Irwin DJ, Brettschneider J, McMillan CT, Cooper F, Olm C, Arnold SE, Van Deerlin VM, Seeley WW, Miller BL, Lee EB, Lee VMY, Grossman M, Trojanowski JQ (2015) Deep clinical and neuropathological phenotyping of Pick disease. *Ann Neurol* 79:272–287.
- [15] Jack CR Jr (2012) Alzheimer Disease: New Concepts on Its Neurobiology and the Clinical Role Imaging Will Play. *Radiology* 263:344–361.
- [16] Jaunmuktane Z, Brandner S (2020) Invited Review: The role of prion-like mechanisms in neurodegenerative diseases. *Neuropathol Appl Neurobiol* 146:1388–24.
- [17] Kobyliński C, Mann DM (2016) Presymptomatic anterior frontal involvement in corticobasal degeneration. *Brain* 139:3059–3062.
- [18] Kovács GG, Lukic MJ, Irwin DJ, Arzberger T, Respondek G, Lee EB, Coughlin D, Giese A, Grossman M, Kurz C, McMillan CT, Gelpi E, Compta Y, van Swieten JC, Laats LD, Troakes C, Al-Sarraj S, Robinson JL, Roeber S, Xie SX, Lee VMY, Trojanowski JQ, Höglinger GU (2020) Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta Neuropathol* 1–21.
- [19] Ling H, Gelpi E, Davey K, Jaunmuktane Z, Mok KY, Jabbari E, Simone R, R'Bibo L, Brandner S, Ellis MJ, Attems J, Mann D, Halliday GM, Al-Sarraj S, Hedreen J, Ironside JW, Kovács GG, Kovari E, Love S, Vonsattel JPG, Allinson KSJ, Hansen D, Bradshaw T, SetóSalvia N, Wray S, de Silva R, Morris HR, Warner TT, Hardy J, Holton JL, Revesz T (2020) Fulminant corticobasal degeneration: a distinct variant with predominant neuronal tau aggregates. *Acta Neuropathol* 139:717–734.
- [20] Ling H, Kovács GG, Vonsattel JPG, Davey K, Mok KY, Hardy J, Morris HR, Warner TT, Holton JL, Revesz T (2016) Astroglial pathology predominates the earliest stage of corticobasal degeneration pathology. *Brain* 139:3237–3252.
- [21] Neumann M, Mackenzie IRA (2018) Neuropathology of non-tau frontotemporal lobar degeneration. *Neuropathol Appl Neurobiol* 1–46.
- [22] Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretschmar HA, Trojanowski JQ, Lee VMY (2006) Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. *Science* 314:130–133.
- [23] Peng C, Gathagan RJ, Covell DJ, Medellin C, Stieber A, Robinson JL, Zhang B, Pitkin RM, Olufemi MF, Luk KC, Trojanowski JQ, Lee VMY (2018) Cellular milieu imparts distinct pathological α -synuclein strains in α -synucleinopathies. *Nature* 557:558–563.

- [24] Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, Ghiso J (2009) Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. *Acta Neuropathol* 118:115–130.
- [25] Saito Y, Ruberu NN, Sawabe M, Arai T, Tanaka N, Kakuta Y, Yamanouchi H, Murayama S (2004) Staging of argyrophilic grains: an age-associated tauopathy. *J Neuropathol Exp Neurol* 63:911–918.
- [26] Spillantini MG, Goedert M (2013) Tau pathology and neurodegeneration. *The Lancet Neurology* 12:609–622.
- [27] Spillantini MG, Goedert M (2018) Neurodegeneration and the ordered assembly of α s7nuclein. *Cell Tissue Res* 373:137–148.
- [28] Thal DR, Rüb U, Orantes M, Braak H (2002) Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 58:1791–1800.
- [29] Walker LC, LeVine H (2012) Corruption and Spread of Pathogenic Proteins in Neurodegenerative Diseases. *J Biol Chem* 287:33109–33115.
- [30] Williams DR, Holton JL, Strand C, Pittman A, de Silva R, Lees AJ, Revesz T (2007) Pathological tau burden and distribution distinguishes progressive supranuclear palsy/parkinsonism from Richardson’s syndrome. *Brain* 130:1566–1576.

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METABOLIC BRAIN IMAGING AS A BIOMARKER OF AN EARLY STAGE OF NEURODEGENERATIVE DISEASES

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Summary

The common neurodegenerative brain diseases have a long and slowly progressive course. Although the diagnosis of dementia and parkinsonisms can be made when the typical clinical presentation develops, pathophysiological processes begin many years earlier. The concepts of a presymptomatic or preclinical and prodromal disease stages are becoming widely accepted in search for the effective causative treatments for neurodegenerative diseases, which is a major unmet need in neurodegenerative brain diseases. One of the possible explanations for many failed trials in search for neuroprotective treatment is that trials were conducted in patients in whom clinical picture was already developed and the neurodegenerative process in brain very pronounced and widespread. The focus of scientists' attention has therefore shifted towards earliest phases of diseases, its detection and course. It is now already possible to identify the neurodegenerative diseases at their "silent" preclinical stages even before the occurrence of the first clinical symptoms. Various imaging and fluid biomarkers are being developed for the detection of preclinical neurodegenerative brain disease stages. Metabolic brain imaging with ¹⁸F-fluorodeoxyglucose and positron emission tomography (2-[¹⁸F]FDG PET) is one of them as it can detect the metabolic brain abnormalities caused by the earliest stages of neuronal dysfunction and neurodegeneration. Besides early disease detection, 2-[¹⁸F]FDG PET brain imaging can be helpful in differential diagnosis and for monitoring the disease progression.

Key words: neurodegeneration, Alzheimer's disease, Parkinson's disease, prodromal, preclinical, metabolic brain imaging, ¹⁸F-fluorodeoxyglucose and positron emission tomography (2-[¹⁸F]FDG PET)

Introduction

Recognizing and understanding early stages of neurodegenerative diseases is of exceptional scientific interest. Neuronal dysfunction and abnormal protein depositions are already detectable in asymptomatic subjects who are developing neurodegenerative brain diseases [1] like Alzheimer's and Parkinson's disease, which are the most common ones and nowadays affect 55 million people worldwide. Preclinical research may provide a powerful tool to study the potential therapeutic and neuroprotective compounds [2], as finding a neuroprotective and neuromodulative medication poses a major unmet need in the field of managing patients with neurodegenerative brain diseases.

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by accumulation of misfolded proteins amyloid β_{42} and tau in the brain [3]. Dementia due to AD represents between 50 and 70% of all dementia cases [4]. It is now generally believed that AD pathological processes start several years prior to the appearance of first symptoms. Firstly, we can observe the accumulation of amyloid β_{42} which can be detected with amyloid PET imaging or as a decreased level of amyloid β_{42} concentration in the cerebrospinal fluid (CSF) analysis. According to modified amyloid cascade hypothesis [3], accumulation of amyloid β_{42} leads to the spread of tau protein beyond medial temporal lobe, seen first as elevated level of phosphorylated tau protein in the CSF and followed by tau PET positivity [5]. The next step is synaptic dysfunction as shown by 2- ^{18}F]FDG PET and finally hippocampal atrophy and increased level of total tau protein in the CSF, followed by cognitive decline [6]. As disease progresses, structural atrophy and pathological protein depositions spread [7] and first clinical symptoms become apparent, ie. impairment in one or more cognitive domains, but typically memory. Patients diagnosed with mild cognitive impairment (MCI) have 5–10% annual conversion rate to dementia, however some of them remain at MCI stage (8) or reverse to normal cognitive state. It would be of great clinical and research importance to find a biomarker with reliable predictive value for conversion from MCI to dementia.

Brain imaging studies in Alzheimer's disease

Structural imaging with MRI has an important role in distinguishing between AD and vascular dementia [9] and furthermore, it can show hippocampal atrophy early in the disease course [6]. In the recent years advancement in radi-

otracers brought several new tracers that can offer new insight in AD pathology. Tracers binding to amyloid plaques can show amyloid β depositions and thus offer *in vivo* evidence of AD pathology. Although amyloid PET binding is not correlated to scores of clinical disability [10], it has an important role especially in patients with an unclear diagnosis [11]. New tracers that bind to tau protein offer a promising alternative that seems more closely correlated with the clinic, although they are still under development and not yet used in routine clinical practice [5]. 2- ^{18}F FDG PET brain imaging is well-established and widely accessible method and it can reveal synaptic dysfunction which antecedes structural atrophy in AD [12]. Novel statistical approaches can further improve 2- ^{18}F FDG PET usefulness in clinical practice. 2- ^{18}F FDG PET brain imaging can be used together with network analysis to identify specific metabolic patterns. The network analysis called scaled subprofile model, which is based on principal component analysis (SSM/PCA) is a type of multivariate network analysis [13]. With this method various specific disease-related metabolic patterns were identified from 2- ^{18}F FDG PET images of patients and healthy controls [14-19]. Additionally, with the use of topographic profile rating (TPR) algorithm the expressions of specific metabolic patterns can be measured from 2- ^{18}F FDG PET images in individual subjects and prospectively [13].

Alzheimer's disease-related pattern (ADRP) has been thus far identified in few different clinical cohorts [15,20,21]. Our group recently identified ADRP for the first time in a cohort of demented patients with pathologically (low amyloid in CSF) confirmed diagnosis of AD [22]. ADRP was characterized by relative hypometabolism in parietal association cortices, temporal cortices and precuneus and relative hypermetabolism in cerebellum (Figure 1).

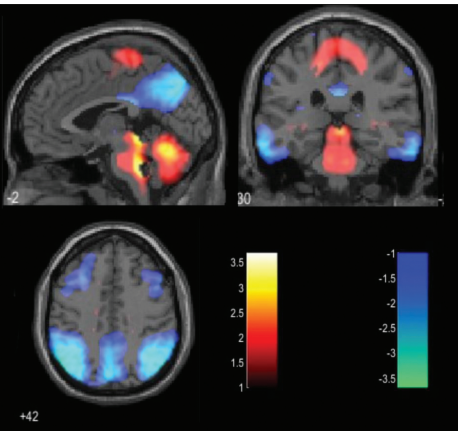


Figure 1. Alzheimer’s disease-related pattern (ADRP) identified by network analysis of 2-[¹⁸F]FDG PET scans from 20 AD patients and 20 age matched normal controls. Relative metabolic decreases are represented by voxels with negative region weights and are color-coded blue, whereas associated metabolic increases are represented by voxels with positive region weights and are color-coded red.

ADRP expression was validated in an independent cohorts of AD and cognitively normal control (NC) subjects (Figure 2).

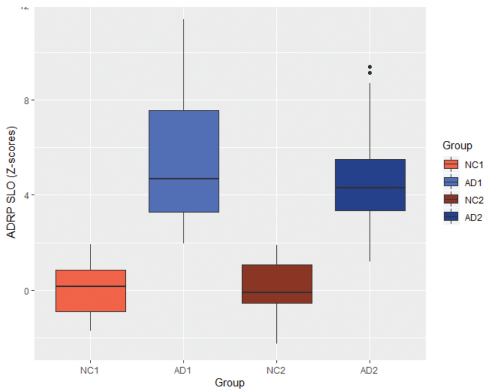


Figure 2. Expression of Alzheimer’s disease related pattern in identification and validation cohort. Pattern identification cohort was comprised of 20 normal controls (NC1) and 20 patients with Alzheimer’s dementia and confirmed Alzheimer’s pathology in the cerebrospinal fluid (AD1). Pattern validation cohort was comprised of 21 NC (NC2) and 43 patients with AD and confirmed AD pathology in cerebrospinal fluid (AD2). The boxplots represent median and interquartile range.

Further, we studied the expression of ADRP in MCI patients. We found that, ADRP expression was significantly higher in patients with MCI and AD CSF profile in comparison to patients with MCI and normal CSF profile (Figure 3). Furthermore, it was already shown that ADRP can enable accurate prediction of conversion from MCI to AD [23]. ADRP is therefore a promising metabolic biomarker for disease diagnosis and prediction of prognosis.

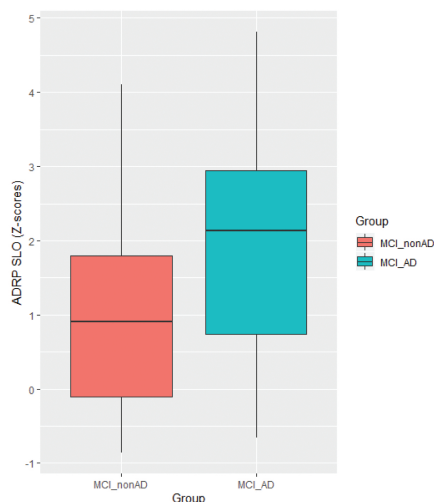


Figure 3. Expression of Alzheimer's disease related pattern (ADRP) in 19 patients with mild cognitive impairment and normal cerebrospinal fluid (MCI_nonAD) and 23 patients with MCI and Alzheimer's pathology in CSF (MCI_AD). ADRP expression was significantly higher in MCI_AD group ($p = 0.02$, two-sided). The boxplots represent median and interquartile range.

Parkinson's disease

PD is the most common movement disorder and represents the second most common degenerative disease of the central nervous system [24] after AD. Degeneration of nigrostriatal dopaminergic neurons, which results in disruption of basal ganglia–thalamo–cortical loops, underlies the classical motor signs and symptoms of PD (i.e., bradykinesia, rigidity, tremor and postural instability). The typical motor PD signs may be preceded by a period that lasts several years to decades, in which neurodegeneration has yet started and spreads throughout the nervous system. In this period various non-motor symptoms often present. Constipation was early identified as a risk factor of PD [25][26] and similarly hyposmia [27] and REM-sleep behavior disorder (RBD) [28][29]. There is however still a lack

of studies to give a more precise idea on the risk of PD in individuals with prodromal [24] symptoms. We need to be aware that prodromal PD is not benign. At PD diagnosis, many patients already have had symptoms of anxiety, apathy, autonomic dysfunction, and motor deficits for several years [2] [30]. Various non-motor as well as motor symptoms are therefore recognized in premotor PD [31] [32]

Brain imaging studies in Parkinson's disease

Structural and functional brain imaging plays a crucial role in clinical diagnostics and research of PD and other basal ganglia disorders. Dopamine transporter (DAT) imaging has been widely available to reveal presynaptic dopaminergic dysfunction [33]. Significant DAT changes may precede the onset of clinical symptoms [34]. Substantia nigra hyperechogenicity detected with transcranial sonography has also been shown to predict onset of PD, and is already included in PD prodromal criteria [35][36]. Meta-iodobenzylguanidine (MIBG) cardiac scintigraphy allows visualisation and quantitative assessment of adrenergic neuronal function of the heart and is a useful tool for the differential diagnosis of neurodegenerative disease [37]. It has also been shown that reduced cardiac MIBG uptake is present in prodromal PD [2] [38].

Metabolic brain imaging represents another valuable tool to improve our understanding of basic molecular mechanisms and pathophysiological processes underlying parkinsonian disorders [39]. As mentioned above 2-[¹⁸F]FDG PET brain imaging can be used with network analysis to identify specific metabolic patterns.

Parkinson's disease related pattern (PDRP) is a specific PD associated metabolic brain pattern, which has been shown to differentiate PD patients from healthy controls and from atypical parkinsonian patients. It is also present in patients with REM sleep behavior disorder [40] [41] [42], which is believed to be the most reliable prodromal PD condition. Furthermore, metabolic brain imaging is an excellent tool to study cognitive changes in PD [43]. A network analysis applied on the 2-[¹⁸F]FDG PET brain was used to identify PD-related cognitive pattern (PDCP). It has been shown that the PDCP expression correlates with patients' cognitive scores [44].

Conclusion

Modern neuroimaging in conjunction with computational algorithms based on metabolic brain pattern recognition are now commonly used in clinical practice and in research. Specific metabolic brain patterns, which are derived from 2-[¹⁸F]FDG PET images are repeatedly proving to be a reliable biomarker of various neurodegenerative brain syndromes.

References

- [1] Katsuno M, Sahashi K, Iguchi Y, Hashizume A. Preclinical progression of neurodegenerative diseases. *Nagoya J Med Sci.* 2018;80(3):289–98.
- [2] Postuma RB, Berg D. Prodromal Parkinson's Disease: The Decade Past, the Decade to Come. *Mov Disord.* 2019;34(5):665–75.
- [3] Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement [Internet].* 2018;14(4):535–62. Available from: <https://doi.org/10.1016/j.jalz.2018.02.018>
- [4] Qiu C, Kivipelto M, Von Strauss E. Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci.* 2009;11(2):111–28.
- [5] Leuzy A, Chiotis K, Lemoine L, Gillberg P-G, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies—still a challenge. *Mol Psychiatry [Internet].* 2019 Aug 11;24(8):1112–34. Available from: <http://www.nature.com/articles/s41380-018-0342-8>
- [6] Dumba M, Khan S, Patel N, Perry L, Malhotra P, Perry R, et al. Clinical 18 F-FDG and amyloid brain positron emission tomography/CT in the investigation of cognitive impairment: where are we now? *Br J Radiol [Internet].* 2019 Sep;92(1101):20181027. Available from: <https://www.birpublications.org/doi/10.1259/bjr.20181027>
- [7] Kovacs GG. Current Concepts of Neurodegenerative Diseases. *EMJ Neurol.* 2014;1(July):78–86.
- [8] Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand [Internet].* 2009 Apr;119(4):252–65. Available from: <http://doi.wiley.com/10.1111/j.1600-0447.2008.01326.x>
- [9] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology [Internet].* 1993 Feb 1;43(2):250–250. Available from: <http://www.neurology.org/cgi/doi/10.1212/WNL.43.2.250>
- [10] Regional β -amyloid burden does not correlate with cognitive or language deficits in Alzheimer's disease presenting as aphasia. *Eur J Neurol [Internet].* 2016 Feb;23(2):313–9. Available from: <http://doi.wiley.com/10.1111/ene.12761>
- [11] Leuzy A, Savitcheva I, Chiotis K, Lilja J, Andersen P, Bogdanovic N, et al. Clinical impact of [18F]flutemetamol PET among memory clinic patients with an unclear diagnosis. *Eur J Nucl Med Mol Imaging [Internet].* 2019 Mar 26; Available from: http://link.springer.com/article/10.1007/s00259-019-04297-5?utm_source=researcher_app&utm_medium=referral&utm_campaign=MKEF_USG_Researcher_inbound
- [12] Chételat G, Desgranges B, Landeau B, Mézange F, Poline JB, De La Sayette V, et al. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. *Brain.* 2008;131(1):60–71.

- [13] Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: Methodological issues. *Neuroimage* [Internet]. 2011 Feb;54(4):2899–914. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1053811910013170>
- [14] Teune LK, Strijkerk F, Renken R, Izaks G, de Vries J, Segbers M, Roerdink J, Dierckx R, Leenders KTA disease-related glucose metabolic brain pattern. *CAR* (2014) 11:725–32. Alzheimer's disease-related glucose metabolic brain pattern. *Curr Alzheimer Res*. 2014;11(8):725–32.
- [15] Mattis PJ, Niethammer M, Sako W, Tang CC, Nazem A, Gordon ML, et al. Distinct brain networks underlie cognitive dysfunction in Parkinson and Alzheimer diseases. *Neurology*. 2016;87(18):1925–33.
- [16] Scarmeas N, Habeck CG, Zarahn E, Anderson KE, Park A, Hilton J, et al. Covariance PET patterns in early Alzheimer's disease and subjects with cognitive impairment but no dementia: utility in group discrimination and correlations with functional performance. *Neuroimage* [Internet]. 2004 Sep;23(1):35–45. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1053811904002411>
- [17] Niethammer M, Tang CC, Feigin A, Allen PJ, Heinen L, Hellwig S, et al. A disease-specific metabolic brain network associated with corticobasal degeneration. *Brain* [Internet]. 2014 Nov;137(11):3036–46. Available from: <https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awu256>
- [18] Tomše P, Jensterle L, Grmek M, Zaletel K, Pirtošek Z, Dhawan V, et al. Abnormal metabolic brain network associated with Parkinson's disease: replication on a new European sample. *Neuroradiology*. 2017;59(5):507–15.
- [19] Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, et al. Abnormal metabolic networks in atypical parkinsonism. *Mov Disord*. 2008;23(5):727–33.
- [20] Iizuka T, Kameyama M. Spatial metabolic profiles to discriminate dementia with Lewy bodies from Alzheimer disease. *J Neurol* [Internet]. 2020 Mar 13;(0123456789). Available from: <https://doi.org/10.1007/s00415-020-09790-8>
- [21] Meles SK, Tang CC, Teune LK, Dierckx RA, Dhawan V, Mattis PJ, et al. Abnormal Metabolic Pattern Associated with Cognitive Impairment in Parkinson's Disease: A Validation Study. *J Cereb Blood Flow Metab* [Internet]. 2015 Sep 10;35(9):1478–84. Available from: <http://journals.sagepub.com/doi/10.1038/jcbfm.2015.112>
- [22] Perovnik M, Rus T, Tomše P, Jensterle L, Emeršič A, Grmek M[1], et al. Identifikacija in validacija specifičnega z boleznijo povezanega presnovnega vzorca pri bolnikih z likvorsko potrjeno alzheimerjevo boleznijo. In: Rakuša M, editor. 4 slovenski nevrološki kongres. 2019. p. 107–8.
- [23] Blazhenets G, Ma Y, Sörensen A, Rücker G, Schiller F, Eidelberg D, et al. Principal component analysis of brain metabolism predicts development of Alzheimer's dementia. *J Nucl Med* [Internet]. 2018 Nov 2;jnumed.118.219097. Available from: <http://jnm.snmjournals.org/lookup/doi/10.2967/jnumed.118.219097>
- [24] Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease.

- [25] Lesser GT. Frequency of bowel movements and future risk of Parkinson's disease [7] (multiple letters). *Neurology*. 2002;58(5):838–9.
- [26] Stirpe P, Hoffman M, Badiali D, Colosimo C. Constipation: an emerging risk factor for Parkinson's disease? *Eur J Neurol*. 2016;23(11):1606–13.
- [27] Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H. Olfactory loss may be a first sign of idiopathic Parkinson's disease. *Mov Disord*. 2007;22(6):839–42.
- [28] Janković M, Svetel M, Kostić V. Učestalost poremećaja REM faze sna kod bolesnika sa Parkinsonovom bolešću. *Vojnosanit Pregl*. 2015;72(5):442–6.
- [29] Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: Preparing for neuroprotective trials. *Neurology*. 2015;84(11):1104–13.
- [30] Darweesh SKL, Verlinden VJA, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of prediagnostic functioning in Parkinson's disease. *Brain*. 2017;140(2):429–41.
- [31] Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*. 2012;72(6):893–901.
- [32] Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: A case-control study. *Lancet Neurol*. 2015;14(1):57–64.
- [33] Ba F, Martin WRW. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. *Park Relat Disord* [Internet]. 2015;21(2):87–94. Available from: <http://dx.doi.org/10.1016/j.parkreldis.2014.11.007>
- [34] Marek KL, Seibyl JP, Zoghbi SS, Zea-Ponce Y, Baldwin RM, Fussell B, et al. [123I] β -CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. *Neurology*. 1996;46(1):231–7.
- [35] Shafieesabet A, Fereshtehnejad SM, Shafieesabet A, Delbari A, Baradaran HR, Postuma RB, et al. Hyperechogenicity of substantia nigra for differential diagnosis of Parkinson's disease: A meta-analysis. *Park Relat Disord*. 2017;42:1–11.
- [36] Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2015;30(12):1600–11.
- [37] Taki J, Yoshita M, Yamada M, Tonami N. Significance of 123I-MIBG scintigraphy as a pathophysiological indicator in the assessment of Parkinson's disease and related disorders: It can be a specific marker for Lewy body disease. *Ann Nucl Med*. 2004;18(6):453–61.
- [38] Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K, Hirata K. Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. *Neurology*. 2006;67(12):2236–8.
- [39] Strafella AP, Bohnen NI, Perlmutter JS, Eidelberg D, Pavese N, Van Eimeren T, et al. Molecular imaging to track Parkinson's disease and atypical parkinsonisms: New imaging frontiers. *Mov Disord*. 2017;32(2):181–92.

- [40] Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. *Neurology*. 2014;82(7):620–7.
- [41] Wu P, Yu H, Peng S, Dauvilliers Y, Wang J, Ge J, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder. *Brain* [Internet]. 2014 Dec;137(12):3122–8. Available from: <https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awu290>
- [42] Meles SK, Renken RJ, Janzen A, Vadasz D, Pagani M, Arnaldi D, et al. The Metabolic Pattern of Idiopathic REM Sleep Behavior Disorder Reflects Early-Stage Parkinson Disease. *J Nucl Med* [Internet]. 2018 Sep;59(9):1437–44. Available from: <http://jnm.snmjournals.org/lookup/doi/10.2967/jnumed.117.202242>
- [43] Trošt M, Perovnik M, Pirtošek Z. Correlations of Neuropsychological and Metabolic Brain Changes in Parkinson's Disease and Other α -Synucleinopathies. *Front Neurol* [Internet]. 2019 Nov 14;10(November):1–10. Available from: <https://www.frontiersin.org/article/10.3389/fneur.2019.01204/full>
- [44] Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage* [Internet]. 2007 Jan;34(2):714–23. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1053811906009323>

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EARLY DETECTION OF MULTIPLE SCLEROSIS: WHEN DOES THE DISEASE REALLY BEGIN?

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Summary

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder of the central nervous system (CNS) that is characterized by widespread demyelinating lesions in both the brain and the spinal cord. The inflammatory lesions are not the only pathophysiological process, with continuous neurodegeneration and atrophy present from the very beginning of the disease. The direct cause of the disease is not known so far but is thought to be a combination of genetic, immune and environmental factors. Significant advances in immunology and neuroscience bring us ever closer to understanding the complex pathophysiology that underly multiple sclerosis, along with enabling us to diagnose the disease earlier than before. The natural course of the disease in both relapsing and progressive phenotypes includes the radiologically isolated syndrome, in which there is evident dissemination in space without any symptoms. The majority of these patients will have radiological progression in five years, with a third experiencing their first clinical symptoms. Early diagnosis facilitates early disease-modifying therapies, which should lead to slower progression and reduced disease activity in most patients. Furthermore, the personalized approach to therapy is now a reality in MS with a comprehensive option of therapy suited for the clinical state of each patient.

Key words: multiple sclerosis; neuroinflammation; diagnosis; clinically isolated syndrome; radiologically isolated syndrome

Background

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder of the central nervous system (CNS) that is characterized by widespread demyelinating lesions in both the brain and the spinal cord [1]. Multiple sclerosis can be considered as a disease of a thousand faces, as the first symptoms vary significantly from one person to the other due to different locations where the lesions occur. The most common symptoms in the start of the disease include blurred vision, vision loss, numbness, paraesthesia and ataxia [2]. The first presentation of the disease most commonly occurs in young adults, and approximately three-quarters of patients suffering from MS are women, which follows the similar sex distribution present in autoimmune diseases [3]. The disease is present in the whole world, but the prevalence varies greatly depending on geography and regions. It is most prevalent in Europe, North America and Australasia [4]. The prevalence in Croatia has been increasing in recent times [5, 6], especially in some regions that have historically had more cases of MS than the rest of the country [7, 8].

Furthermore, MS is among the leading causes of disability in young adult and adult age groups, thus being a significant burden on society in Europe [9]. The direct cause of the disease is not known so far but is thought to be a combination of genetic, immune and environmental factors [10]. Pinpointing the start of the disease is impossible without a clear cause; however, we do know the disease is active for some time before the first clinical events are present [11]. Significant advances in immunology and neuroscience bring us ever closer to understanding the complex pathophysiology that underly multiple sclerosis, along with enabling us to diagnose the disease earlier than before. These give us the ability to focus on the early phases and treatment of the disease while bringing us within reach of finding the real beginning of the disease.

Pathophysiological evolution of multiple sclerosis

The original descriptions of multiple sclerosis by Charcot describe sclerosing plaques in the periventricular area, pons and the spinal cord, a demonstration of the dissemination in space, which is crucial in today's diagnostic criteria [12]. However, in modern times we do not depend solely on clinical features and pathology, but also on modern neuroimaging and laboratory techniques to diagnose and measure the progression of the disease. Demyelinating lesions in MS occur in both the white and gray matter, with each having specific characteristics [11]. In general, acute white matter lesions that are present in the relapsing forms of the disease are characterized by acute inflammation that can be quite

heterogenous between each person [13]. At the start, most lesions have a marked innate immune response with classical and alternative microglial activation, bloodborne macrophage infiltration and subsequent initiation of the adaptive immune response [14, 15]. Unfortunately, the intrinsic or extrinsic factors that cause the lesions to form are still unknown. Recent research reveals that microglial activation remote from established lesions could represent the earliest stage of lesion development [16]. Importantly, microglia also initiate the processes of repair during the early phase of the disease, which follows the inflammation at the same time [17]. What occurs after initial lesion activation is the recruitment of either predominantly T-cells or B-cells, which begins the complex interplay between the immune system, glial cells and neurons, and ultimately can bring the acute lesions into the chronic phase [18]. The possible outcomes of this process is a chronic inactive lesion that is characterized by a complete lack of remyelination, or a remyelinated lesion that can lead to partial restitution of function. Another possibility is a low-grade inflammation smouldering lesion, fueled by chronic microglial activation and subsequent chronic neurodegeneration, which is most common in progressive forms of multiple sclerosis [19, 20].

Gray matter lesions show a lesser inflammatory component than the white matter lesions, with significantly less disrupted blood-brain barrier [21]. They most commonly occur in the perivascular cortical space and near the leukocortical junction, which affects both white and gray matter [22]. The evolution of the lesions is less severe than in acute white matter lesions, with a more marked innate immune response, while the adaptive immune response is present in a lesser capacity. The leukocortical lesions show a more profound inflammation than the pure cortical lesions, which only encompass the gray matter [23]. Interestingly, they are more prevalent in the early stages of the disease and are rarely present in the chronic, later stages [23]. Furthermore, gray matter lesions can be present even before white matter lesions, while also predicting higher progression of disability, even in patients with a clinically isolated syndrome (CIS) [24].

The presence of lesions and focal inflammation is only one part of the pathophysiology in MS. There is clear evidence that continuous neurodegeneration, or „silent progression, is present from the very beginning of the disease and continually leads to irreversible damage of nervous tissue [25]. Regional gray matter atrophy occurs from the start and progresses through the natural course of the disease [26]. The atrophy is especially evident in the thalamus, which happens in the earliest stages of the disease and increases the risk of disease progression [27]. Deep gray matter volume loss has been shown to drive the disability progression in patients, with lacking improvement to disease-modifying therapy

[28, 29]. The progression of atrophy appears to correlate with the lesion load in MS, but it is not clear whether there is a direct connection between the two [30]. A study by Pontillo et al. confirmed the diffuse involvement of the deep gray matter (DGM) in MS, with differences between the progressive and relapsing phenotype. The atrophy in the relapsing forms was determined by the white matter lesion burden, while in progressive forms, the microstructural damage and thalamic susceptibility changes accounted for the development of DGM volume loss [31]. Therefore, the pathophysiological evolution of neurodegeneration in both forms appears to be driven by inflammation, with the atrophy in relapsing forms occurring due to structural disconnection in neuron networks, while in progressive forms as a consequence of local microstructural damage. Overall, it appears that the chronic neurodegeneration in MS is a direct consequence of chronic CNS inflammation, with production of reactive oxygen and nitrogen species, low-grade hypoxia, cytokine and glutamate release being the main drivers of damage. The homeostasis of the neurons in such a milieu is disturbed, leading to oxidative stress and mitochondrial damage that causes ion imbalances and ultimately neuroaxonal damage by apoptosis and necrosis [32]. Whether the disease beginning is driven purely by inflammation or if there is an underlying cause for neurodegeneration is not known yet as the search for the direct cause continues [33].

Clinical evolution of multiple sclerosis

Our understanding of the clinical disease evolution has improved in recent times. Multiple sclerosis is classified into two primary phenotypes based on disease progression; the relapsing forms and the progressive forms [34]. The initial evolution of the disease is similar for both phenotypes, as the disease in both cases starts before the clinical threshold is passed and observed. Early asymptomatic lesions can be detected with magnetic resonance imaging (MRI) long before first clinical events, which is called the radiologically isolated syndrome (RIS) [35]. Studies have shown that patients with RIS can progress to both the relapsing and progressive forms of multiple sclerosis [36].

On the other hand, clinically isolated syndrome (CIS) encompasses the first clinical manifestation of the relapsing form of MS and is characterized by present demyelinating lesions on MRI with neurological symptoms, but without proven dissemination in time [35]. In both cases, we should follow the patients prospectively, as the majority of cases will progress to relapsing or progressive MS within ten years [37, 38]. However, even a single clinical event can be enough to diagnose a patient with multiple sclerosis, provided it is possible to prove the

dissemination in time and space according to the latest diagnostic criteria [39]. The fast-changing diagnostic criteria have reduced the number of patients that are diagnosed with these syndromes; however, they still represent a stepping-stone in the evolution of the disease.

Radiologically isolated syndrome

Incidental MRI findings suggestive of multiple sclerosis without any neurological symptoms define the radiologically isolated syndrome (RIS) [40]. Prospective monitoring of the patients is critical as approximately two-thirds of people with RIS will show radiological progression, while one-third will develop symptoms in five years from discovery. Importantly, the patients with RIS can progress to both progressive and relapsing forms of MS [36]. The risk increases if the lesions are present in the cervical cord at first discovery, if the age of the patient is less than 37 years old, and if the gender is male [40]. Patients with RIS have evidence of brain atrophy, mild cognitive deficits, increased incidence of psychiatric diseases, axonal loss and even a subclinical inflammatory disease [41].

The current modified criteria for RIS include a demonstration of lesion dissemination in space, similar to that in MS, with the exclusion criteria being any clinical evidence of neurological dysfunction. Likewise, it is required that MRI abnormalities cannot be explained by any other disease process, especially ageing, vascular-associated damage and exposure to toxins or drugs [42]. Particular caution should be given in RIS patients who present with frequent headaches, seizures, various paroxysmal symptoms or psychiatric disturbances, as those can also be a sign of subclinical MS [43]. The likelihood is increased if there is evident dissemination in time on MRI, infratentorial or spinal cord lesions, the presence of oligoclonal bands in the cerebrospinal fluid or abnormal visual evoked potentials [43]. On the other hand, there is a debate in the field whether the term RIS is antiquated, with an overlap in both symptoms and diagnostic criteria as the McDonald criteria for MS keep evolving [44]. There is a lack of detailed epidemiological data for RIS. A population-based study conducted by Forslin et al. revealed a small incidence of RIS (0.8 cases per 100,000) in a high-incidence region for MS (10.2 cases per 100,000), although there is a need for a higher number of participants to increase the accuracy of the study [45]. Currently, there is no evidence to support treatment in patients with RIS, even if there is a suspicion of subclinical MS. However, active monitoring is advisable, provided the patients agree to it [42].

Clinically isolated syndrome

Multiple sclerosis for a vast majority of patients starts with a clinically isolated syndrome, which by definition entails the first clinical presentation that shows characteristics of inflammatory demyelination but does not meet criteria for the dissemination in time [46]. Nearly 88% of people that experience CIS with abnormal MRI will have a second episode and progress to clinically definite multiple sclerosis in within 20 years of onset [47]. The natural evolution of CIS encompasses progression to relapse-remitting multiple sclerosis after proven dissemination in time, which can be followed by continuous relapses, secondary progression or remain stationary [48]. CIS most occurs in young adults, with presenting symptoms predominately involving optic nerves, brain stem, cerebellum or spinal cord [49]. The risk rate of progression appears to be the same regardless of the presenting symptom [50]. In general, the risk for disease progression increases patients who have either abnormal MRI or positive oligoclonal bands in the cerebrospinal fluid [51].

Relapse-remitting multiple sclerosis (RRMS)

Nearly 85% of MS patients will have the relapsing form of the disease, with an established natural progression (Figure 1.). This phenotype is characterized by intermittent periods of increasing neurological disability called relapses, along with periods of clinical stability called remissions. Almost half of the relapses leave residual deficits that accumulate over time, leading to increasing disability as the disease progresses [34]. Individual states such as infections and stress appear to be associated with increased risks for relapses [52]. Pregnancy, on the other hand, has a variable effect on the risk of relapses, with significantly reduced risk of relapses during pregnancy, which increases above baseline risk during the postpartum year [53]. A significant number of patients invariably progresses into the secondary progressive multiple sclerosis (SPMS) (Figure 1.), but it is still not clear what causes this progression [48].

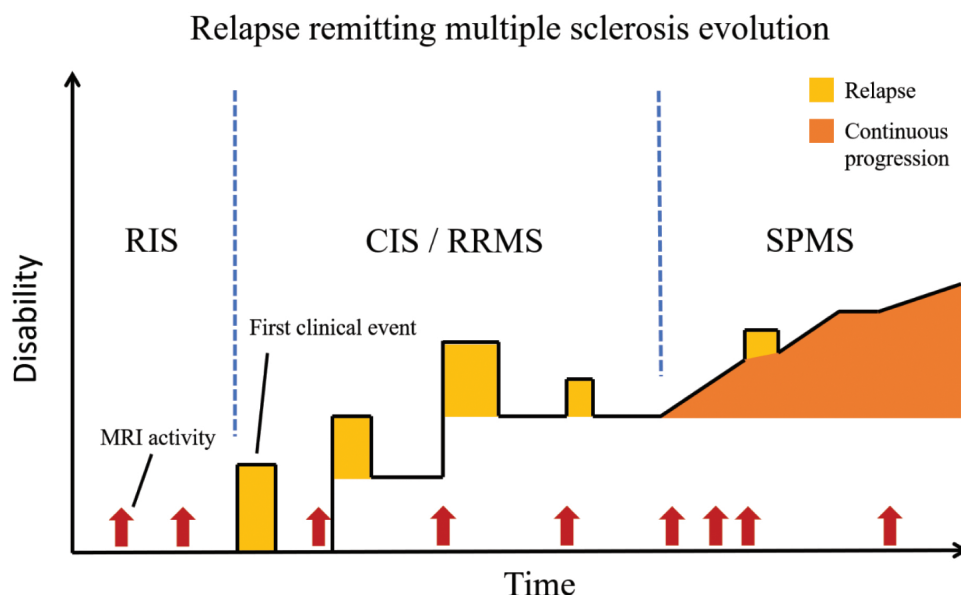


Figure 1. The evolution of the relapsing forms in multiple sclerosis. Figure style partially adapted from the National Multiple Sclerosis Society.

Abbreviations: RIS - the radiologically isolated syndrome; CIS - clinically isolated syndrome ; RRMS - Relapse-remitting multiple sclerosis ; SPMS - secondary progressive multiple sclerosis

Progressive forms of multiple sclerosis

As stated previously, the natural evolution of the relapsing form of MS leads to a progression to SPMS for most of the patients [37]. The cause for the disease progression is unknown so far, and there are no definitive clinical diagnostic criteria due to no available laboratory or imaging biomarkers [54]. The diagnosis is usually retrospective and can be delayed up to 3 years in some patients [55]. This has to be improved, as novel therapies that can be effective in SPMS create an opportunity for intervention in this stage as well. The progression of SPMS is characterised by periods of continuous progression of the disease, periods of relative stability, and possible superimposed relapse activity (Figure 1.) [50]. Much of the pathophysiological characteristics are similar in both SPMS and

primary progressive multiple sclerosis (PPMS), involving predominantly the innate immune system and a more closed off inflammation of the CNS than in the relapsing forms of MS [56].

Around 10% of MS patients have progressive phenotype as the presenting form of the disease, which is characterized by an ongoing progression of disability [57]. The natural evolution of the disease is similar to SPMS, with possible superimposed relapses and also periods of the relative stability of disability progression [50]. Novel research shows that RIS can also precede PPMS as a first possible sign of MS (Figure 2.) [36]. Lunde et al. published a 60-year old longitudinal study that showed a two-fold increased mortality rate in PPMS compared to RRMS, with a seven-year shorter life expectancy [58]. The recent gulf in treatment options between the two only means that this difference could widen. Therefore, the progressive forms of the disease are under intense pre-clinical and clinical research in order to elucidate the pathophysiological mechanisms that could lead to novel treatment and improve patient outcomes.

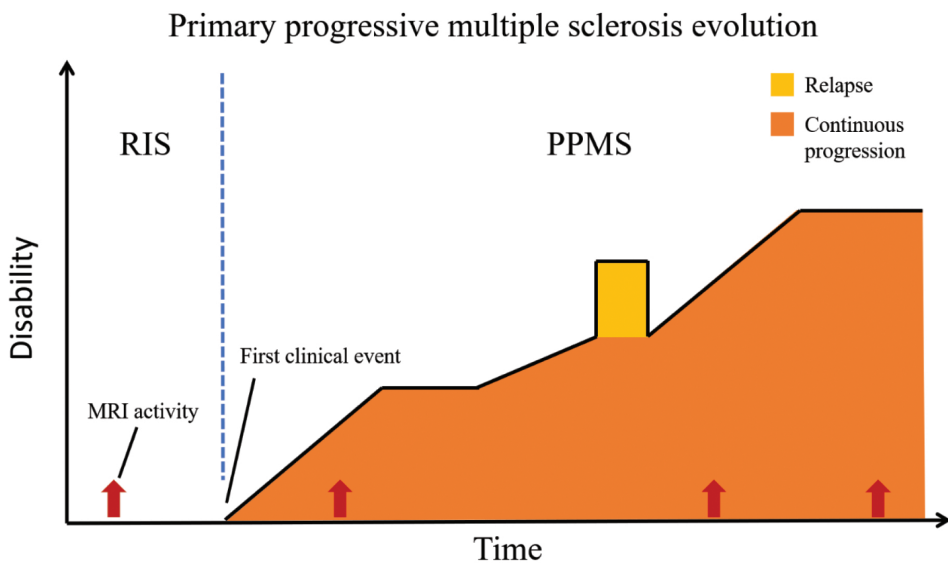


Figure 2. The evolution of primary progressive multiple sclerosis (PPMS). Figure style partially adapted from the National Multiple Sclerosis Society
Abbreviations: RIS - the radiologically isolated syndrome; PPMS – primary progressive multiple sclerosis evolution

Evolution of the diagnostic criteria

Main principles of MS diagnosis are demonstrating the dissemination in time (DIT) and space (DIS) with objective clinical and paraclinical evidence. There have been many changes to the diagnostic criteria over the last half-century. Schumacher proposed the first criteria in use at al. in the '60s of the last century, which included both dissemination in time and space using only clinical signs as there were no paraclinical markers except evoked potentials [59]. The Poser criteria included the presence of oligoclonal bands to the diagnostic criteria and expanded the possible diagnostic conclusions, although still requiring concrete clinical findings for DIT and DIS [60]. The discovery and use of MRI in clinical practice have been central to increasing speed and accuracy of the diagnosis in recent times, with the demonstration of DIS and DIT with MRI possible with criteria set by Paty (1988) [61], Barkhof (1997) [62], Tintore (Revised Barkhof, 2000) [63] and Swanton (2006) [64]. The MRI findings are central to the McDonald criteria, that is still in use today after four revisions [65]. Each iteration modified and reduced the number of lesions required for dissemination in space, while also shortening the time for a follow-up MRI's to prove the dissemination in time with gadolinium-enhancing active lesions. The 2010 revision reduced the mean time for diagnosis from the onset from 2 years (Poser criteria) to just six months [66]. Latest revision into the McDonald criteria in 2017 added the possibility of using CSF specific oligoclonal bands to demonstrate dissemination in time, drastically reducing the time required to make the diagnosis of MS [67]. The recent revisions allow us to initiate treatment earlier than ever before and have brought a significant change to the clinical management of multiple sclerosis.

Importance of early treatment

It is clear from the pathophysiological and clinical evolution of the disease that treatment must be timely to disrupt the debilitating mechanisms that lead to disability. The treatment of MS has improved significantly over the past years, with a growing number of disease-modifying therapies available for patients. All of the disease-modifying therapy (DMT) focuses on modulating the immune system. It works via three possible ways: immunosuppressive (E.g. natalizumab, siponimod, fingolimod, ocrelizumab), immunomodulatory (E.g. interferon-beta, dimethyl fumarate, glatiramer acetate, teriflunomide) or via immune reconstitution (E.g. cladribine, alemtuzumab, autologous haematopoietic stem cell transplantation) [2]. Many of these therapeutics overlap in their way of affecting the immune system and require a careful approach in consideration which is most suitable for each patient. The goal of therapy is to reduce the disease activity

as much as possible and attain no evidence of disease activity (NEDA), which in turn slows down progression. It is well known that DMTs are capable of delaying disease progression and changing the natural course of the disease that was outlined earlier in this review [68]. The general safety profile for all DMTs is favourable, with the potency being proportionately related to potential adverse events. General adverse event profiles are related to immunosuppression, with a higher incidence of infections, induction of secondary autoimmunity and possible malignancies. More studies are required as currently safety outcomes are poorly reported in most primary studies of DMTs [69].

Current guidelines for treating RRMS implemented in most European countries initially include the escalation approach in which the start of therapy is with less potent and potentially more safe DMTs such as interferon-beta or teriflunomide [70]. The therapy can then be escalated to more potent DMTs such as natalizumab or fingolimod if there is no adequate control over disease activity or progression. However; novel research by William et al. point out that starting therapy with more potent DMTs leads to lower risk of conversion to SPMS [71]. This is evident when observing the NEDA scores for various DMTs in their phase 3 trials, with the rates of patients achieving NEDA in ocrelizumab, cladribine and alemtuzumab being significantly higher than those of first-line DMTs such as interferon-beta and teriflunomide [2]. Moreover, the treatment should be initiated as soon as possible to reduce the risk of disease activity and progression [72], with current recommendations that support the use of DMTs even in CIS with abnormal MRIs [70].

The second possible strategy for treatment is the immune reconstitution therapy, which aggressively induces depletion and reconstitution of lymphocytes [73]. This method of therapy is the closest to a possible cure, as it aims to repair the aberrant immune response and induce long-term beneficial changes in the adaptive immune system [74]. Aside from the mechanism of action, the main differences between the two strategies lie in the fact that chronic immunosuppressive and immunomodulatory therapies need to be administered continuously in order to remain active. In contrast, immune reconstitution therapy is given in pulses and is effective long after the administration. The risk of such aggressive therapy is the development of secondary autoimmunity, particularly in the case of alemtuzumab [75]. Other adverse effects include the reactivation of latent infections like tuberculosis or herpes zoster [76]. The early results of this type of therapy are encouraging as nearly 60% of patients did not need additional cycles of alemtuzumab [77], while nearly 75% of patients remained relapse-free in the fourth year after cladribine treatment [78].

Unfortunately, most DMTs that are used for RRMS are not effective in preventing disease progression in the progressive forms of MS [79]. The only DMTs that have shown promise are the anti-CD20 monoclonal antibodies rituximab [80] and ocrelizumab, with the latter approved for treatment due to a favourable effect on disease progression [81]. The positive effect of these antibodies increases in younger patients who had an active inflammation on initial MRI scans. Therefore, treatment with anti-CD20 DMTs should be considered in patients with PPMS or SPMS, especially in those with shorter disease duration or signs of activity on MRI [82].

The plethora of options and the variations in their efficacy has provided us with the tools to provide highly individualized choices in treatment [83]. Starting the treatment as early as possible is the only thing clear in every patient [70]. Deciding which treatment strategy to use from the start must include a personalized analysis of prognosis in each patient. Poor prognosis is determined by demographic factors (E.g. older age, male sex, vitamin D levels), clinical factors (PPMS, high relapse rate, short interval between relapses, poor recovery, high initial Expanded Disability Status Scale score), MRI observations (high number of T2 lesions, highly active lesions, infratentorial and spinal cord lesions, significant brain atrophy) and biomarkers (oligoclonal bands in the CSF, high levels of neurofilament light chain) [83]. Patients with poor prognostic factors should be considered for early aggressive therapy to delay the progression of the disease as much as possible, although the recommendations are not equivocal in this field and further studies are required [84]. Other factors which influence the treatment decision include the patient preferences, possible pregnancy, route of administration, efficacy and cost. Therefore, two major principles in treating MS is that every diagnosed patient should be given therapy as soon as possible and that every patient deserves a personalized approach to receive the most appropriate therapy possible as safer is not necessarily better.

Final Thoughts

Our understanding of the beginning of MS has been challenged over recent years by discoveries in the field. The concept of the radiologically isolated syndrome (RIS) has shown that the disease mechanisms of MS can be visible on MRI scans several years before the first clinical symptoms. Nearly 2/3 of patients with RIS show radiological progression and 1/3 will develop neurological symptoms during mean follow-up times of up to five years. Therefore, it can be considered as the beginning in both MS phenotypes, until the mechanisms and cause for the disease are elucidated. RIS and CIS are getting obsolete and

rare with new criteria for MS, with the syndromes gradually being incorporated into the natural disease evolution of MS. Our understanding of the neurodegeneration and “silent progression” is increasing, and it is clear that these aspects are present from the onset of MS. In general, relapsing MS patients experience clinically significant worsening of disability that is independent of relapses or accumulation of new T2 lesions on brain MRI. Silent progression patients have similar imaging characteristics to patients with SPMS, which likely represents the same pathological process as SPMS but is not recognized

as such by either clinicians or patients. Early diagnosis will facilitate early disease-modifying therapies, which should lead to slower progression and reduced disease activity in most patients. Furthermore, the personalized approach to therapy is now a reality in MS with a comprehensive option of therapy suited for the clinical state of each patient. Ultimately, perhaps a more pertinent question, in the end, is not when the disease begins, but how fast can we detect it and initiate treatment to slow down the progression.

References

- [1] Popescu BFG, Pirko I, Lucchinetti CF (2013) Pathology of multiple sclerosis: where do we stand? *Continuum* (Minneapolis) 19:901–21. doi: 10.1212/01.CON.0000433291.23091.65
- [2] Dobson R, Giovannoni G (2019) Multiple sclerosis – a review. *Eur J Neurol* 26:27–40. doi: 10.1111/ene.13819
- [3] Ascherio A, Munger KL (2016) Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention--An Update. *Semin Neurol* 36:103–114. doi: 10.1055/s-0036-1579693
- [4] Wallin MT, Culpepper WJ, Nichols E, et al (2019) Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 18:269–285. doi: 10.1016/S1474-4422(18)30443-5
- [5] Benjak T, Štefančić V, Draušnik Ž, Cerovecki I, Roginić D, Habek M, Mihel S, Stevanović R (2018) Prevalence of multiple sclerosis in Croatia: Data from national and non-governmental organization registries. *Croat Med J* 59:65–70. doi: 10.3325/cmj.2018.59.65
- [6] Materljan E, Sepcic J (2002) Epidemiology of multiple sclerosis in Croatia. In: *Clin. Neurol. Neurosurg.* Elsevier, pp 192–198
- [7] Sepcic J, Mesaroš E, Materljan E, Šepić-Grahovac D (1993) Nutritional factors and multiple sclerosis in Gorski Kotar, Croatia. *Neuroepidemiology* 12:234–240. doi: 10.1159/000110322
- [8] Peterlin B, Ristić S, Sepčić J, Vračko BK, Rako A, Lovrečić L, Brajenović-Milić B, Rude J, Materljan E, Kapović M (2006) Region with persistent high frequency of multiple sclerosis in Croatia and Slovenia. *J Neurol Sci* 247:169–172. doi: 10.1016/j.jns.2006.04.002

- [9] Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J (2017) New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler* 23:1123–1136. doi: 10.1177/1352458517694432
- [10] Leray E, Moreau T, Fromont A, Edan G (2016) Epidemiology of multiple sclerosis. *Rev Neurol (Paris)* 172:3–13. doi: 10.1016/j.neurol.2015.10.006
- [11] Reich DS, Lucchinetti CF, Calabresi PA (2018) Multiple sclerosis. *N Engl J Med* 378:169–180. doi: 10.1056/NEJMr1401483
- [12] Pearce JMS (2005) Historical descriptions of multiple sclerosis: The stories of Augustus d’Este and The Journal of a Disappointed Man. *Eur Neurol* 54:49–53. doi: 10.1159/000087387
- [13] Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H (2000) Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Ann Neurol* 47:707–717. doi: 10.1002/1531-8249(200006)47:6<707::AID-ANA3>3.0.CO;2-Q
- [14] Mishra MK, Wee Yong V (2016) Myeloid cells-targets of medication in multiple sclerosis. *Nat Rev Neurol* 12:539–551. doi: 10.1038/nrneurol.2016.110
- [15] Prinz M, Priller J, Sisodia SS, Ransohoff RM (2011) Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nat Neurosci* 14:1227–1235. doi: 10.1038/nn.2923
- [16] Van Der Valk P, Amor S (2009) Preactive lesions in multiple sclerosis. *Curr Opin Neurol* 22:207–213. doi: 10.1097/WCO.0b013e32832b4c76
- [17] Aguzzi A, Barres BA, Bennett ML (2013) Microglia: Scapegoat, saboteur, or something else? *Science* (80-) 339:156–161. doi: 10.1126/science.1227901
- [18] Metz I, Weigand SD, Popescu BFG, Frischer JM, Parisi JE, Guo Y, Lassmann H, Brück W, Lucchinetti CF (2014) Pathologic heterogeneity persists in early active multiple sclerosis lesions. *Ann Neurol* 75:728–738. doi: 10.1002/ana.24163
- [19] Absinta M, Sati P, Schindler M, et al (2016) Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions. *J Clin Invest* 126:2597–2609. doi: 10.1172/JCI86198
- [20] Elliott C, Belachew S, Wolinsky JS, et al (2019) Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. *Brain* 142:2787–2799. doi: 10.1093/brain/awz212
- [21] Peterson JW, Bö L, Mörk S, Chang A, Trapp BD (2001) Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol* 50:389–400. doi: 10.1002/ana.1123
- [22] Kutzelnigg A, Lucchinetti CF, Stadelmann C, Brück W, Rauschka H, Bergmann M, Schmidbauer M, Parisi JE, Lassmann H (2005) Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain* 128:2705–2712. doi: 10.1093/brain/awh641
- [23] Lucchinetti CF, Popescu BFG, Bunyan RF, et al (2011) Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med* 365:2188–2197. doi: 10.1056/NEJMoa1100648

- [24] Calabrese M, Poretto V, Favaretto A, Alessio S, Bernardi V, Romualdi C, Rinaldi F, Perini P, Gallo P (2012) Cortical lesion load associates with progression of disability in multiple sclerosis. *Brain* 135:2952–61. doi: 10.1093/brain/awr246
- [25] Ziemssen T, Derfuss T, de Stefano N, Giovannoni G, Palavra F, Tomic D, Vollmer T, Schippling S (2016) Optimizing treatment success in multiple sclerosis. *J Neurol* 263:1053–1065. doi: 10.1007/s00415-015-7986-y
- [26] Eshaghi A, Marinescu R V., Young AL, et al (2018) Progression of regional grey matter atrophy in multiple sclerosis. *Brain* 141:1665–1677. doi: 10.1093/brain/awy088
- [27] Zivadinov R, Havrdová E, Bergsland N, et al (2013) Thalamic atrophy is associated with development of clinically definite multiple sclerosis. *Radiology* 268:831–841. doi: 10.1148/radiol.13122424
- [28] Koskimäki F, Bernard J, Yong J, Arndt N, Carroll T, Lee SK, Reder AT, Javed A (2018) Gray matter atrophy in multiple sclerosis despite clinical and lesion stability during natalizumab treatment. *PLoS One* 13:
- [29] Eshaghi A, Prados F, Brownlee WJ, et al (2018) Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Ann Neurol* 83:210–222. doi: 10.1002/ana.25145
- [30] Richert ND, Howard T, Frank JA, Stone R, Ostuni J, Ohayon J, Bash C, McFarland HF (2006) Relationship between inflammatory lesions and cerebral atrophy in multiple sclerosis. *Neurology* 66:551–556. doi: 10.1212/01.wnl.0000197982.78063.06
- [31] Pontillo G, Lanzillo R, Russo C, et al (2019) Determinants of deep gray matter atrophy in multiple sclerosis: A multimodal MRI study. *Am J Neuroradiol* 40:99–106. doi: 10.3174/ajnr.A5915
- [32] Friese MA, Schattling B, Fugger L (2014) Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. *Nat Rev Neurol* 10:225–238. doi: 10.1038/nrneurol.2014.37
- [33] Correale J, Marrodan M, Ysraelit MC (2019) Mechanisms of neurodegeneration and axonal dysfunction in progressive multiple sclerosis. *Biomedicines*. doi: 10.3390/biomedicines7010014
- [34] Lublin FD, Reingold SC, Cohen JA, et al (2014) Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 83:278–286. doi: 10.1212/WNL.0000000000000560
- [35] Niino M, Miyazaki Y (2017) Radiologically isolated syndrome and clinically isolated syndrome. *Clin Exp Neuroimmunol* 8:24–32. doi: 10.1111/cen3.12346
- [36] Kantarci OH, Lebrun C, Siva A, et al (2016) Primary Progressive Multiple Sclerosis Evolving from Radiologically Isolated Syndrome. *Ann Neurol* 79:288–294. doi: 10.1002/ana.24564
- [37] Hou Y, Jia Y, Hou J (2018) Natural Course of Clinically Isolated Syndrome: A Longitudinal Analysis Using a Markov Model. *Sci Rep* 8:1–7. doi: 10.1038/s41598-018-29206-y
- [38] Lebrun C Radiologically isolated syndrome: a 10-year follow-up study to identify factors predicting a clinical event. . *ECTRIMS Online Libr* 279420.

- [39] Carroll WM (2018) 2017 McDonald MS diagnostic criteria: Evidence-based revisions. *Mult Scler* 24:92–95. doi: 10.1177/1352458517751861
- [40] Granberg T, Martola J, Kristoffersen-Wiberg M, Aspelin P, Fredrikson S (2013) Radiologically isolated syndrome--incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. *Mult Scler* 19:271–80. doi: 10.1177/1352458512451943
- [41] Yamout B, Al Khawajah M (2017) Radiologically isolated syndrome and multiple sclerosis. *Mult Scler Relat Disord* 17:234–237. doi: 10.1016/j.msard.2017.08.016
- [42] De Stefano N, Giorgio A, Tintoré M, et al (2018) Radiologically isolated syndrome or sub-clinical multiple sclerosis: MAGNIMS consensus recommendations. *Mult Scler* 24:214–221. doi: 10.1177/1352458517717808
- [43] Charil A, Yousry TA, Rovaris M, et al (2006) MRI and the diagnosis of multiple sclerosis: expanding the concept of “no better explanation.” *Lancet Neurol* 5:841–852. doi: 10.1016/S1474-4422(06)70572-5
- [44] Avasarala J, Yousuf F (2019) Radiologically isolated syndrome is antiquated amidst evolving McDonald criteria for multiple sclerosis. *CNS Spectr* 1–3. doi: 10.1017/S1092852919001202
- [45] Forslin Y, Granberg T, Jumah AA, Shams S, Aspelin P, Kristoffersen-Wiberg M, Martola J, Fredrikson S (2016) Incidence of radiologically isolated syndrome: A population-based study. *Am J Neuroradiol* 37:1017–1022. doi: 10.3174/ajnr.A4660
- [46] Efendi H (2015) Clinically Isolated Syndromes: Clinical Characteristics, Differential Diagnosis, and Management. *Noro Psikiyatr Ars* 52:S1–S11. doi: 10.5152/npa.2015.12608
- [47] Brex PA, Ciccarelli O, O’Riordan JI, Sailer M, Thompson AJ, Miller DH (2002) A Longitudinal Study of Abnormalities on MRI and Disability from Multiple Sclerosis. *N Engl J Med* 346:158–164. doi: 10.1056/NEJMoa011341
- [48] Tedeholm H, Skoog B, Lisovskaja V, Runmarker B, Nerman O, Andersen O (2015) The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset. *J Neurol* 262:1148–1163. doi: 10.1007/s00415-015-7674-y
- [49] Miller DH, Chard DT, Ciccarelli O (2012) Clinically isolated syndromes. *Lancet Neurol* 11:157–169. doi: 10.1016/S1474-4422(11)70274-5
- [50] Klineova S, Lublin FD (2018) Clinical course of multiple sclerosis. *Cold Spring Harb. Perspect. Med.* 8:
- [51] Tintoré M, Rovira A, Río J, et al (2008) Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* 70:1079–1083. doi: 10.1212/01.wnl.0000280576.73609.c6
- [52] Vollmer T (2007) The natural history of relapses in multiple sclerosis. *J. Neurol. Sci.* 256:
- [53] McCombe P (2018) The Short and Long-Term Effects of Pregnancy on Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis. *J Clin Med* 7:494. doi: 10.3390/jcm7120494

- [54] Rovaris M, Confavreux C, Furlan R, Kappos L, Comi G, Filippi M (2006) Secondary progressive multiple sclerosis: Current knowledge and future challenges. *Lancet Neurol* 5:343–354. doi: 10.1016/S1474-4422(06)70410-0
- [55] Inojosa H, Proschmann U, Akgün K, Ziemssen T (2019) A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol* 1–12. doi: 10.1007/s00415-019-09489-5
- [56] Abdelhak A, Weber MS, Tumani H (2017) Primary progressive multiple sclerosis: Putting together the Puzzle. *Front Neurol* 8:234. doi: 10.3389/fneur.2017.00234
- [57] Ontaneda D, Fox RJ (2015) Progressive multiple sclerosis. *Curr Opin Neurol* 28:237–243. doi: 10.1097/WCO.0000000000000195
- [58] Lunde HMB, Assmus J, Myhr KM, Bø L, Grytten N (2017) Survival and cause of death in multiple sclerosis: A 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry* 88:621–625. doi: 10.1136/jnnp-2016-315238
- [59] Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, McDowell F, Nagler B, Sibley WA, Tourtellotte WW, Willmon TL (1965) PROBLEMS OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS: REPORT BY THE PANEL ON THE EVALUATION OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS. *Ann N Y Acad Sci* 122:552–568. doi: 10.1111/j.1749-6632.1965.tb20235.x
- [60] Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW (1983) New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Ann Neurol* 13:227–231. doi: 10.1002/ana.410130302
- [61] Paty DW, Oger JFF, Kastrukoff LF, et al (1988) MRI in the diagnosis of MS: A prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 38:180–185. doi: 10.1212/wnl.38.2.180
- [62] Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Adèr HJ, Losseff N, Valk J (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069. doi: 10.1093/brain/120.11.2059
- [63] Tintoré M, Rovira A, Brieva L, Grivé E, Jardí R, Borrás C, Montalban X (2001) Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different MR imaging criteria to predict conversion to CDMS. *Mult Scler* 7:359–63. doi: 10.1177/135245850100700603
- [64] Swanton JK, Fernando K, Dalton CM, Miszkiel KA, Thompson AJ, Plant GT, Miller DH (2006) Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. *J Neurol Neurosurg Psychiatry* 77:830–833. doi: 10.1136/jnnp.2005.073247
- [65] Chataway J (2018) Evolving diagnostic criteria for multiple sclerosis. *Lancet Neurol* 17:118. doi: 10.1016/S1474-4422(17)30463-5
- [66] Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH (2015) Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. *J Neurol Neurosurg Psychiatry* 86:584–585. doi: 10.1136/jnnp-2014-308675

- [67] Schwenkenbecher P, Wurster U, Konen FF, Gingele S, Sühs K-W, Wattjes MP, Stangel M, Skripuletz T (2019) Impact of the McDonald Criteria 2017 on Early Diagnosis of Relapsing-Remitting Multiple Sclerosis. *Front. Neurol.* 10:
- [68] Brown MG, Kirby S, Skedgel C, Fisk JD, Murray TJ, Bhan V, Sketris IS (2007) How effective are disease-modifying drugs in delaying progression in relapsing-onset MS? *Neurology* 69:1498–1507. doi: 10.1212/01.wnl.0000271884.11129.f3
- [69] Lucchetta RC, Leonart LP, Becker J, Pontarolo R, Fernandez-Llimós F, Wiens A (2019) Safety outcomes of disease-modifying therapies for relapsing–remitting multiple sclerosis: A network meta-analysis. *Mult Scler Relat Disord* 35:7–15. doi: 10.1016/j.msard.2019.06.036
- [70] Montalban X, Gold R, Thompson AJ, et al (2018)ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 24:96–120. doi: 10.1177/1352458517751049
- [71] Brown JWL, Coles A, Horakova D, et al (2019) Association of Initial Disease-Modifying Therapy with Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA - J Am Med Assoc* 321:175–187. doi: 10.1001/jama.2018.20588
- [72] Cerqueira JJ, Compston DAS, Geraldles R, Rosa MM, Schmierer K, Thompson A, Tinelli M, Palace J (2018) Time matters in multiple sclerosis: Can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? *J Neurol Neurosurg Psychiatry* 89:844–850. doi: 10.1136/jnnp-2017-317509
- [73] Sorensen PS, Sellebjerg F (2019) Pulsed immune reconstitution therapy in multiple sclerosis. *Ther Adv Neurol Disord.* doi: 10.1177/1756286419836913
- [74] Wiendl H (2017) Cladribine - An old newcomer for pulsed immune reconstitution in MS. *Nat Rev Neurol* 13:573–574. doi: 10.1038/nrneurol.2017.119
- [75] Tuohy O, Costelloe L, Hill-Cawthorne G, et al (2015) Alemtuzumab treatment of multiple sclerosis: Long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 86:208–215. doi: 10.1136/jnnp-2014-307721
- [76] Giovannoni G, Comi G, Cook S, et al (2010) A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 362:416–426. doi: 10.1056/NEJMoa0902533
- [77] Havrdova E, Arnold DL, Cohen JA, et al (2017) Alemtuzumab CARE-MS i 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. *Neurology* 89:1107–1116. doi: 10.1212/WNL.0000000000004313
- [78] Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan K, Rieckmann P, Comi G, Dargatzis F, Adeniji AK, Vermersch P (2018) Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Mult Scler J* 24:1594–1604. doi: 10.1177/1352458517727603
- [79] Filippini G, Del Giovane C, Vacchi L, D’Amico R, Di Pietrantonj C, Beecher D, Salanti G (2013) Immunomodulators and immunosuppressants for multiple sclerosis: A network meta-analysis. *Cochrane Database Syst Rev.* doi: 10.1002/14651858.CD008933.pub2

- [80] Hawker K, O'Connor P, Freedman MS, et al (2009) Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol* 66:460–471. doi: 10.1002/ana.21867
- [81] Montalban X, Hauser SL, Kappos L, et al (2017) Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 376:209–220. doi: 10.1056/NEJMoa1606468
- [82] Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA (2018) Multiple sclerosis. *Nat Rev Dis Prim* 4:1–27. doi: 10.1038/s41572-018-0041-4
- [83] Rotstein D, Montalban X (2019) Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. *Nat Rev Neurol* 15:287–300. doi: 10.1038/s41582-019-0170-8
- [84] Examining Whether Early Aggressive Therapy Can Prevent or Delay Disability in People with Multiple Sclerosis: the TREAT-MS Study | PCORI. <https://www.pcori.org/research-results/2017/examining-whether-early-aggressive-therapy-can-prevent-or-delay-disability>. Accessed 15 Apr 2020

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EARLY DIAGNOSIS OF FRONTOTEMPORAL DEMENTIA

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Summary

Frontotemporal dementia (FTD) is a heterogeneous disease characterized by atrophy of the frontal and / or temporal cortex and deposits of pathological inclusions in brain. FTD can be difficult to diagnose, and because of its various behavioural features and variable clinical presentation it can mimic many psychiatric and neurodegenerative disorders. Therefore, the development of diagnostic markers is crucial for distinguishing FTD from other neurodegenerative dementias and to differentiate FTD subtypes. An important goal of using biomarkers is to detect the disease in the presymptomatic phase. To this end, a number of neuroimaging methods are used to detect morphological and functional changes in the brain, present years before the onset of symptoms. FTD is characterized with intracellular inclusions of various proteins, but in order to enable targeted therapy, it is necessary to determine the underlying pathology. This is very difficult based just on clinical presentation and numerous studies are focused on detection of changes in specific protein concentrations in CSF which may reflect pathophysiological changes in the brain. Finally, FTD is a highly hereditary disease and knowledge of genetic changes is also becoming increasingly important. There is a known genotype phenotype correlation in pathological mutations in common FTD genes, which is of great importance for prognosis assessment and for asymptomatic family members. Early diagnosis requires understanding of the neuropathology of the disease and its neuroimaging features as well as its genetic background.

Key words: Frontotemporal dementia, neuroimaging, protein accumulation, biomarker, genetics

Background

Frontotemporal dementia (FTD) is a group of clinical entities causing progressive changes in personality, behavior, and speech with multiple underlying pathological and genetic causes. [1; 2]. FTD is characterized by atrophy of the frontal and / or temporal cortex and deposits of pathological inclusions in the cytoplasm and nucleus of glial cells and neurons [3]. It is the second most common cause of dementia after Alzheimer's disease (AD) with a prevalence of 10 to 30 per 100,000 people aged 45 to 65 years [4]. The characteristic age of onset is typically younger than in AD (20-75 years of age), and affects both men and women equally. Genetic background is an important risk factor for FTD and there is a positive family history in 25-50% of cases [5]. The term FTD encompasses two main phenotypes of clinical presentation: behavioural variant FTD (bvFTD; 60%) and primary progressive aphasia (PPA; 40%). The latter can further be divided into three main subtypes: nonfluent/agrammatic variant (nfvPPA), semantic variant (svPPA), logopenic variant (lvPPA). The bvFTD is associated with early behavioural and executive deficits, nfvPPA with progressive deficits in speech while svPPA is associated with deficits of semantic knowledge and naming. Over time, the symptoms of the clinical variants can converge until patients finally develop global cognitive impairment and motor deficits. Clinical, genetic, and pathological overlap with different neurological syndromes is also common [6]. **Because of prominent behavioural features it can also mimic many psychiatric disorders which makes the diagnosis even more challenging.** The basic clinical presentation in the form of behavioral changes and speech disorders directly reflects atrophy of the frontal and temporal lobe cortex [7]. However, in addition to the decay of gray matter, changes in white matter [8] and in basal ganglia [9] have also been shown. Early diagnosis requires understanding of the neuropathology of the disease and its neuroimaging features as well as the genetic background of the disease.

Protein biomarkers

FTD is a heterogeneous disease with intracellular inclusions of various proteins. The most common accumulating proteins are tau, TDP-43 (TAR DNA-binding protein 43) and FUS (fused in sarcoma). Tau (MAPT, microtubule-associated tau protein; FTLD-tau) or TDP-43 (FTLD-TDP) inclusions have been identified in the majority of cases ($\leq 40-50\%$), while FUS ($\leq 10\%$; FTLD-FUS) and ubiquitin / p62 inclusions are less common (1–2%; FTLD-UPS) [10]. Because of an unclear correlation between clinical syndrome and underlying neuropathology it is still challenging to predict the underlying pathological process according to clinical picture.

In most FTD-tau patients, there is a mutation in the *MAPT* gene located on chromosome 17. Tau protein is the most common protein that forms intracellular inclusions in neurodegenerative diseases. These inclusions consist of an abnormally hyperphosphorylated form of tau protein in the absence of amyloid β deposits. FTD-TDP form may be sporadic, but may also be associated with mutations in *TARDBP*, *GRN* (progranulin), or *C9orf72* (open-frame reading chromosome 72) genes [11]. There is accumulation of TDP-43 protein (TAR DNA binding protein 43) consisting of 414 amino acids which is encoded by the *TARDBP* gene located on chromosome 1 [12]. The TDP-43 protein has the function of a transcription regulator involved in maintaining RNA stability. FTD-FUS patients do not have a clear genetic background. FUS is a DNA / RNA binding protein that regulates gene expression. FTD-FUS inclusions are morphologically and by distribution similar to TDP-43 inclusions [13]. Also, a rare form of FTD-UPS has been associated with mutations in the *CHMP2B* gene [11, 14]. There is no unambiguous link between genes and molecular pathology of FTD and it is considered that pathological changes are a result of complex molecular mechanisms.

Predicting the underlying pathology in FTD is one of the biggest challenges in FTD diagnostics because distinguishing the accumulated proteins will be the key for targeted therapy. Direct analysis of accumulated proteins is not easily available but analysis of changes in specific protein concentrations in CSF may reflect pathophysiological changes in the brain. An increase in CSF levels of tTau and pTau and a decrease in A β 1 have been shown to identify AD pathology with high accuracy and are used to differentiate it from FTD. Furthermore, an AD-like profile is often found in patients with lvPPA, but not in patients with svPPA nor nfvPPA [2]. On the other hand, studies of CSF values of tTau, pTau, or TDP-43 did not show convincing results in predicting FTD [15], however it has been shown that the p-tau : t-tau ratio is lower in FTD-TDP than in FTD-tau subtype [2]. Neurofilament light chain (NfL) is another promising biomarker for FTD disease monitoring and prognosis. Blood and CSF levels of NfL are higher in patients with FTD than in control individuals, and its CSF values correlate with disease severity, survival, and cerebral atrophy [16]. However, CSF NfL is not disease specific because it is also increased in other neurodegenerative diseases. Furthermore, levels of NfL can not distinguish FTD subtypes [2].

Genetic biomarkers

FTD is a highly heritable disease with a positive family history in about 40% of patients, while a clear autosomal dominant inheritance is present in only 10%. Several genes associated with disease development have been identified, but

genes encoding tau protein (*MAPT*), progranulin (*GRN*), and *C9orf72* gene are responsible for almost 60% of hereditary forms. The mean age of disease onset in patients with *MAPT* gene mutation is 52.4 ± 5.9 years, while the mean age of disease onset in *GRN* mutation carriers is 61.8 ± 9.9 years [17]. Both genes have extremely high penetration, and 90-95% of mutation carriers develop the disease by the age of 70.

The *C9orf72* gene mutation causes about 25% of familial cases of FTD and is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS) [2, 18]. Both, *MAPT* and *GRN* mutations cause about 5-20% of cases of familial FTD. Mutations in *MAPT* gene and *C9orf72* repeats are more common associated with bvFTD. *MAPT* is also associated with svPPA. The clinical phenotype caused by *GRN* mutations includes bvFTD, bvFTD with parkinsonisms, nfvPPA, as well as corticobasal syndrome (CBS) (Table 1). Today, in addition to the most common *MAPT*, *GRN*, and *C9orf72* mutations, many other genes are known to be involved in FTD development, including rare variants of *CHMP2B*, *VCP* (valosin-containing protein), *SQSTM1* (sequestosome 1), and *UBQLN2* (ubiquiline 2) genes [11]. Interestingly, pathogenic variants of *TARDBP* and *FUS* genes are absent in patients with FTD as opposed to ALS or ALS-FTD cases [19]. The connection between ALS and FTD is extremely interesting. Both are progressive, severe neurodegenerative diseases with significant clinical, genetic, and pathological overlap. In recent years, genetic research has irrefutably linked these two diseases, and a significant number of genes (*TDP-43*, *VCP*, *C9orf72*) have been identified that can cause both diseases, and there are also genes that cause predominantly only one form of ALS / FTD spectrum which can be diagnostically of great importance (Table 2). Genome wide association studies have also revealed an association of FTD with the *TMEM106B* gene (modifying transmembrane factor 106B) and two risk loci: *RAB38*, a member of the RAS oncogenic family and *CTSC* gene for cathepsin C, and an association with the HLA locus [11].

Table 1. Genes associated with frontotemporal dementia

<i>Gene</i>	<i>Chromosomal location</i>	<i>Inheritance</i>	<i>FTD phenotype/s</i>
<i>Microtubule-associated protein tau (MAPT)</i>	17q21	AD	<ul style="list-style-type: none"> • bvFTD • bvFTD with parkinsonism, • CBS (more rarely PSPs) • semantic PPA
<i>Progranulin (GRN)</i>	17q21.31	AD	<ul style="list-style-type: none"> • bvFTD • bvFTD with parkinsonism, • CBS, • nonfluent PPA, • FTD-ALS
<i>Chromosome 9 open reading frame 72 (C9orf72)</i>	9p21.2	AD	<ul style="list-style-type: none"> • bvFTD • ALS-FTD • PPA
<i>Fused in sarcoma (FUS)</i>	16p11.2	AD/AR	<ul style="list-style-type: none"> • FTD-ALS
<i>Valosin-containing protein (VCP)</i>	9p13.3	AD	<ul style="list-style-type: none"> • IBM-FTD • bvFTD • semantic PPA • FTD-ALS
<i>Charged multivesicular body protein 2B (CHMP2B)</i>	3p11.2	AD	<ul style="list-style-type: none"> • bvFTD • bvFTD with parkinsonism • FTD-ALS
<i>Sequestosome 1 (SQSTM1)</i>	5q35	AD	<ul style="list-style-type: none"> • bvFTD • bvFTD with parkinsonism
<i>Ubiquilin-2 (UBQLN2)</i>	Xp11.21	X-dominant	<ul style="list-style-type: none"> • FTD-ALS
<i>TAR DNA binding protein (TARDBP)</i>	1q36	AD/AR	<ul style="list-style-type: none"> • FTD-ALS • bvFTD • semantic FTD

Table adapted from: Filippi M, Agosta F, Ferraro PM. Charting Frontotemporal Dementia: From Genes to Networks. J Neuroimaging. 2016;26(1):16-27 [12]

Table 2. Genetic differences and overlaps between FTD and ALS

Major phenotype	Gene	Clinical Presentation(s)	Brain pathology
FTD	CHMP2B	FTD	ubiquitin/p62
	GRN	FTD	TDP43
	MAPT	FTD	tau
FTD-ALS	CHCHD10	ALS, FTD, myopathy	Not reported
	C9orf72	ALS, FTD, AD, PD, CBS, ataxia	TDP43/p62/ repeatdipeptides/ ubiquitin
	CCNF	ALS, FTD	Not reported
	DCTN1	ALS, HMN7B, Perry syndrome, FTD	TDP43
	OPTN	ALS, FTD	TDP43/OPTN/ubiquitin
	SQSTM1	ALS, FTD, IBM, Paget's disease	TDP43/p62
	TBK1	ALS, FTD	TDP43/p62
	UBQLN2	ALS, FTD	TDP43/p62/UBQLN2/FUS/ OPTN
	VCP	ALS, FTD, IBM, Paget's disease	TDP43/p62
ALS	KIF5A	spastic paraplegia, ALS	TDP43
	FUS	ALS, FTD	FUS/ubiquitin/EWS/ TAF15
	MATR3	ALS, myopathy	MATR3
	SOD1	ALS	SOD1/ubiquitin
	TARDBP (TDP43)	ALS, FTD	TDP43
	TIA1a	ALS, myopathy, FTD	TDP43

Key: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; FTD, frontotemporal dementia; HMN7B, hereditary motor neuropathy, type 7B; IBM, inclusion body myopathy; PD, Parkinson's disease

Table adapted from: Ferrari R, Manzoni C, Hardy J. Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. *Neurobiol Aging*. 2019;78:98-110 [20]

Neuroimaging biomarkers

The main feature of FTD is the presence of different patterns of atrophy and / or hypometabolism with variable frontal or temporal predominance, varying degrees of asymmetry, and involvement of other cortical and subcortical structures [2; 21]. Research on the application of neuroimaging methods in FTD is mainly aimed at improving the differentiation from other neurodegenerative diseases, as well as at distinguishing clinical, pathological and genetic subtypes of FTD [21]. It has been shown that there are different neuroimaging patterns of FTD depending on the underlying gene changes. In patients with *GRN* mutation, clear asymmetric atrophy of either the left or right hemisphere involving the frontal, temporal and inferior part of the parietal lobe, atrophy of caudatus and thalamus and extensive lesions of white matter are present [12]. Parietal lobe involvement is unique to *GRN* mutation and is not present in patients with *MAPT* or *C9orf72* mutations [22]. On the other hand, in patients with *MAPT* mutation a more symmetrical pattern of frontotemporal atrophy is seen, involving predominantly the anterior part of temporal lobes [22]. The most variable neuroimaging patterns are found in patients with hexanucleotide repeats in the *C9orf72* gene, but relatively symmetrical atrophy of predominantly frontal lobes with decay of both posterior regions and cerebellum and thalamus is most commonly seen [22]. A small number of studies have also investigated FTD patients with rare mutations. Thus, the *TARDBP* mutation has been shown to be predominantly manifested by temporal lobe atrophy, while *TREM2* (triggering receptor expressed on myeloid cells) mutation is manifested by frontotemporal atrophy and white matter abnormalities [12].

Neuroimaging methods have the potential to be used as biomarkers for early detection and measurement of disease progression, and to be used as sensitive markers for assessing efficacy of disease-modifying therapies. MRI is considered to be an effective biomarker for FTD also in the presymptomatic phase, years before the clinical onset [15]. Rohrer and colleagues found that neuroimaging changes in carriers of mutations of genes associated with FTD are visible at least 10 years before the onset of first symptoms. It is emphasized that presymptomatic changes are seen significantly earlier in carriers of gene mutations compared to individuals who are not carriers of FTD-related mutations [7]. It has been shown that decay of insula and temporal cortex occurs first (about 10 years before the onset of first symptoms), followed by decay of the frontal cortex and subcortical areas (about 5 years before the onset of first symptoms), followed by decay of the parietal and cingulate cortex (at the time of first symptoms), and eventually there is atrophy of the occipital cortex (5 years after first symptom

onset) and the cerebellum (10 years after onset) [7]. The earliest changes occur in *MAPT* mutation carriers, affecting medial temporal structures. Carriers of *GRN* mutations have first changes in the insula, about 15 years before symptom onset, while the earliest change in carriers of *C9orf72* mutations occur as atrophy of the thalamus and posterior cortical regions [7].

Although the basic feature of FTD is gray matter atrophy, research has shown that white matter changes, visible by diffuse tensor imaging (DTI), are probably more sensitive for detecting early changes in FTD than gray matter changes [2]. A significant change in white matter of frontotemporal, frontoparietal, and parietooccipital regions was also found in asymptomatic carriers of *GRN* or *MAPT* mutations [12]. Furthermore, there is a difference in white matter involvement in FTD-tau and FTD-TDP-43 cases with significantly more damage in white matter of patients with tau accumulation [23].

In addition to brain atrophy in FTD, changes are also visible in brain metabolism. The use of FDG-PET (PET with 18F-fluorodeoxyglucose) allows the visualization of changes in brain metabolism that precede gray matter atrophy in FTD. Most significant findings have been shown in patients with bvFTD showing low glucose metabolism in the orbitofrontal cortex, dorsolateral cortex, medial prefrontal cortex, anterior temporal lobes, and basal ganglia, which may distinguish them from those with other types of dementia [2].

Concluding remarks

FTD is a neurodegenerative disorder with significant clinical, pathohistological and genetical variability. Because of the overlap of symptoms of FTD with psychiatric disorders and other neurodegenerative diseases diagnosis is often challenging. The development of diagnostic markers is crucial to distinguish FTD from other neurodegenerative dementias and to differentiate clinical, genetic, or pathological subtypes. Research in the field of biomarkers in FTD has made significant progress in recent years while the main goal of further development of new biomarkers is to detect the disease in the presymptomatic stage.

References

- [1] Graff-Radford NR, Woodruff BK. Frontotemporal dementia. *Semin Neurol* 2007;27:48–57.
- [2] Meeter LH, Kaat LD, Rohrer JD, van Swieten JC. Imaging and fluid biomarkers in frontotemporal dementia. *Nat Rev Neurol*. 2017 Jul;13(7):406–419. doi: 10.1038/nrneurol.2017.75.
- [3] Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012;8:423–34.
- [4] Sieben A, Van Langenhove T, Engelborghs S et al. The genetics and neuropathology of frontotemporal lobar degeneration. *Acta Neuropathol*. 2012;124:353–372.
- [5] Rohrer JD, Guerreiro R, Vandrovicova J et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009;73:1451–6.
- [6] Geser F, Martinez-Lage M, Robinson J et al. Clinical and pathological continuum of multisystem TDP-43 proteinopathies. *Arch Neurol* 2009;66:180–9.
- [7] Rohrer JD, Nicholas JM, Cash DM et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol* 2015;14(3):253–62.
- [8] Mahoney CJ, Ridgway GR, Malone IB et al. Profiles of white matter tract pathology in frontotemporal dementia. *Hum Brain Mapp* 2014;35:4163–79.
- [9] Perry DC, Sturm VE, Seeley WW, Miller BL, Kramer JH, Rosen HJ. Anatomical correlates of reward-seeking behaviours in behavioural variant frontotemporal dementia. *Brain* 2014;137:1621–6.
- [10] Halliday G, Bigio EH, Cairns NJ, Neumann M, Mackenzie IR, Mann DM. Mechanisms of disease in frontotemporal lobar degeneration: gain of function versus loss of function effects. *Acta Neuropathol* 2012;124:373–82.
- [11] Ferrari R, Momeni P. *Molecular Genetics of Frontotemporal Dementia*. In: eLS. John Wiley & Sons, Ltd: Chichester. 2013.
- [12] Filippi M, Agosta F, Ferraro PM. Charting Frontotemporal Dementia: From Genes to Networks. *J Neuroimaging* 2016;26(1):16–27.
- [13] Colombrita C, Onesto E, Megiorni et al. TDP-43 and FUS RNA-binding proteins bind distinct sets of cytoplasmic messenger RNAs and differently regulate their post-transcriptional fate in motoneuron-like cells. *J. Biol. Chem*. 2012; 287:15635–47.
- [14] Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol*. 2011;24(6):542–9. doi: 10.1097/WCO.0b013e32834cd442.
- [15] Borroni B, Benussi A, Premi E, et al. Biological, Neuroimaging, and Neurophysiological Markers in Frontotemporal Dementia: Three Faces of the Same Coin. *J Alzheimers Dis*. 2018;62(3):1113–1123. doi:10.3233/JAD-170584
- [16] Meeter LH, Doppler EG, Jiskoot LC, et al. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Ann Clin Transl Neurol*. 2016;3(8):623–636. doi:10.1002/acn3.325

- [17] Seelaar H, Kamphorst W, Rosso SM et al. Distinct genetic forms of frontotemporal dementia. *Neurology* 2008;17:1220–1226.
- [18] DeJesus-Hernandez M, Mackenzie IR, Boeve BF et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9orf72 causes chromosome 9p-linked FTD and ALS. *Neuron* 2011; 72: 245–56.
- [19] Hardy J, Rogaeva E. Motor neuron disease and frontotemporal dementia: sometimes related, sometimes not. *Exp Neurol* 2013;262:75–83.
- [20] Ferrari R, Manzoni C, Hardy J. Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. *Neurobiol Aging*. 2019;78:98-110. doi: 10.1016/j.neurobiolaging.2019.02.006.
- [21] Gordon E, Rohrer JD, Fox NC. Advances in neuroimaging in frontotemporal dementia. *J Neurochem*. 2016;138 Suppl 1:193-210.
- [22] Rohrer JD, Lashley T, Schott JM et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 2011;134:2565-81.
- [23] McMillan CT, Irwin DJ, Avants BB et al. White matter imaging helps dissociate tau from TDP-43 in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2013;84:949-55.

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EARLY DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

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Summary

Deep brain stimulation (DBS) is well known safe and effective method in reducing motor disability and improving quality of life in patients with advanced Parkinson's disease (PD). DBS is typically performed in late-stage PD, a mean of 14 to 15 years after diagnosis. Recent studies have proved that DBS could be beneficial at an earlier stage of Parkinson's disease for motor function, dyskinesia, Quality of life (QoL), freezing of gait (FOG), neuropsychiatric symptoms, social adaptation, occupational, and psychosocial function in patients with PD. It is beneficial also for reducing medications, polypharmacy and delaying secondary physical and psychosocial consequences. The DBS team always weighs the benefit and risk individually and carefully. A positive decision is supported by a judgment of low risk factors for complications and worse outcomes. We have to provide careful follow-up of patients with early DBS. So, in conclusion, early DBS is good option when patients might be able to derive greater long-term benefit.

We review the current application of deep brain stimulation (DBS) in Parkinson disease (PD) and consider the evidence that earlier use of DBS confers long-term symptomatic benefit for patients compared to best medical therapy.

Key words: DBS; early phase; Parkinson disease; Quality of life

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Based on worldwide data, the prevalence of PD is 428/100 000 in people aged between 60 and 69 years. The incidence rate of PD

is 12 to 20 per 100,000 annually in Northern Europe [1]. It is estimated that there are approximately 1 million PD sufferers in the USA and 120,000 in the United Kingdom, 1 in 20 of whom are under the age of 40 years [2]. An analysis of PD epidemiology suggests that the number of individuals aged >50 years with PD in the world's most populated countries will be double between 10 and 14 million in 2030 [3]. Parkinson's disease is a chronic progressive neurodegenerative disease in which abnormal aggregates are deposited in the area of the pars compacte substantie nigre, leading to loss of dopaminergic neurons and striatal dopamine deficiency [4]. It is the second most common neurodegenerative disorder affecting as many as 2-3% of the population aged ≥ 65 years [5]. The disease is usually diagnosed by the appearance of the first motor symptoms, such as bradykinesia, rigidity, tremor at rest, or postural instability. In addition to motor symptoms, non-motor symptoms (NMS) appear, such as lack of emotional involvement and interest (apathy), excessive daytime sleepiness, sleep problems and constipation, hyposmia, which can begin up to 10 years before diagnosis [6].

The global economic cost of PD is increasing, not only for the medication, but also for nursing homes and social care [7]. The most significant increase of costs is in later stage PD [8].

The typical treatment of PD is currently medical, surgical, and supportive. But despite optimal medical therapy, there remains significant morbidity, disability and decrease of QoL yet to be addressed in PD. Medication side effects, psychological morbidity, inadequate quality of life, and the burden on caregivers are important components which make difficult to manage PD [5].

Deep brain stimulation in Parkinson's disease

Deep brain stimulation (DBS) is the therapeutic use of chronic electrical stimulation in the deep brain targets points via an implanted electrode. DBS in PD is present more than 34 years. In movement disorders it is used mostly in PD and there are almost 200.000 implanted DBS worldwide. Although DBS is so present as treatment, the mechanism of DBS is still unknown. It is hypothesized that several mechanisms are included like local and network-wide electrical and neurochemical effects of stimulation, modulation of oscillatory activity, synaptic plasticity, neuroprotection and neurogenesis [9].

There is currently level 1 evidence that deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the globus pallidus internus (GPi) is effective in improving L-dopa-responsive signs in PD patients [10-13]. Many studies have shown that with proper patient selection, there is improvement in PD patients seen with: standard scales/measures of disease, quality of life measures, co-mor-

bid conditions, medication intake and chronic care costs [10-19]. We know in everyday clinical practice that many patients (especially younger, working age) in time gradually develop motor fluctuations, dyskinesias, impulse control disorder. Unfortunately, PD patients more often lose employment and independence.

Nevertheless, DBS has been typically left until late-stage PD, a mean of 14 to 15 years after diagnosis when quality of life, social adjustment (psychosocial competence), and professional activity are already severely impaired. In that late phase, the possibility is existing that disease could progress to the point that the patient may no longer be fit for neurosurgical intervention. It is proven that neurostimulation improves quality of life due to improvement motor and non-motor symptoms but in this late stage of the disease, features unresponsive to dopaminergic treatment (and DBS) often predominate. Group of researchers have hypothesized that neurostimulation would be beneficial at an earlier stage of Parkinson's disease with mild complications and fluctuation of symptoms. The concept of earlier DBS therapy emerged as a therapeutic tool to prevent the development of motor complications and prolong quality of life for PD patients [20].

Early Deep brain stimulation in Parkinson's disease

In EARLYSTIM study, researchers randomly assigned patients with Parkinson's disease and a recent onset of motor complications to receive neurostimulation plus medical therapy or medical therapy only. So, the EARLYSTIM study compared DBS with best medical treatment (BMT) over 2-years. Disease-related quality of life was chosen as the primary outcome and secondary outcomes were parkinsonian motor disability, activities of daily living, levodopa-induced motor complications (as assessed with the use of the Unified Parkinson's Disease Rating Scale, parts III, II, and IV, respectively), and time with good mobility and no dyskinesia.

Inclusion criteria were idiopathic PD, age >18 years and 60, Hoehn and Yahr stage 2.5 in the best ON, disease duration > 4 years, fluctuations and/or dyskinesias < 3 years, and one of the two following forms of impairment: impairment of social and occupational functioning impairment in activities of daily living. In the studied patients mean duration of Parkinson's disease was 7.5 years, a mean of 1.7 years of the onset of levodopa-induced motor complications and mean age was 52 years. QoL was improved from baseline to 24 months by 26% in the neurostimulation group but worsened by 1% in the medical-therapy group. Neurostimulation was superior to medical therapy with respect to motor disability, activities of daily living, levodopa-induced motor complications, and time with good mobility and no dyskinesia. Serious adverse events were similar in both groups [21].

Specific challenges of DBS in earlier stage of PD and inclusion criteria (duration 4 years) are the risk of inclusion of patients who later evolve to atypical parkinsonism, the risk of a floor effect for the benefit from DBS, the need for experienced multidisciplinary care including prevention of suicidal behavior, and the need for highly qualified long-term follow-up.

Although the EARLYSTIM trial suggested that the effect of DBS in PD is independent of the duration and severity of motor complications, earlier is not necessarily better [22]. Most authorities agree that STN-DBS should be considered before the occurrence of severe psychosocial and professional limitations and deterioration of QoL because of difficulties reversing this situation once it is established. The suggestion is that DBS should be offered when there is a favorable clinical benefit-to risk ratio, rather than routinely considering it at the onset of motor complications. The appropriate time for surgery is when the needs and expected benefits outweigh the risks. Patients have to be educated, informed with objective and comprehensive information about individualized risks and benefits of DBS. It is necessary to differ younger versus older patients. In that area, the role of the DBS multidisciplinary team is key especially in discussion about all these issues. Some researchers and clinicians think that the most relevant issue is not when to operate but on whom [22]. The EARLYSTIM study provides level A evidence in favor of DBS over BMT in PD patients under 61 years with recent onset of motor complications. DBS is a powerful tool to improve our patients, and particularly their QoL. Early DBS should be carefully discussed with all patients who can potentially benefit from it. The EARLYSTIM group eliminates the possibility of a placebo effect and a lessebo effect of DBS . [23]

This EARLYSTIM group of researchers and clinicians performed a few secondary analyses of data from the previously published EARLYSTIM study. In one, impaired QOL as subjectively evaluated by the patient is the most important predictor of benefit in patients with PD and early motor complications [24]. We need systematically include evaluation of disease specific QOL when selecting patients with PD for DBS.

Other secondary analyses have shown in the large cohort with Parkinson's disease and early motor complications, better overall behavioral outcomes in group of patients treated by DBS plus medical therapy compared with medical therapy alone. The presence of hyperdopaminergic behaviors and neuropsychiatric fluctuations can be judged additional arguments in favor of subthalamic stimulation if surgery is considered for disabling motor complications [25].

Within the first 2 years of DBS, freezing of gait and other axial signs improved in the medication-off condition with DBS compared to best medical treatment, proven also in secondary analysis EARLYSTIM patients [26].

In the other sub analysis of early DBS, it was provided significant improvements in social, occupational, and psychosocial function, but not in the actual work engagement compared with BMT at 2 years for patients aged ≤ 60 years with PD and early motor complications, They suggest that apathy may impact ability to work [27].

DBS is a cost-effective intervention in PD patients with early motor complications, offering additional health benefits at acceptable incremental cost as study have proved. The most crucial factor in reducing the costs is possibility of maintaining a simplified, low dose medication regimen [28].

One group reported the results of a pilot trial investigating preliminary safety and tolerability of DBS in early PD with thirty subjects with idiopathic PD (Hoehn & Yahr Stage II off medication), age 50–75, on medication ≥ 6 months but < 4 years, and without motor fluctuations or dyskinesias. They were randomized to optimal drug therapy (ODT) (n=15) or DBS+ODT (n=15). Co-primary endpoints were the time to reach a 4-point worsening from baseline in the UPDRS-III off therapy and the change in levodopa equivalent daily dose from baseline to 24 months. This study provided preliminary evidence that DBS is well tolerated in early PD [29]. In the next report they have shown 5-year outcomes from the subthalamic nucleus (STN) deep brain stimulation (DBS) in early-stage Parkinson disease (PD). The pilot was a prospective, single-blind clinical trial that randomized patients with early-stage PD (Hoehn & Yahr II off medications) to receive bilateral STN DBS plus optimal drug therapy (ODT) vs ODT alone. Participants who completed the 2-year trial participated in this observational follow-up study, which included annual outpatient visits through 5 years. This analysis includes 28 patients who were taking PD medications for 6 months to 4 years at enrollment. This study provides Class II evidence that DBS implanted in early-stage PD decreases the risk of disease progression and polypharmacy compared to optimal medical therapy alone [30]. The same investigator group have published results that suggest the possibility that DBS in early PD may slow rest tremor progression. Future investigation in a larger cohort is needed [31].

After all these studies it is essential to emphasize that for beneficial effect of early DBS are important: good individual patients' selection, knowing predictors of good and bad outcomes, adverse effects, prognosis, thinking about possible neuroprotection and ask for patients' preferences.

Conclusion

Current evidence has shown that DBS is safe and effective method in experience hand. Studies suggest that DBS is typically performed in late-stage PD, a mean of 14 to 15 years after diagnosis. Current guidelines recommend that PD patients who are resistant to medical therapies, have significant medication side effects and lengthening off periods, but are otherwise cognitively intact and medically fit for surgery be considered for DBS.

If these criteria are rigidly interpreted, it may be that, by the time medical treatment options have been exhausted, the disease has progressed to the point that the patient may no longer be fit for neurosurgical intervention.

We need more studies that will give us better prediction of outcome and long-term improvement. As previous studies have shown early DBS improve motor function, dyskinesia, QoL, freezing of gait, neuropsychiatric symptoms, social adaptation, occupational, and psychosocial function in patients with PD. It is beneficial also for reducing medications, polypharmacy and delaying secondary physical and psychosocial consequences.

From the evidence available, we conclude that surgical management of PD alone or in combination with medical therapy results in greater improvement of motor symptoms and quality of life than medical treatment alone. There is evidence to support the use of DBS in earlier stages of the disease than for which it is currently used. The improving short and long-term safety profile of DBS makes early application a realistic possibility. The evaluation and decision must be individual. We must consider and include evaluation of disease specific QoL in every day clinical practice. Early DBS is particularly important for patients in younger age and working age. Adverse effects on medications are also often reason for earlier DBS. DBS is the best method for disabling tremor and it could be provided in an early phase. We must also consider patients' preferences and what are the main disability. The DBS team always weighs the benefit and risk individually and carefully. A positive decision is supported by a judgment of minimal risk factors for complications and worse outcomes. We must provide careful follow-up of patients with early DBS.

In conclusion, early DBS is good option when patients might be able to derive greater long-term benefit.

References

- [1] Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord* 2003;18:19–31.
- [2] Wickremaratchi MM, Ben-Shlomo Y, Morris HR. The effect of onset age on the clinical features of Parkinson's disease. *Eur J Neurol* 2009;16:450–456.
- [3] Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007;68:384–386.
- [4] Rafael ASR, Barbosa JMP, Rosas MJSL, Garrett MCLA. Parkinson's disease and development of Levodopa induced motor complications: Influence of baseline features and first medical approach. Vol. 1, *Porto Biomedical Journal*. 2016. p. 136–41.
- [5] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Prim*. 2017;3:1–21.
- [6] Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem* 2016;139:318–24.
- [7] Winter Y, Balzer-Geldsetzer M, Spottke A, et al. Longitudinal study of the socioeconomic burden of Parkinson's disease in Germany. *Eur J Neurol* 2010;17:1156–1163.
- [8] Chen JJ. Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. *Am J Manag Care* 2010;16:S87–S93.
- [9] Chiken S, Nambu A. Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption?. *Neuroscientist*. 2016;22(3):313–322.
- [10] Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896–908.
- [11] Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 2009;65:586–595.
- [12] Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301:63–73.
- [13] Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010;362:2077–2091.
- [14] Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 2006;21(suppl 14):S290–S304.
- [15] Volkmann J, Allert N, Voges J, et al. Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Ann Neurol* 2004;55:871–875.
- [16] Houeto JL, Damier P, Bejjani PB, et al. Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. *Arch Neurol* 2000;57:461–465.
- [17] Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 2012;79:55–65.

- [18] Evidente VG, Premkumar AP, Adler CH, et al. Medication dose reductions after pallidal versus subthalamic stimulation in patients with Parkinson's disease. *Acta Neurol Scand* 2011;124:211–214.
- [19] Moro E, Lozano AM, Pollak P, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord* 2010;25:578–586.
- [20] Deuschl G, Schüpbach M, Knudsen K, Pinsker MO, Cornu P, Rau J, Agid Y, Schade-Brittinger C. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. *Parkinsonism Relat Disord*. 2013 Jan;19(1):56-61.
- [21] Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368:610–622.
- [22] Mestre TA, Espay AJ, Marras C, Eckman MH, Pollak P, Lang AE. Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease-the EARLYSTIM trial: early is not always better. *Mov Disord*. 2014;29(14):1751-6.
- [23] Schüpbach WM, Rau J, Houeto JL, Krack P, Schnitzler A, Schade-Brittinger C, Timmermann L, Deuschl G. Myths and facts about the EARLYSTIM study. *Mov Disord*. 2014;29(14):1742-50.
- [24] Schuepbach WMM, Tonder L, Schnitzler A, Krack P, Rau J, Hartmann A, Hälbig TD, Pineau F, Falk A, Paschen L, Paschen S, Volkmann J, Dafsari HS, Barbe MT, Fink GR, Kühn A, Kupsch A, Schneider GH, Seigneuret E, Fraix V, Kistner A, Chaynes PP, Ory-Magne F, Brefel-Courbon C, Vesper J, Wojtecki L, Derrey S, Maltête D, Damier P, Derkinderen P, Sixel-Döring F, Trenkwalder C, Gharabaghi A, Wächter T, Weiss D, Pinsker MO, Regis JM, Witjas T, Thobois S, Mertens P, Knudsen K, Schade-Brittinger C, Houeto JL, Agid Y, Vidailhet M, Timmermann L, Deuschl G; EARLYSTIM study group. Quality of life predicts outcome of deep brain stimulation in early Parkinson disease. *Neurology*. 2019;92(10):e1109-e1120.
- [25] Lhommée E, Wojtecki L, Czernecki V, Witt K, Maier F, Tonder L, Timmermann L, Hälbig TD, Pineau F, Durif F, Witjas T, Pinsker M, Mehdorn M, Sixel-Döring F, Kupsch A, Krüger R, Elben S, Chabardès S, Thobois S, Brefel-Courbon C, Ory-Magne F, Regis JM, Maltête D, Sauvaget A, Rau J, Schnitzler A, Schüpbach M, Schade-Brittinger C, Deuschl G, Houeto JL, Krack P; EARLYSTIM study group. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. *Lancet Neurol*. 2018;17(3):223-231.
- [26] Barbe MT, Tonder L, Krack P, Debû B, Schüpbach M, Paschen S, Dembek TA, Kühn AA, Fraix V, Brefel-Courbon C, Wojtecki L, Maltête D, Damier P, Sixel-Döring F, Weiss D, Pinsker M, Witjas T, Thobois S, Schade-Brittinger C, Rau J, Houeto JL, Hartmann A, Timmermann L, Schnitzler A, Stoker V, Vidailhet M, Deuschl G; EARLYSTIM study group. Deep Brain Stimulation for Freezing of Gait in Parkinson's Disease With Early Motor Complications. *Mov Disord*. 2020;35(1):82-90.

- [27] Stoker, V.; Krack, P.; Tonder, L.; Barnett, G.; Durand-Zaleski, I.; Schnitzler, A.; Houeto, J.L.; Timmermann, L.; Rau, J.; SchadeBrittinger, C.; et al. Deep Brain Stimulation Impact on Social and Occupational Functioning in Parkinson's Disease with Early Motor Complications. *Mov. Disord. Clin. Pract.* 2020; 7: 672–680.
- [28] Fundament T, Eldridge PR, Green AL, Whone AL, Taylor RS, Williams AC, Schuepbach WM. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. *PLoS One*. 2016;11(7):e0159340.
- [29] Charles D, Konrad PE, Neimat JS, Molinari AL, Tramontana MG, Finder SG, Gill CE, Bliton MJ, Kao C, Phibbs FT, Hedera P, Salomon RM, Cannard KR, Wang L, Song Y, Davis TL. Subthalamic nucleus deep brain stimulation in early stage Parkinson's disease. *Parkinsonism Relat Disord.* 2014;20(7):731-7.
- [30] Hacker ML, Turchan M, Heusinkveld LE, et al. Deep brain stimulation in early-stage Parkinson disease: Five-year outcomes. *Neurology*. 2020;95(4):e393-e401.
- [31] Hacker ML, DeLong MR, Turchan M, Heusinkveld LE, Ostrem JL, Molinari AL, Currie AD, Konrad PE, Davis TL, Phibbs FT, Hedera P, Cannard KR, Drye LT, Sternberg AL, Shade DM, Tonascia J, Charles D. Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease. *Neurology*. 2018;91(5):e463-e471.

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PUBLIC HEALTH GENOMICS IN PARKINSON'S DISEASE: UTILIZING NOVEL GENOTYPE AND PHARMACOGENOMIC FINDINGS

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Summary

Parkinson's disease (PD), as the second most frequent neurodegenerative disease, is a significant public health challenge, which is increasing in time due to the ageing of the population and lifestyle changes. The current numerous therapeutic options are mostly symptomatic and do little to alter the underlying pathological changes. Furthermore, there is a big challenge for the optimisation of therapies since patients not only respond differently to current treatment options but also develop different side effects of the treatment. Genetic variability in the human genome may not only serve as a biomarker for the metabolism and availability of drugs but also, due to heterogeneity of pathogenesis, serve as a biomarker for stratification of patients for best therapies. Unravelling the genetic variability and utilizing appropriate treatment is the ultimate goal of personalized medicine that will surely develop during this century. The goal of this review is to assess currently available literature in order to see if there is any possibility for translating current knowledge into improving public health and clinical practice.

Key words: Parkinson's disease; pharmacogenomics; personalized medicine; genetics

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease present today. The incidence and prevalence are highest in the population aged ≥ 65 years old, making it a significant public health challenge in the elderly [1]. The clinical course of the disease is progressive and is defined by motor symptoms such as resting tremor, bradykinesia and rigidity, along with a wide variety of non-motor symptoms like autonomic dysfunction, sleep disorders, cognitive deficits and behavioural changes [2]. The first symptoms appear several years before the classic motor symptoms during the prodromal PD, which is marked by non-specific symptoms like constipation and insomnia [3]. Our understanding of underlying mechanisms in PD has significantly increased over recent years. The main postulated pathological mechanisms in PD are the intracellular aggregation of α -synuclein, which form Lewy bodies [4], and the loss of dopaminergic neurons that begin in the substantia nigra and becomes more widespread as the disease progresses [5]. The landmark paper published by Braak et al. describes a gradually evolving pathological severity, starting from the lower brainstem, with a progression to the limbic and neocortical brain regions in the later stages of PD [6].

The variations of clinical states between patients can be significant, even though the underlying mechanisms are similar. Efforts have been made to categorise the disease into varying subtypes. Seyed-Mohammad et al. propose three subtypes based predominantly on clinical characteristics: the mild motor, intermediate and diffuse malignant subtypes. Importantly, evidence from the study indicated that neuroimaging correlated better with the subtypes than genetic information, even after incorporating a single "genetic risk score" that encompassed 30 specific PD-related mutations. However, this could also be a consequence of a lack of patients with particular variations in the population they studied [7]. The need to categorise the disease comes from variabilities in presentation, response to treatment and incidence of side-effects.

Current treatment options for PD are plentiful, at least in comparison to other neurodegenerative diseases, which gives PD patients more extended control of symptom severity and improved quality of life. Unfortunately, no treatment halts the pathological mechanisms that drive disease progression, with most treatment being focused on replacing or enhancing dopamine availability. The golden standard in pharmacologic therapy is dopamine replacement therapy, mainly levodopa, used in synergy with dopamine receptor agonists, monoamine oxidase (MAO) inhibitors or catechol-O-methyltransferase (COMT) inhibitors [8]. The challenge that stems from this type of therapy is the delicate balance

between the beneficial and harmful effects that can arise [9]. The consequence of this is the need to fine-tune and personalise the therapy to each patient to account for the variability in drug response, which occurs due to various clinical, environmental and genetic factors [8].

Even though it has been thought until 20 years ago that genes do not play a more significant role in the pathogenesis of Parkinson's disease, we know today that around 15% of patients have a positive familial history, with an estimation of 5-10% of patients having a monogenic form of the disease according to Mendelian inheritance patterns. The development and broader availability of crucial technology like the whole genome and exome sequencing lead to the discovery of newer, rarer mutations. Discovering the genes that could lead to the disease is essential, but the focus of current research is the insight into the pathophysiology of the disease through gene function, which could, in turn, lead to new treatment plans or even prevention [10]. Current research has pointed to a total of 90 risk loci that have an association with PD, which represents a higher percentage (16-36%) of heritability than was previously thought [11]. The number of mutations related to both the monogenic types of PD and the genes related to complex phenotypes that encompass the PARK loci grows continuously [1]. "Culprit" genes which have been discovered so far display a variety of functions on a cellular level and encompass disorders concerning: mitochondrial function, endocytosis, autophagy, lysosome function and immune response [12]. A disturbance in any of these areas of cellular function could causally lead to the accumulation of the intracellular protein α -synuclein, a step considered to be the key in the development of the disease [13]. It is certain that the importance of genetics in Parkinson's disease will only grow with discoveries and that, at this point, it is crucial to determine the risk behind its inheritability, trying to predict the course of the disease and eventually intervene with the help of gene therapy.

Personalised medicine driven by genetics

The modern concept of personalised medicine encompasses genetic and pharmacogenomic properties, along with disease type and lifestyle specific adjustments [14]. Our knowledge of the human genome is increasing exponentially, driven by strong initiatives in the field and cooperation between countries. The heterogeneity and nature of Parkinson's disease makes it a good fit for developing personalised treatment. From a genetics standpoint, the main aspects currently being studied are the genotype specific treatment, currently in clinical trials, as well as pharmacogenomic properties of existing PD treatment.

Genotype specific treatment

Gene variations that influence pharmacogenomic properties and treatment in PD are not only focused on the metabolic and activity pathways of the drugs. There is a wide number of genes that are linked to monogenic PD, but only some had their association proven continuously in various research studies. Mutations in the genes coding α -Synuclein (SNCA), Leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting-associated protein 35 (VPS35), parkin RBR E3 ubiquitin-protein ligase (PRKN), PTEN-induced putative kinase 1 (PINK1), glucocerebrosidase (GBA), Parkin (PARK2) and oncogene DJ-1 [15] have mostly been found before the onset of genome-wide association studies, while many candidate genes found after are yet to be definitively proven to cause a significant risk for PD. Importantly, the currently known candidate genes can explain only a small fraction of cases where there is a known higher familial incidence of PD [11]. It is remarkable, however, that assessing polygenic risk scores and combining those with specific clinical parameters can yield impressive sensitivity of 83.4% and specificity of 90% [16]. The unfortunate consequence of the rapid expansion of knowledge in the field and amount of target genes is that the studies assessing pharmacogenomics of these gene variants are not keeping up.

Current evidence, albeit limited, points to differences in treatment response between various genotypes of monogenic PD. Mutations in the LRRK2 gene are known to cause familial PD, especially in North African and Ashkenazi Jew populations [17]. LRRK2 protein has a variety of physiological functions in intracellular trafficking and cytoskeleton dynamics, along with a substantial role in the cells of innate immunity. It is yet unclear how mutations in LRRK2 influence the pathogenesis of PD, but there is numerous evidence that links it to a disorder in cellular homeostasis and subsequent α -synuclein aggregation [18]. Results in-vitro and in-vivo animal model studies for inhibition of mutant LRRK2 are promising, and in most cases, confirm a reduced degeneration of dopaminergic neurons [19]. The biggest challenge of human trials has been creating an LRRK2 inhibitor that can pass the blood-brain barrier, which was overcome by Denali Therapeutics, and the phase-1b trial for their novel LRRK2 inhibitor has been completed and is awaiting official results [18]. Furthermore, LRRK2-associated PD has a similar response to L-dopa compared to sporadic PD, with conflicting results for the possible earlier development of motor symptoms [20].

SNCA gene encodes the protein α -synuclein, that is now considered a central player in the pathogenesis of PD due to its aggregation into Lewy-bodies. SNP's in the SNCA gene are consistently linked to an increased risk of developing PD in GWAS studies in both familial and even sporadic PD [21]. In cases of auto-

somal dominant mutations, there is a solid L-dopa and classical PD treatment response, albeit with early cognitive and mental problems, akin to GBA mutations [22]. There are several planned therapeutic approaches suited for SNCA polymorphism genotypes and include: targeted monoclonal antibody immunotherapy of α -synuclein [23], downregulation of SNCA expression by targeted DNA editing [24] and RNA interference of SNCA [25]. Roche Pharmaceuticals has developed an anti- α -synuclein monoclonal antibody that is now in phase 2 of clinical trials that is still ongoing [26]. Other two methods are still in preclinical testing, and their development shows promise for the future.

Glucocerebrosidase mutations represent a known risk factor for developing PD. GBA mutation associated PD is characterised by the earlier onset of the disease, followed by a more pronounced cognitive deficit and a significantly higher risk of dementia [27]. Gaucher's disease (GD) is an autosomal recessive genetic disorder that also arises from mutations in the GBA gene. The current enzyme replacement and chaperone treatment options for systemic manifestations of GD are not effective in treating the neurological manifestations of the disease as they are not able to reach the CNS [28]. Three genotype-specific therapies to address the cognitive decline are currently being tested with promising early results, two focusing on the chaperones ambroxol [29] and LTI-291 to increase glucocerebrosidase activity, and the third focusing on reducing the levels of glucocerebrosidase with ibiglustat [27]. Current research does not show a significant influence of GBA mutations on L-dopa response properties and is generally followed by adequate motor symptom control [30]. A single study by Lesage et al. in a population of European origin linked a higher incidence of dyskinesias in GBA-PD patients [31], but that has not been replicated in a more recent study by Zhang et al. in a population of Chinese origin [32].

Pharmacogenomic properties and genotype-specific treatment of several other gene mutations in PD such as VPS35, PINK1, PRKN and DJ1 have not yet been characterised fully and are currently a focus of several studies that as of writing do not have preliminary results available [15, 33, 34].

Pharmacogenomics of Parkinson's Disease

The general principles and goals of pharmacogenomics are to identify the genetic factors behind the varied drug response in individuals, thereby predicting response and paving the way for personalised medicine [35]. The focus in the early days was centred on testing of single genes; however, the advent of genome-wide association studies (GWAS) promises an increased understanding in variation to therapy drug response [36]. The large sizes of cohorts are a

prerequisite for the strength of GWAS, which favours common diseases such as PD. Only approximately 10% of current GWAS focus on pharmacogenomics, signifying the need for further studies in this field [36].

The two main areas where the variability of drug response is studied are the pharmacokinetics and pharmacodynamics of the drug. Pharmacokinetics incorporates all processes that affect how the drug is absorbed, distributed, metabolised, and excreted in the body, while pharmacodynamics is focused on the target actions of the drug. Current evidence points out that genetic variability and its effects on drug characteristics are concentrated in three major steps: the initial pharmacokinetic processes that ultimately affect the plasma concentration, the capability of drugs in passing the blood-brain barrier (BBB), and finally, the modification of target pharmacodynamic properties of the drug [20]. Expanding the knowledge of the variations that affect these three factors will pave the way for predicting drug response, thus improving personalised medicine in all diseases. It is crucial to bear in mind that genetic factors can also modify the pathological characteristics of the disease, creating sub-types, even though that is still not the case in PD, as mentioned earlier [7].

Pharmacogenomics of Parkinson's disease treatment

Current treatment in PD is focused on alleviating the symptoms and does little to slow down the pathophysiological progression of the disease. As such, the therapy goal is to increase the amount of dopamine to compensate for the loss of dopaminergic neurons. The therapeutic of choice for this is levodopa, or L-dopa, which relieves the motor symptoms by increasing the availability of dopamine in the central nervous system (CNS) [37]. All the current pharmaceutical treatment options centre around the dopamine metabolic pathway. Unlike dopamine, L-dopa can cross the blood-brain barrier. However, it is primarily metabolised outside of the CNS by aromatic L-amino acid decarboxylase (DDC) and to a lesser extent by catechol-O-methyltransferase (COMT) enzymes. The metabolism of L-dopa continues in the presynaptic neurons, where DDC converts it to dopamine. Ideally, this causes an increase in synaptic dopamine vesicles and subsequently an increase in dopamine neurotransmission, but some of the dopamine is lost due to the enzyme monoamine oxidase B (MAO-B) that converts it to 3,4-dihydroxyphenylacetic acid (DOPAC). The final step in dopamine activity is the activation of dopamine receptors 1 through 5 (DRD1-5) on the postsynaptic terminal that exerts the function of this pathway in the postsynaptic neurons [38]. There is a significant variation in therapy response and side-effect incidence in treating PD, which can be linked to the varied subtypes

mentioned earlier, along with increasing evidence of complex environmental and genetic factor interaction [39, 40]. Understanding the key players in the metabolism of L-dopa has put the pharmacogenomic research focus on genes that influence the enzymes and receptors that are present in the metabolic pathway of L-dopa [20].

Drug specific pharmacogenomic properties

Levodopa

Clinically L-dopa is always combined with DDC inhibitors, which causes a switch in L-dopa metabolism to the COMT pathway, thereby increasing the bio-availability of L-dopa in the CNS [37]. The genetic variability of several genes has been implicated in varied response to L-dopa. catechol-O-methyltransferase (COMT) gene is a protein-coding gene that provides instructions for creating the COMT enzyme, and its polymorphisms are involved in the varied response to numerous CNS diseases and treatments [41, 42]. The most studied polymorphism of the COMT gene is rs4680 (G>A), which results in a valine to methionine substitution at codon 158 (Val158Met). Single nucleotide polymorphisms of the COMT gene form haplotypes that result in lower (A_C_C_G), medium (A_T_C_A) and higher (G_C_G_G) enzyme activity, which in the case of higher activity impacted the required dosage compared to noncarriers [43]. Studies have shown that the higher dosage is required during chronic administration in patients with greater COMT activity, while acute L-dopa administration was unchanged [44–46]. Similar changes were observed in a recent study by Sampaio et al., where higher COMT enzyme activity was linked to higher doses of L-dopa required, while no significant changes in dosage were found in lower COMT enzymatic activity compared to the control [47]. Common characteristics of patients that required the higher L-dopa dosage in multiple studies were advanced PD and earlier onset. A contradicting result was published in patients of Korean origins, with no significant association between the rs4680 polymorphism and the response to L-dopa; however, the study population did not have a considerable number of patients with advanced PD [48]. Higher L-dopa doses were needed for patients with SLC22A1 gene rs622342A>C polymorphism that encodes the Organic Cation Transporter 1, along with the patients having higher mortality than the control population [49]. On the other hand, lower required doses of L-dopa were found in patients with SV2C rs30196 polymorphism, as well as in SLC6A3 polymorphism after multivariate analysis [50].

Increased incidence of adverse events in L-dopa treatment has been linked with various gene polymorphisms. Although the variations in COMT enzymat-

ic activity on the onset of adverse events is still under debate, several studies have linked the lower COMT enzymatic activity to the increased incidence of motor complications such as dyskinesia, especially in advanced PD [47, 51]. Hypothetically, more moderate COMT enzymatic activity could lead to inadequate dopamine inactivation and the accumulation of dopamine in the synaptic cleft, thereby causing the dyskinesias. The same result was not replicated in studies by Watanabe et al. [52] and Contin et al. [46].

There is some evidence that the activation of the mTOR signalling pathway contributes to L-dopa induced dyskinesia. It was indicative of earlier animal studies that the inhibition of mTOR pathways reduces the L-dopa related dyskinesia, most likely due to impaired metabolic homeostasis [53]. These findings were corroborated in a recent human study by Martin-Flores et al. that found significant associations with several SNPs affecting the mTOR pathway, indicating that the mTOR pathway contributes genetically to L-dopa induced dyskinesia susceptibility [54]. Similarly, a functional BDNF Val66Met polymorphism can lead to aberrant synaptic plasticity, which has been associated with L-dopa induced dyskinesia in a single study by Foltynie et al. [55]. Increased risk for developing L-dopa induced dyskinesia was seen in the DRD3 rs6280 polymorphism in a Korean population [56]. The effect of DRD2 SNP's on dyskinesia is a point of contention in current literature, as some studies indicate an increased risk of developing dyskinesia [57, 58], while others revealed a protective effect on the incidence of dyskinesia [59, 60]. Interestingly, both studies that show reduced dyskinesias were made in the Italian population with the polymorphism DRD2 CAn-STR. Lower risk of L-dopa associated dyskinesias was also found in patients with HOMER1 rs4704560 G allele polymorphism [61].

There is contradicting evidence whether COMT polymorphisms can influence the incidence of daytime sleepiness in PD patients, with differing results of the pilot and follow-up studies by the same authors [62, 63]. Two additional studies by the same primary author revealed an association between sudden-sleep onset and the polymorphisms in hypocretin and DRD2, which was unrelated to a specific drug [64, 65]. Furthermore, increased risk of sleep attacks was found in DRD4 48-bp VNTR polymorphism in a German population [66]. The L-dopa adverse effects affecting emetic activity are not uncommon in PD treatment. DRD2 and DRD3 polymorphisms both showed an association with an increased risk of developing gastrointestinal adverse effects that do not respond well to therapy in a Brazilian population [57, 67]. However, that has not been reproduced in a recent study in a Slovenian population by Redenšek et al. [68].

Mental and cognitive adverse effects of L-dopa are common due to the shared physiological dopaminergic pathways. A significant interaction was found be-

tween L-dopa and the COMT gene polymorphism in causing a detrimental effect on the activity in task-specific regions of the pre-frontal cortex due to altered availability of dopamine [69, 70]. Interestingly, carriers of at least one COMT rs165815 C allele had a decreased risk of developing visual hallucinations [68]. In the same study carriers of DRD3 rs6280 C allele had higher odds of developing visual hallucinations [68], which is in line with a previous study published by Goetz et al. [71]. Increased risk of developing hallucinations is seen in patients that have polymorphisms in the DRD2 gene [72], cholecystokinin gene [73] and HOMER1 rs4704559 A allele [74], which encodes a protein that possesses a vital function for synaptic plasticity and glutamate signalling. On the other hand, the HOMER 1 rs4704559 G allele appears to decrease the risk of visual hallucinations [61]. Furthermore, several studies link BDNF Val66Met polymorphism to impaired cognitive functioning in PD, but it appears to be irrespective of dopamine replacement therapy and is a genotype-specific trait [75].

The complication of impulse control disorder (ICD) is well known that can occur in some PD patients after initiating dopamine replacement therapy by either L-dopa or dopamine agonists [76]. Heritability of ICD in a cohort of PD patients has been estimated at 57%, particularly for OPRK1, HTR2a and DDC genotypes [77]. A recent study found a suggestive association for developing ICD in variants of the opioid receptor gene OPRM1 and the dopamine transporter gene DAT1 [78]. Furthermore, there is evidence that polymorphisms in DRD1 (rs4857798, rs4532, rs265981), DRD2/ANKK1 (rs1800497) and Grin2B (rs7301328) bear an increased risk of developing ICD [79, 80]. On the other hand, there was no significant association found in COMT Val158Met and DRD2 Taq1A polymorphisms [80]. Even though current data suggests high heritability for developing ICD after initiating dopamine replacement therapy, it should be noted that the effects of individual genes are small, and the development is most likely multigenic.

COMT inhibitors

COMT inhibitors are potent drugs that increase the bioavailability of L-dopa by stopping the physiological O-methylation of levodopa to its metabolite 3-O-methyldopa, and can work in tandem with DDC inhibitors [81]. Similar to L-dopa, the presence of the previously mentioned rs4608 COMT gene polymorphism modified the motor response to COMT inhibitors entacapone in a small-sample study [82]. Patients with higher COMT enzyme activity had greater response compared to patients with lower COMT enzyme activity during the acute challenge with entacapone [82]. Subsequent studies have not found clinically signifi-

cant with repeated administration with both entacapone [83] or tolcapone [84], with the impact on opicapone still unknown and merit further study. Increased doses of carbidopa with levodopa and entacapone improved “off” times in a recent randomised trial by Trenkwalder et al., with an even more pronounced effect in patients that had higher COMT enzymatic activity due to COMT gene polymorphisms [85].

Pharmacokinetic studies have shown that COMT inhibitors are metabolised in the liver by glucuronidation, in particular by UDP-glucuronyltransferase UGT1A and UGT1A9 enzymes [86]. Hepatotoxicity is a known rare side-effect of tolcapone [87], with only sparse reports of entacapone hepatotoxicity [88]. Several studies indicate that SNPs in the UGT1A and UGT1A9 are responsible for these adverse events, which can cause inadequate metabolism and subsequent damage to the liver by the drugs [89–92]. Interestingly, opicapone does not have evident hepatotoxicity related adverse events, while *in-vitro* show a favourable effect on hepatocytes when compared to entacapone and tolcapone [93].

Monoamine oxidase (MAO) inhibitors

MAO inhibitors are used with L-dopa to extend its duration due to reduced degradation in the CNS. Most MAO inhibitors used today in PD treatment (e.g. selegiline, rasagiline) are focused on blocking the MAO-B enzyme that is the main isoform responsible for the degradation of dopamine [94]. There have not been many studies performed to assess MAO inhibitor pharmacogenetic properties. Early clinical studies with rasagiline did reveal an inter-individual variation in the quality of response that could not be adequately explained at that time [95]. Masellisi et al. conducted an extensive study using the ADAGIO study data to identify possible genetic determinants that can alter the response to rasagiline. They identified two SNPs on the DRD2 gene that were associated with statistically significant improvement of both motor and mental functions after 12 weeks of treatment [96].

Dopamine receptor agonists

Dopamine receptor agonists (DAs) are often the first therapy initiated in PD patients and are the main alternative to L-dopa [86]. The effectiveness of DAs is lower than L-dopa, and almost a majority of patients discontinue treatment with three years. Some significance has been found in polymorphisms of the DRD2 and DRD3 genes that could influence drug effectiveness and tolerability. A retrospective study by Arbouw et al. revealed that a DRD2 (CA)*n*-repeat polymorphism is linked with a decreased discontinuation of non-ergoline DA treatment,

although the sample size in this study was small [97]. A pilot study that included Chinese PD patients revealed that the DRD3 Ser9Gly (rs6280) polymorphism is associated with a varied response to pramipexole [98], which has since been confirmed in a recent study by Xu et al. [99].

Interestingly, the same polymorphism has also been linked with depression severity in PD, indicating that in DRD3 Ser9Gly patients with Ser/Gly and Gly/Gly genotypes more care should be given to adjusting therapy and caring for non-motor complications [100]. Furthermore, there is evidence from the aforementioned studies that DRD2 TaqIA polymorphism does not play a significant role in response to DA treatment [98, 99, 101]. As mentioned earlier, another crucial pharmacogenomic characteristic of DA to bear in mind when administering therapy is the possibility of genotype driven impulse control disorders, which is a problem, especially in *de-novo* PD patients starting DA therapy [77].

A future perspective on personalised therapy in Parkinson's disease

There has been tremendous progress in the field of genetics relating to Parkinson's disease. The number of discovered risk mutations and loci rise fast due to more affordable and widespread genomic testing. Many of the familial cases of PD still cannot be explained by the currently associated risk genes, which points to a clear objective for the near future. Even though the number of studies with pharmacogenomic data in PD is increasing, there is a lack of high quality, large population size studies that are required for adequate data interpretation. Additionally, most pharmacogenomic data present today is still not consistent enough to be entered into clinical practice, and more work needs to be done to enable a more personalised approach to therapy for each patient. The recent clinical trials that focus on specific genotypes are encouraging; however, most are still in the early phases or ongoing.

The next few years will bring an improvement to assessing the risk for developing PD using composite polygenic risk scores, along with more precise guidelines for patients with specific disease genotypes like GBA, LRRK2 or SNCA. The approval of first genotype-specific treatment will usher in the age of true translation of pharmacogenomics and personalised medicine into the clinics, and hopefully, bring better therapy and improve the quality of life in PD patients.

References

- [1] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, Schrag AE, Lang AE (2017) Parkinson disease. *Nat Rev Dis Prim* 3:1–21. doi: 10.1038/nrdp.2017.13
- [2] Vuletic V, Racki V, Chudy D, Bogdanovic N (2019) Deep Brain Stimulation in Non-motor Symptoms of Neurodegenerative diseases. *Neuromodulation - Guid. Adv. Res. Ther.* [Working Title]
- [3] Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB (2019) Update of the MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 34:1464–1470. doi: 10.1002/mds.27802
- [4] Braak H, Del Tredici K, Rüb U, De Vos RAI, Jansen Steur ENH, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24:197–211. doi: 10.1016/S0197-4580(02)00065-9
- [5] Damier P, Hirsch EC, Agid Y, Graybiel AM (1999) The substantia nigra of the human brain: II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain* 122:1437–1448. doi: 10.1093/brain/122.8.1437
- [6] Braak H, Del Tredici K, Rüb U, De Vos RAI, Jansen Steur ENH, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24:197–211. doi: 10.1016/S0197-4580(02)00065-9
- [7] Fereshtehnejad S-M, Zeighami Y, Dagher A, Postuma RB (2017) Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain* 140:1959–1976. doi: 10.1093/brain/awx118
- [8] Ciccacci C, Borgiani P (2019) Pharmacogenomics in Parkinson's disease: Which perspective for developing a personalized medicine? *Neural Regen Res* 14:75–76. doi: 10.4103/1673-5374.243706
- [9] Olanow CW, Obeso JA, Stocchi F (2006) Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 5:677–687. doi: 10.1016/S1474-4422(06)70521-X
- [10] Mastrangelo L (2017) The Genetics of Parkinson Disease. In: *Adv. Genet.* pp 43–62
- [11] Bandres-Ciga S, Diez-Fairen M, Kim JJ, Singleton AB (2020) Genetics of Parkinson's disease: An introspection of its journey towards precision medicine. *Neurobiol Dis* 137:104782. doi: 10.1016/j.nbd.2020.104782
- [12] Deng H, Wang P, Jankovic J (2018) The genetics of Parkinson disease. *Ageing Res Rev* 42:72–85. doi: 10.1016/j.arr.2017.12.007
- [13] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, Schrag A-E, Lang AE (2017) Parkinson disease. *Nat Rev Dis Prim* 3:17013. doi: 10.1038/nrdp.2017.13
- [14] Titova N, Chaudhuri KR (2017) Personalized medicine in Parkinson's disease: Time to be precise. *Mov Disord* 32:1147–1154. doi: 10.1002/mds.27027
- [15] Repici M, Giorgini F (2019) DJ-1 in Parkinson's Disease: Clinical Insights and Therapeutic Perspectives. *J Clin Med* 8:1377. doi: 10.3390/jcm8091377

- [16] Nalls MA, McLean CY, Rick J, et al (2015) Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: A population-based modelling study. *Lancet Neurol* 14:1002–1009. doi: 10.1016/S1474-4422(15)00178-7
- [17] Benamer HTS, De Silva R (2010) LRRK2 G2019S in the North African population: A review. *Eur Neurol* 63:321–325. doi: 10.1159/000279653
- [18] Chen J, Chen Y, Pu J (2018) Leucine-Rich Repeat Kinase 2 in Parkinson's Disease: Updated from Pathogenesis to Potential Therapeutic Target. *Eur Neurol* 79:256–265. doi: 10.1159/000488938
- [19] Yue Z (2009) LRRK2 in Parkinson's disease: In vivo models and approaches for understanding pathogenic roles. *FEBS J* 276:6445–6454. doi: 10.1111/j.1742-4658.2009.07343.x
- [20] Corvol JC, Poewe W (2017) Pharmacogenetics of Parkinson's Disease in Clinical Practice. *Mov Disord Clin Pract* 4:173–180. doi: 10.1002/mdc3.12444
- [21] Alkanli N, Ay A (2020) The Relationship between Alpha-Synuclein (SNCA) Gene Polymorphisms and Development Risk of Parkinson's Disease. *Synucleins - Biochem. Role Dis.*
- [22] Nishioka K, Ross OA, Ishii K, et al (2009) Expanding the clinical phenotype of SNCA duplication carriers. *Mov Disord* 24:1811–1819. doi: 10.1002/mds.22682
- [23] Wang Z, Gao G, Duan C, Yang H (2019) Progress of immunotherapy of anti- α -synuclein in Parkinson's disease. *Biomed Pharmacother* 115:108843. doi: 10.1016/j.biopha.2019.108843
- [24] Kantor B, Tagliafierro L, Gu J, Zamora ME, Ilich E, Grenier C, Huang ZY, Murphy S, Chiba-Falek O (2018) Downregulation of SNCA Expression by Targeted Editing of DNA Methylation: A Potential Strategy for Precision Therapy in PD. *Mol Ther* 26:2638–2649. doi: 10.1016/j.ymthe.2018.08.019
- [25] Lin JY, Xie CL, Zhang SF, Yuan W, Liu ZG (2017) Current experimental studies of gene therapy in Parkinson's disease. *Front Aging Neurosci* 9:126. doi: 10.3389/fnagi.2017.00126
- [26] Jankovic J, Goodman I, Safirstein B, et al (2018) Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti-Synuclein Monoclonal Antibody, in Patients with Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol* 75:1206–1214. doi: 10.1001/jamaneurol.2018.1487
- [27] Riboldi GM, Di Fonzo AB (2019) GBA, Gaucher Disease, and Parkinson's Disease: From Genetic to Clinic to New Therapeutic Approaches. *Cells* 8:364. doi: 10.3390/cells8040364
- [28] Sidransky E, Lopez G (2012) The link between the GBA gene and parkinsonism. *Lancet Neurol* 11:986–998. doi: 10.1016/S1474-4422(12)70190-4
- [29] Silveira CRA, MacKinley J, Coleman K, et al (2019) Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: Protocol for a single-centre, randomized, double-blind, placebo-controlled trial. *BMC Neurol* 19:1–10. doi: 10.1186/s12883-019-1252-3
- [30] Avenali M, Blandini F, Cerri S (2020) Glucocerebrosidase Defects as a Major Risk Factor for Parkinson's Disease. *Front Aging Neurosci* 12:97. doi: 10.3389/fnagi.2020.00097

- [31] Zhang Y, Sun QY, Zhao YW, Shu L, Guo JF, Xu Q, Yan XX, Tang BS (2015) Effect of GBA mutations on phenotype of Parkinson's disease: A study on Chinese population and a meta-analysis. *Parkinsons. Dis.* 2015:
- [32] Lesage S, Anheim M, Condroyer C, et al (2011) Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. *Hum Mol Genet* 20:202–210. doi: 10.1093/hmg/ddq454
- [33] Kuhl McGuire M Next in Line for Parkinson's Therapies: PRKN and PINK1 | Parkinson's Disease. <https://www.michaeljfox.org/news/next-line-parkinsons-therapies-prkn-and-pink1>. Accessed 20 May 2020
- [34] Rahman AA, Morrison BE (2019) Contributions of VPS35 Mutations to Parkinson's Disease. *Neuroscience* 401:1–10. doi: 10.1016/j.neuroscience.2019.01.006
- [35] Krebs K, Milani L (2019) Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. *Hum Genomics* 13:39. doi: 10.1186/s40246-019-0229-z
- [36] Giacomini KM, Yee SW, Mushiroda T, Weinshilboum RM, Ratain MJ, Kubo M (2016) Genome-wide association studies of drug response and toxicity: An opportunity for genome medicine. *Nat Rev Drug Discov* 16:1. doi: 10.1038/nrd.2016.234
- [37] Salat D, Tolosa E (2013) Levodopa in the treatment of Parkinson's disease: Current status and new developments. *J Parkinsons Dis* 3:255–269. doi: 10.3233/JPD-130186
- [38] Politi C, Ciccacci C, Novelli G, Borgiani P (2018) Genetics and Treatment Response in Parkinson's Disease: An Update on Pharmacogenetic Studies. *NeuroMolecular Med.* doi: 10.1007/s12017-017-8473-7
- [39] Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG (2016) Advances in understanding genomic markers and pharmacogenetics of Parkinsons disease. *Expert Opin Drug Metab Toxicol* 12:433–448. doi: 10.1517/17425255.2016.1158250
- [40] Džoljić E, Novaković I, Krajinovic M, Grbatinić I, Kostić V (2015) Pharmacogenetics of drug response in Parkinson's disease. *Int J Neurosci* 125:635–644. doi: 10.3109/00207454.2014.963851
- [41] Craddock N, Owen MJ, O'Donovan MC (2006) The catechol-O-methyl transferase (COMT) gene as a candidate for psychiatric phenotypes: Evidence and lessons. *Mol Psychiatry* 11:446–458. doi: 10.1038/sj.mp.4001808
- [42] Stein DJ, Newman TK, Savitz J, Ramesar R (2006) Warriors versus worriers: The role of COMT gene variants. *CNS Spectr* 11:745–748. doi: 10.1017/S1092852900014863
- [43] Bialecka M, Kurzawski M, Klodowska-Duda G, Opala G, Tan EK, Drozdziak M (2008) The association of functional catechol-O-methyltransferase haplotypes with risk of Parkinsons disease, levodopa treatment response, and complications. *Pharmacogenet Genomics* 18:815–821. doi: 10.1097/FPC.0b013e328306c2f2
- [44] Cheshire P, Bertram K, Ling H, O'Sullivan SS, Halliday G, McLean C, Bras J, Foltynie T, Storey E, Williams DR (2013) Influence of single nucleotide polymorphisms in COMT, MAO-A and BDNF genes on dyskinesias and levodopa use in Parkinson's disease. *Neurodegener Dis* 13:24–28. doi: 10.1159/000351097

- [45] Białecka M, Drożdżik M, Kłodowska-Duda G, Honczarenko K, Gawrońska-Szklarz B, Opala G, Stankiewicz J (2004) The effect of monoamine oxidase B (MAOB) and catechol-O-methyltransferase (COMT) polymorphisms on levodopa therapy in patients with sporadic Parkinson's disease. *Acta Neurol Scand* 110:260–266. doi: 10.1111/j.1600-0404.2004.00315.x
- [46] Contin M, Martinelli P, Mochi M, Riva R, Albani F, Baruzzi A (2005) Genetic polymorphism of catechol-O-methyltransferase and levodopa pharmacokinetic-pharmacodynamic pattern in patient with parkinson's disease. *Mov Disord* 20:734–739. doi: 10.1002/mds.20410
- [47] Sampaio TF, dos Santos EUD, de Lima GDC, dos Anjos RSG, da Silva RC, Asano AGC, Asano NMJ, Crovella S, de Souza PRE (2018) MAO-B and COMT Genetic Variations Associated With Levodopa Treatment Response in Patients With Parkinson's Disease. *J Clin Pharmacol* 58:920–926. doi: 10.1002/jcph.1096
- [48] Lee MS, Lyoo CH, Ulmanen I, Syvänen AC, O Rinne J (2001) Genotypes of catechol-O-methyltransferase and response to levodopa treatment in patients with Parkinson's disease. *Neurosci Lett* 298:131–134. doi: 10.1016/S0304-3940(00)01749-3
- [49] Becker ML, Visser LE, Van Schaik RHN, Hofman A, Uitterlinden AG, Stricker BHC (2011) OCT1 polymorphism is associated with response and survival time in anti-Parkinsonian drug users. *Neurogenetics* 12:79–82. doi: 10.1007/s10048-010-0254-5
- [50] Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CRM, Hutz MH (2016) Influence of genetic, biological and pharmacological factors on levodopa dose in Parkinson's disease. *Pharmacogenomics* 17:481–488. doi: 10.2217/pgs.15.183
- [51] De Lau LML, Verbaan D, Marinus J, Heutink P, Van Hilten JJ (2012) Catechol-O-methyltransferase Val158Met and the risk of dyskinesias in Parkinson's disease. *Mov Disord* 27:132–135. doi: 10.1002/mds.23805
- [52] Watanabe M, Harada S, Nakamura T, Ohkoshi N, Yoshizawa K, Hayashi A, Shoji S (2003) Association between catechol-O-methyltransferase gene polymorphisms and wearing-off and dyskinesia in Parkinson's disease. *Neuropsychobiology* 48:190–193. doi: 10.1159/000074637
- [53] Santini E, Heiman M, Greengard P, Valjent E, Fisone G (2009) Inhibition of mTOR signaling in parkinson's disease prevents L-DOPA-induced dyskinesia. *Sci. Signal.* 2:
- [54] Martín-Flores N, Fernández-Santiago R, Antonelli F, Cerquera C, Moreno V, Martí MJ, Ezquerro M, Malagelada C (2019) MTOR Pathway-Based Discovery of Genetic Susceptibility to L-DOPA-Induced Dyskinesia in Parkinson's Disease Patients. *Mol Neurobiol* 56:2092–2100. doi: 10.1007/s12035-018-1219-1
- [55] Foltynie T, Cheeran B, Williams-Gray CH, Edwards MJ, Schneider SA, Weinberger D, Rothwell JC, Barker RA, Bhatia KP (2009) BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 80:141–144. doi: 10.1136/jnnp.2008.154294
- [56] Lee JY, Cho J, Lee EK, Park SS, Jeon BS (2011) Differential genetic susceptibility in diphasic and peak-dose dyskinesias in Parkinson's disease. *Mov Disord* 26:73–79. doi: 10.1002/mds.23400

- [57] Rieck M, Schumacher-Schuh AF, Altmann V, Francisconi CL, Fagundes PT, Monte TL, Callegari-Jacques SM, Rieder CR, Hutz MH (2012) DRD2 haplotype is associated with dyskinesia induced by levodopa therapy in Parkinson's disease patients. *Pharmacogenomics* 13:1701–1710. doi: 10.2217/pgs.12.149
- [58] Strong JA, Dalvi A, Revilla FJ, Sahay A, Samaha FJ, Welge JA, Gong J, Gartner M, Yue X, Yu L (2006) Genotype and smoking history affect risk of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 21:654–659. doi: 10.1002/mds.20785
- [59] Zappia M, Annesi G, Nicoletti G, et al (2005) Sex differences in clinical and genetic determinants of levodopa peak-dose dyskinesias in Parkinson disease: An exploratory study. *Arch Neurol* 62:601–605. doi: 10.1001/archneur.62.4.601
- [60] Oliveri RL, Annesi G, Zappia M, et al (1999) Dopamine D2 receptor gene polymorphism and the risk of levodopa-induced dyskinesias in PD. *Neurology* 53:1425–1430. doi: 10.1212/wnl.53.7.1425
- [61] Schumacher-Schuh AF, Altmann V, Rieck M, Tovo-Rodrigues L, Monte TL, Callegari-Jacques SM, Medeiros MS, Rieder CRM, Hutz MH (2014) Association of common genetic variants of HOMER1 gene with levodopa adverse effects in Parkinson's disease patients. *Pharmacogenomics J* 14:289–294. doi: 10.1038/tpj.2013.37
- [62] Frauscher B, Högl B, Maret S, Wolf E, Brandauer E, Wenning GK, Kronenberg MF, Kronenberg F, Tafti M, Poewe W (2004) Association of daytime sleepiness with COMT polymorphism in patients with parkinson disease: a pilot study. *Sleep* 27:733–736. doi: 10.1093/sleep/27.4.733
- [63] Rissling I, Frauscher B, Kronenberg F, et al (2006) Daytime sleepiness and the COMT val158met polymorphism in patients with Parkinson disease. *Sleep* 29:108–111.
- [64] Rissling I, Körner Y, Geller F, Stiasny-Kolster K, Oertel WH, Möller JC (2005) Preprohypocretin polymorphisms in Parkinson disease patients reporting "sleep attacks". *Sleep* 28:871–875. doi: 10.1093/sleep/28.7.871
- [65] Rissling I, Geller F, Bandmann O, Stiasny-Kolster K, Körner Y, Meindorfner C, Krüger HP, Oertel WH, Möller JC (2004) Dopamine receptor gene polymorphisms in Parkinson's disease patients reporting "sleep attacks." *Mov Disord* 19:1279–1284. doi: 10.1002/mds.20245
- [66] Paus S, Gadow F, Knapp M, Klein C, Klockgether T, Wüllner U (2009) Motor complications in patients from the German Competence Network on Parkinson's disease and the DRD3 Ser9Gly polymorphism. *Mov Disord* 24:1080–1084. doi: 10.1002/mds.22508
- [67] Rieck M, Schumacher-Schuh AF, Altmann V, Callegari-Jacques SM, Rieder CRM, Hutz MH (2018) Association between DRD2 and DRD3 gene polymorphisms and gastrointestinal symptoms induced by levodopa therapy in Parkinson's disease. *Pharmacogenomics J* 18:196–200. doi: 10.1038/tpj.2016.79
- [68] Redenšek S, Flisar D, Kojovic M, Kramberger MG, Georgiev D, Pirtošek Z, Trošt M, Dolžan V (2019) Dopaminergic pathway genes influence adverse events related to dopaminergic treatment in Parkinson's disease. *Front. Pharmacol.* 9:

- [69] Nombela C, Rowe JB, Winder-Rhodes SE, et al (2014) Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. *Brain* 137:2743–2758. doi: 10.1093/brain/awu201
- [70] Williams-Gray CH, Hampshire A, Barker RA, Owen AM (2008) Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. *Brain* 131:397–408. doi: 10.1093/brain/awm313
- [71] Goetz CG, Burke PF, Leurgans S, Berry-Kravis E, Blasucci LM, Raman R, Zhou L (2001) Genetic variation analysis in Parkinson disease patients with and without hallucinations: Case-control study. *Arch Neurol* 58:209–213. doi: 10.1001/archneur.58.2.209
- [72] Makoff AJ, Graham JM, Arranz MJ, Forsyth J, Li T, Aitchison KJ, Shaikh S, Grünewald RA (2000) Association study of dopamine receptor gene polymorphisms with drug-induced hallucinations in patients with idiopathic Parkinson's disease. *Pharmacogenetics* 10:43–48. doi: 10.1097/00008571-200002000-00006
- [73] Wang J, Si YM, Liu ZL, Yu L (2003) Cholecystokinin, cholecystokinin-A receptor and cholecystokinin-B receptor gene polymorphisms in Parkinson's disease. *Pharmacogenetics* 13:365–369. doi: 10.1097/00008571-200306000-00008
- [74] De Luca V, Annesi G, De Marco EV, De Bartolomeis A, Nicoletti G, Pugliese P, Muscettola G, Barone P, Quattrone A (2009) HOMER1 promoter analysis in Parkinson's disease: Association study with psychotic symptoms. *Neuropsychobiology* 59:239–245. doi: 10.1159/000230689
- [75] Wang Q, Liu J, Guo Y, Dong G, Zou W, Chen Z (2019) Association between BDNF G196A (Val66Met) polymorphism and cognitive impairment in patients with Parkinson's disease: A meta-analysis. *Brazilian J. Med. Biol. Res.* 52:
- [76] Gatto EM, Aldinio V (2019) Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. *Front. Neurol.* 10:
- [77] Kraemmer J, Smith K, Weintraub D, Guillemot V, Nalls MA, Cormier-Dequaire F, Moszer I, Brice A, Singleton AB, Corvol JC (2016) Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 87:1106–1111. doi: 10.1136/jnnp-2015-312848
- [78] Cormier-Dequaire F, Bekadar S, Anheim M, et al (2018) Suggestive association between OPRM1 and impulse control disorders in Parkinson's disease. *Mov Disord* 33:1878–1886. doi: 10.1002/mds.27519
- [79] Zainal Abidin S, Tan EL, Chan S-C, et al (2015) DRD and GRIN2B polymorphisms and their association with the development of impulse control behaviour among Malaysian Parkinson's disease patients. *BMC Neurol* 15:59. doi: 10.1186/s12883-015-0316-2
- [80] S B (2017) Impulse Control Disorders in Parkinson's Disease: Pathophysiology, Effect of Genetic Polymorphism and Future Research Directions. *Austin J. Clin. Neurol.* 4:
- [81] Bonifácio MJ, Palma PN, Almeida L, Soares-da-Silva P (2007) Catechol-O-methyltransferase and Its Inhibitors in Parkinson's Disease. *CNS Drug Rev* 13:352–379. doi: 10.1111/j.1527-3458.2007.00020.x

- [82] Corvol JC, Bonnet C, Charbonnier-Beaupel F, et al (2011) The COMT Val158Met polymorphism affects the response to entacapone in Parkinson's disease: A randomized crossover clinical trial. *Ann Neurol* 69:111–118. doi: 10.1002/ana.22155
- [83] Lee MS, Kim HS, Cho EK, Lim JH, Rinne JO (2002) COMT genotype and effectiveness of entacapone in patients with fluctuating Parkinson's disease. *Neurology* 58:564–567. doi: 10.1212/WNL.58.4.564
- [84] Chong DJ, Suchowersky O, Szumlanski C, Weinshilboum RM, Brant R, Campbell NRC (2000) The relationship between COMT genotype and the clinical effectiveness of tolcapone, a COMT inhibitor, in patients with Parkinson's disease. *Clin Neuropharmacol* 23:143–148. doi: 10.1097/00002826-200005000-00003
- [85] Trenkwalder C, Kuoppamäki M, Vahteristo M, Müller T, Ellmén J (2019) Increased dose of carbidopa with levodopa and entacapone improves "off" time in a randomized trial. *Neurology* 92:E1487–E1496. doi: 10.1212/WNL.00000000000007173
- [86] Agúndez JAG, García-Martín E, Alonso-Navarro H, Jiménez-Jiménez FJ (2013) Anti-Parkinson's disease drugs and pharmacogenetic considerations. *Expert Opin Drug Metab Toxicol* 9:859–874. doi: 10.1517/17425255.2013.789018
- [87] Borges N (2005) Tolcapone in Parkinson's disease: Liver toxicity and clinical efficacy. *Expert Opin Drug Saf* 4:69–73. doi: 10.1517/14740338.4.1.69
- [88] Martignoni E, Cosentino M, Ferrari M, Porta G, Mattarucchi E, Marino F, Lecchini S, Nappi G (2005) Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. *Neurology* 65:1820–1822. doi: 10.1212/01.wnl.0000187066.81162.70
- [89] Liu W, Ramírez J, Gamazon ER, et al (2014) Genetic factors affecting gene transcription and catalytic activity of UDP-glucuronosyltransferases in human liver. *Hum Mol Genet* 23:5558–5569. doi: 10.1093/hmg/ddu268
- [90] Yamanaka H, Nakajima M, Katoh M, Hara Y, Tachibana O, Yamashita J, McLeod HL, Yokoi T (2004) A novel polymorphism in the promoter region of human UGT1A9 gene (UGT1A9*22) and its effects on the transcriptional activity. *Pharmacogenetics* 14:329–332. doi: 10.1097/00008571-200405000-00008
- [91] Kaplowitz N (2005) Idiosyncratic drug hepatotoxicity. *Nat Rev Drug Discov* 4:489–499. doi: 10.1038/nrd1750
- [92] Ferrari M, Martignoni E, Blandini F, Riboldazzi G, Bono G, Marino F, Cosentino M (2012) Association of UDP-glucuronosyltransferase 1A9 polymorphisms with adverse reactions to catechol-O-methyltransferase inhibitors in Parkinson's disease patients. *Eur J Clin Pharmacol* 68:1493–1499. doi: 10.1007/s00228-012-1281-y
- [93] Bonifácio MJ, Torão L, Loureiro AI, Palma PN, Wright LC, Soares-Da-Silva P (2015) Pharmacological profile of opicapone, a third-generation nitrocatechol catechol-O-methyl transferase inhibitor, in the rat. *Br J Pharmacol* 172:1739–1752. doi: 10.1111/bph.13020
- [94] Youdim MBH, Edmondson D, Tipton KF (2006) The therapeutic potential of monoamine oxidase inhibitors. *Nat Rev Neurosci* 7:295–309. doi: 10.1038/nrn1883

- [95] Guay DRP (2006) Rasagiline (TVP-1012): A new selective monoamine oxidase inhibitor for Parkinson's disease. *Am J Geriatr Pharmacother* 4:330–346. doi: 10.1016/j.amjopharm.2006.12.001
- [96] Masellis M, Collinson S, Freeman N, et al (2016) Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson's disease: a pharmacogenetic study. *Brain* 139:2050–2062. doi: 10.1093/brain/aww109
- [97] Arbouw MEL, Movig KLL, Egberts TCG, Poels PJE, Van Vugt JPP, Wessels JAM, Van Der Straaten RJHM, Neef C, Guchelaar HJ (2009) Clinical and pharmacogenetic determinants for the discontinuation of non-ergoline dopamine agonists in Parkinson's disease. *Eur J Clin Pharmacol* 65:1245–1251. doi: 10.1007/s00228-009-0708-6
- [98] Liu YZ, Tang BS, Yan XX, et al (2009) Association of the DRD2 and DRD3 polymorphisms with response to pramipexole in Parkinson's disease patients. *Eur J Clin Pharmacol* 65:679–683. doi: 10.1007/s00228-009-0658-z
- [99] Xu S, Liu J, Yang X, Qian Y, Xiao Q (2017) Association of the DRD2 CAn-STR and DRD3 Ser9Gly polymorphisms with Parkinson's disease and response to dopamine agonists. *J Neurol Sci* 372:433–438. doi: 10.1016/j.jns.2016.08.005
- [100] Zhi Y, Yuan Y, Si Q, Wang M, Shen Y, Wang L, Zhang H, Zhang K (2019) The Association between DRD3 Ser9Gly Polymorphism and Depression Severity in Parkinson's Disease. *Parkinsons Dis* 2019:1642087. doi: 10.1155/2019/1642087
- [101] Paus S, Grünewald A, Klein C, Knapp M, Zimprich A, Janetzky B, Möller JC, Klockgether T, Wüllner U (2008) The DRD2 TaqIA polymorphism and demand of dopaminergic medication in Parkinson's disease. *Mov Disord* 23:599–602. doi: 10.1002/mds.21901

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LIFESTYLE FACTORS IN PREVENTION OF COGNITIVE DECLINE

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Summary

Greater population life expectancy is one explanation for increased incidence of cognitive impairment and dementia. A large number of people with cognitive impairment and dementia is becoming one of the most important medical and social problems worldwide, a kind of a modern epidemic, what is leading to a number of research in this particular field.

As there is still no cure for dementia, the focus is on prevention and acting now on dementia prevention, intervention, and care will vastly improve living for individuals with dementia and their families, and in doing so, will transform the future for society.

The Lancet Commission on dementia aimed to review the best available evidence and produce recommendations on how to best manage, or even prevent, the dementia epidemic.

Dementia is not an inevitable consequence of ageing and in 2017. the Commission identifies nine potentially modifiable health and lifestyle factors from different phases of life that, if eliminated, might prevent dementia. With further efforts in investigation of this particular field, the Commission in 2020. adds three more potential preventable factors: traumatic brain injury, alcoholism and air pollution. Although therapies are currently not available to modify the underlying disease process, the Commission outlines pharmacological and social interventions that are able to help manage the manifestations of dementia.

The Commission comes up with a hypothetical life-course model, that estimates about 40% of dementia cases could be prevented if certain risk factors were eliminated; hence, a key recommendation of the Commission is to “be ambitious about prevention” of dementia, focusing on interventions to build up resilience

and brain reserve, to activate neuroplasticity, detect and treat risk factors and to live healthier lifestyles.

Having in mind, a century old sentence of Santiago Ramon y Cajal that „Every man can, if he so desires, become a sculptor of his own brain“ , the time has obviously come to teach the people how to work on that.

Key words: cognitive decline, dementia, lifestyle factors, prevention, neuroplasticity

Lifestyle factors in prevention of cognitive decline

The threat of cognitive decline is present in everyday life of an individual as well as on global scale, especially due to increasing life expectancy and to greater number of older people.

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][3].

Recent data have shown that air pollution should be considered as a new modifiable cerebrovascular and neurodegenerative risk factor. This massive worldwide public health problem requires environmental health policies able to reduce air pollution and thus the stroke and dementia burden [4][5].

In July 2017. The Lancet Commission on Dementia prevention, intervention and care presented a life-course model showing potentially modifiable and non-modifiable, risk factors for dementia [2] [1]. 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 being: less education, hypertension, hearing loss, obesity, smoking, depression, physical inactivity, diabetes and social isolation, belong to potentially modifiable risk factors and they account for about 35%.

The same group of authors, members of The Lancet Commission on Dementia prevention, intervention and care, published their new report in July 2020, adding three more factors for dementia, with newer, convincing evidence. These factors are excessive alcohol consumption, traumatic brain injury and air pollution. They completed new reviews and meta- analyses and incorporated these into an updated 12 risk factors life-course model of dementia prevention. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed. The potential for prevention is high and might be higher in low-income and middle-income countries (LMIC) where more dementias occur [6].

In early childhood, we need to start taking care of an important 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][7] [8].

The modifiable risk factors for dementia during midlife are hearing loss, hypertension and obesity. These three factors attack people at the age of 40 or 45 (45 is officially the beginning of middle age), and if they are present for the rest of the middle age or longer, they cause an increased risk for developing dementia [2]. So, keeping fit, taking care of the extra weight, as well as early recognition and treatment of hypertension will not only guard the body from disease but also the brain [9][10].

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 [11] [12]. Later on in life it is necessary to take care of smoking, depression, physical inactivity, social isolation, and diabetes [7] [12][13][14].

Change from a sedentary lifestyle to moderate physical activity has beneficial effects on cognitive functioning, and preliminary evidence suggests that such change may reduce the incidence of dementia. [15] [16] [17]

Dance is very useful complex activity and dance training is superior to repetitive physical exercise in inducing brain plasticity in the elderly [18].

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 [19] [20] [21]. 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 [7]. The working group identified seven metrics to define optimal brain health in adults, and these originated from well-known Life's simple 7 [22], 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/m², 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. (23) 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 [23].

SPRINT Memory and Cognition in Decreased Hypertension (MIND), a sub study of SPRINT MIND Study [24] evaluated the effect of intensive systolic blood pressure lowering on mild cognitive impairment and probable dementia, with a subset of participants completing MRI. Intensive lowering of blood pressure did not result in a significant reduction in the incidence of probable dementia, compared with standard management of blood pressure (the primary outcomes in SPRINT MIND). However, mild cognitive impairment and the composite of mild cognitive impairment and probable dementia (the secondary outcomes in SPRINT MIND) were significantly reduced in the intensive lowering group compared with the standard treatment group [25]

Intensive lowering of systolic blood pressure was also associated with a significantly smaller increase in cerebral white matter change but a greater de-

crease in total brain volume compared with standard treatment, although the changes were small [25].

Several studies showed that increased arterial stiffness has greater value in predicting the cognitive decline in healthy subjects, than blood pressure [26]. 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. [27][28][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][36][37].

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 [38].

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 [14] [39] [41].

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 [40].

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 [41]. 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 ϵ 4 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.

In another study it was found that lifestyle factors, such as physical activity, sleep, and social activity appear to be associated with cognitive function among older people. Physical activity

and appropriate durations of sleep and conversation are important for cognitive function [42].

To quantify the impact of a healthy lifestyle on the risk of Alzheimer dementia, using data from the Chicago Health and Aging Project (CHAP; $n = 1,845$) and the Rush Memory and Aging Project (MAP; $n = 920$), a healthy lifestyle score was defined on the basis of nonsmoking, ≥ 150 min/wk moderate/vigorous-intensity physical activity, light to moderate alcohol consumption, high-quality Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet (upper 40%), and engagement in late-life cognitive activities (upper 40%), giving an overall score ranging from 0 to 5. The results suggest that a healthy lifestyle as a composite score is associated with a substantially lower risk of Alzheimer dementia [43].

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 [44][45].

As already mentioned the Lancet Commission continued its work and published the new report in September 2020. adding three more risk factors to their model of preventing cognitive decline and dementia [6].

TBI is usually caused by car, motorcycle, and bicycle injuries; military exposures; boxing, horse riding, and other recreational sports; firearms; and falls [46]. A nationwide Danish cohort study of nearly 3 million people aged 50 years or older, followed for a mean of 10 years, found an increased dementia and Alzheimer's disease risk [47]. Dementia risk was highest in the 6 months after TBI and increased with number of injuries in people with TBI to reduce reverse causation bias [47].

Similarly, a Swedish cohort of over 3 million people aged 50 years or older, found TBI increased 1-year dementia risk; and risk remained elevated, albeit attenuated over 30 years [48].

The term chronic traumatic encephalopathy describes sports head injury, which is not yet fully characterized and covers a broad range of neuropathologies and outcomes, with current views largely conjecture [49].

Heavy drinking is associated with brain changes, cognitive impairment, and dementia, a risk known for centuries [50]. An increasing body of evidence is emerging on alcohol's complex relationship with cognition and dementia outcomes from a variety of sources including detailed cohorts and large-scale record-based studies. Alcohol is strongly associated with cultural patterns and other sociocultural and health-related factors, making it particularly challenging to understand the evidence base. A number of studies are analyzing the role of alcohol consumption to cognitive impairments, each of them with varying quantity of alcohol and based upon these results the Lancet Commission proposed the quantity of more than 21 units of alcohol per week as a risk factor [6].

As previously mentioned, air pollution and particulate pollutants are associated with poor health outcomes, including those related to non-communicable diseases, with a special attention to their potential effect on the brain. [4][5] A systematic review of studies until 2018 including 13 longitudinal studies with 1–15 years follow-up of air pollutants exposure and incident dementia, found exposure to PM 2-5, NO 2, and carbon monoxide were all associated with increased dementia risk [51].

Lifestyle changes for modifying 12 risk factors might prevent or delay up to 40% of dementias. We should be ambitious about prevention. Contributions to

the risk and mitigation of dementia begin early and continue throughout life, so it is never too early or too late to act. These actions require both public health programs and individually tailored interventions [6] [39].

References

- [1] Frankish H, Horton R. Prevention and management of dementia: a priority for public health. *Lancet*. 2017; (390)10113:2614-2615.
- [2] FLivingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017; 390:10113.
- [3] Anstey KJ, Peters R, Yheng L, et al. Future Directions for Dementia Risk Reduction and Prevention Research: An International Research Network. *Journal of Alzheimer's Disease* . 2020; 78:3–12.
- [4] Demarin V, Morović S, Đerke F. Air pollution: A new risk factors for developing Stroke, RAD CASA – Medical Sciences. 2019; 540=48-49:51-57.
- [5] Béjot Y, Reis J, Giroud M, Feigin V. A review of epidemiological research on stroke and dementia and exposure to air pollution. *International Journal of Stroke*. 2018; 13[7] :687-695. doi:10.1177/1747493018772800.
- [6] Livingston G, Huntley J, Sommerlad A. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Published: July 30, 2020. DOI:[https://doi.org/10.1016/S0140-6736\[20\] 30367-6](https://doi.org/10.1016/S0140-6736[20] 30367-6).
- [7] Gorelick PB, Furie KL, Iadecola C, et al. Defining Optimal Brain Health in Adults: A Presidential Advisory from the American Heart Association/American Stroke Association. , *Stroke*, 2017; 48[10] :284-303.
- [8] Demarin V, Morović S. Possibilities of Dementia Prevention. In: *Neurodegenerative diseases-dementias*, ed. Vuletic V and Rukavina D, Zagreb-Rijeka, 2019, 29-37.
- [9] McMaster M, Kim S, Clare L, et al. Lifestyle Risk Factors and Cognitive Outcomes from the Multidomain Dementia Risk Reduction Randomized Controlled Trial, Body Brain Life for Cognitive Decline (BBL-CD). *JAGS* 2020; 00:1-9.
- [10] Klimova B, Valis M, Kuca K, et al. Cognitive decline in normal aging and its prevention: a review on non-pharmacological lifestyle strategies. *Clinical Interventions in Aging*. 2017;12 903–910.
- [11] Larson EB. Prevention of Late-Life Dementia: No Magic Bullet. *Ann Intern Med*. 2018; 168[1]:77-79.
- [12] Thomson RS, Auduong P, Miller AT, et al. Hearing loss as a risk factor for dementia: A systematic review. *Laryngoscope Investig Otolaryngol*. 2017; 2[2] : 69–79.

- [13] Almeida OP, Hankey GJ, Yeap BB, et al. Depression as a modifiable factor to decrease the risk of dementia. *Translat Psych* 2017; 7:e1117.
- [14] Morović S, Demarin V. Role of physical activity on human brain functions. *Periodicum biologorum*. 2014; 116[2] :219-221.
- [15] Lovden M, Xu W, Wang HX. Lifestyle change and the prevention of cognitive decline and dementia: what is the evidence? *Curr Opin Psychiatry*. 2013;26:239–243 DOI:10.1097/YCO.0b013e32835f4135.
- [16] Borhan ASM, Hewston P, Merom D, et al. Effects of dance on cognitive function among older adults: a protocol for systematic review and meta-analysis. *Systematic Reviews* (2018) 7:24 DOI 10.1186/s13643-018-0689-6.
- [17] Salinas J, Beiser A, Himali JJ, et al. Associations between social relationship measures, serum brain-derived neurotrophic factor, and risk of stroke and dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2017; 3:229-237.
- [18] Rehfeld K, Lueders A, Hoekrlmann, et al. Dance training is superior to repetitive physical exercise in inducing brain plasticity in the elderly. Published: July 11, 2018 <https://doi.org/10.1371/journal.pone.0196636>.
- [19] Stephen R, Hongisto K, Solomon A, et al. Physical Activity and Alzheimer's Disease: A Systematic Review. *J Gerontol A Biol Sci Med Sci*. 2017;72[6] :733-739.
- [20] Rebok GW, Ball K, Lin T, et al. Ten-Year Effects of the Advanced Cognitive Training for Independent and Vital Elderly Cognitive Training Trial on Cognition and Everyday Functioning in Older Adults. *JAGS*. 2014; 62:16-24.
- [21] Yaffe K. Modifiable Risk Factors and Prevention of Dementia. What Is the Latest Evidence? *AMA. Intern Med*. 2018;178[2] :281-282.
- [22] Sacco RL. Achieving ideal cardiovascular and brain health: opportunity amid crisis: presidential address at the American Heart Association 2010 Scientific Sessions. *Circulation*. 2011; 123:2653-2657.
- [23] L, Koenig J, Sgoifo A, et al. Autonomic and Brain Morphological Predictors of Stress Resilience. *Front. Neurosci*. 2018; 12:228.
- [24] The SPRINT MIND Investigators for the SPRINT Research Group. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA*. 2019;321[6] :553–561. doi:10.1001/jama.2018.21442.
- [25] Gorelick PB, Sorond F. Cognitive function in SPRINT: where do we go next? 2020; 19[11] :880-881. DOI:[https://doi.org/10.1016/S1474-4422\[20\] 30356-2](https://doi.org/10.1016/S1474-4422[20] 30356-2).
- [26] Marfella R, Paolisso G. Increased Arterial Stiffness Trumps on Blood Pressure in Predicting Cognitive Decline in Low-Risk Populations. *Hypertension*. 2015; 67:30.
- [27] Hajjar I, Goldstein FC, Martin GS. et al. The Roles Of Arterial Stiffness And Blood Pressure In Hypertension-Associated Cognitive Decline In Healthy Adults. *JAD*. 2020; 78:3-12.
- [28] Morovic S, et al. Vascular Characteristics Of Patients With Dementia. *Journal of Neurological Sciences*. 2009; 283:41-43.

- [29] Demarin V, Morovic S. Ultrasound subclinical markers in assessing vascular changes in cognitive decline and dementia. *J Alzheimers Dis.* 2014; 42[3] :S259-66.
- [30] Wang C, Chan JS, Ren L, et al. Obesity Reduces Cognitive and Motor Functions across the Lifespan. *Neural Plasticity.* 2016, Article ID 2473081, 13 p.
- [31] Spyridaki EC, Avgoustinaki PD, Margioris AN. Obesity, inflammation and cognition. *Current Opinion in Behavioral Sciences.* 2016; 9:169-175.
- [32] Stephen R, Hongisto K, Solomon A, et al. Physical Activity and Alzheimer's Disease: A Systematic Review. *J Gerontol A Biol Sci Med Sci.* 2017;72[6] :733-739.
- [33] Medic N, Ziauddeen H, Ersche KD, et al. Increased body mass index is associated with specific regional alterations in brain structure. *Int J Obes (Lond).* 2016; 40[7] :1177-82.
- [34] Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 2018; 17[11] :1006-1015.
- [35] Demarin V, Morovic S. Neuroplasticity. *Periodicum biologorum* 2014; 116[2] :209-211.
- [36] Mediterranean diet in healthy lifestyle and prevention of stroke. *Acta Clin Croat* 2011; 50[1]:67-77.
- [37] *Healthy Lifestyle and Prevention of Stroke and Other Brain Impairment*, ed. Demarin V, CASA – Medical Sciences, Zagreb, 2019.
- [38] Forsman A. et al. Psychosocial interventions for prevention of depression in older people. *Cochrane Database Syst Rev.* 2018 Oct; 2018[10] : CD007804. Published online 2018 Oct 23. doi: 10.1002/14651858.CD007804.pub2 PMID: PMC6516841
- [39] Morovic S, Budincevic H, Govori V, Demarin V. Possibilities of Dementia Prevention - It is Never Too Early to Start. *J Med Life.* 2019; 12[4] :332-337. doi:10.25122/jml-2019-0088
- [40] Loneliness, Social Integration, and Incident Dementia Over 6 Years: Prospective Findings From the English Longitudinal Study of Ageing. *The Journals of Gerontology, Series B.* <https://doi.org/10.1093/geronb/gbx087>
- [41] Ngandu T, Lethisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial. *Lancet.* 2015; 385(9984);2255-2263. DOI:[https://doi.org/10.1016/S0140-6736\(15\) 60461-5](https://doi.org/10.1016/S0140-6736(15) 60461-5).
- [42] Kimura N, Aso Y, Yabuuci K, et al. Modifiable Lifestyle Factors and Cognitive Function in Older People: A Cross-Sectional Observational Study. *Front. Neurol.*, 24 April 2019. <https://doi.org/10.3389/fneur.2019.00401>.
- [43] Dhana K, Evans DA, Rajan KB, et al. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. *Neurology.* 2020 Jul 28;95[4] :e374-e383. doi: 10.1212/WNL.0000000000009816. E pub 2020 Jun 17.
- [44] Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimer's & Dementia*, 2013. <https://doi.org/10.1016/j.jalz.2012.09.012>

- [45] Norton S, Matthews FE, Barnes DE, et al. Potential for primary prevention of Alzheimer's disease: an analysis of population based data. *Lancet Neurol.* 2014;13 [8] :788-794.
- [46] Bruns J Jr, Hauser WA. The epidemiology of traumatic brain injury: a review. *Epilepsia* 2003; 44:2–10.
- [47] Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *Lancet Psychiatry.* 2018; 5:424–31.
- [48] Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. *PLoS Med* 2018; 15:e1002496.
- [49] Smith DH, Johnson VE, Trojanowski JQ, et al. Chronic traumatic encephalopathy - confusion and controversies. *Nat Rev Neurol* 2019; 15:179–83.
- [50] Rehm J, Hasan OSM, Black SE, et al. Alcohol use and dementia: a systematic scoping review. *Alzheimers Res Ther.* 2019;11:1.
- [51] Peters R, Ee N, Peters J, et al. Air pollution and dementia: a systematic review. *J Alzheimers Dis.* 2019; 70:S145–63.

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OVERCOMING CHALLENGES IN CLINICAL TRIALS OF MULTIPLE SYSTEM ATROPHY AND DEMENTIA WITH LEWY BODIES

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Summary

Multisystem atrophy (MSA) and Dementia of Lewy body (DLB) as well as idiopathic Parkinson's disease are belonging to the neurodegenerative group disorders called synucleinopathies due to an excessive accumulation of alpha synuclein in the brain. MSA and DLB have progressive courses with an average life expectation less than 10 years from the onset. They are characterized by parkinsonism, failure of autonomic nervous system, dementia and various sleep disorders. Both disorders are representing diagnostic and therapeutic challenges, due to lack of either diagnostic or longitudinal biomarkers. Apart of the symptomatic treatment, the causal treatment is not available.

Key words: Multisystem atrophy, Dementia of Lewy body, synucleinopathies

Multiple-system atrophy (MSA) is a rare (global estimated incidence of 1.8/100.000, and prevalence of 3.5/100.000) progressive, neurodegenerative disease that is characterised by autonomic failure in addition to various features of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. In fact, the term multiple-system atrophy was introduced in 1969 as an efficient way to encompass the disease entities of olivopontocerebellar ataxia, striatonigral degeneration, and the Shy-Drager syndrome. The more recent detection of α -synuclein, aggregates which make glial cytoplasmic inclusions (GCI) in all three of these diseases, lends credence to a unified concept of MSA [1]. The origin of α -synuclein in GCI as well as the pathogenesis of MSA remain uncertain, although there has been some recognition that the misfolding and aggregation of α -synuclein

plays an important role in pathogenesis. What is clear is that neuronatomically, MSA is characterised by severe neuron loss supratentorially in the substantia nigra and posterior putamen; infratentorially in the pons, cerebellum and inferior olives; and spinally in the intermediolateral cell columns. Nonetheless, the pathogenic mechanisms underlying MSA remain unknown, making it difficult to develop effective treatment therapies targeted at specific pathophysiological mechanisms, and to date there are no available treatments aimed at slowing or halting disease progression.

Clinical Presentation of MSA

Clinically, MSA is typically classified into two subtypes: subtype C (MSA-C) characterised predominantly by cerebellar ataxia, and subtype P (MSA-P) characterised predominantly by parkinsonism. Of note, the MSA-C subtype has been reported to be relatively more prevalent than subtype P in Japanese populations, whereas subtype P has been reported to be more prevalent than subtype C in European and North American populations. MSA-P and MSA-C appear to share a similar natural history, with a median duration from onset to death of almost 10 years. Rapid eye movement (REM) sleep behavioural disorder, although not specific for MSA, is often one of the earliest symptoms of MSA, which curiously typically improves as the disease progresses. Sleep breathing disorders including stridor and sleep apnea may also appear years before the presence of motor symptoms. Additionally, depressive symptoms often precede the onset of motor symptoms. Autonomic failure, expressed either as urinary incontinence (UI) or orthostatic decrease of blood pressure (ODBP) must be present for a clinical diagnosis in both subtypes of MSA. However, standard measurements of blood pressure over three minutes to detect orthostatic hypotension may prove too short a duration and often miss ODBP in a significant number of MSA patients compared to measurements conducted over 10 minutes [2]. It has been recommended therefore to conduct blood pressure measurements for this period of time [3]. Regardless of subtype and initial presentation, virtually all patients with MSA will develop parkinsonism during the course of the disease [4]. An akinetic-rigid syndrome typically presents bilaterally but can be asymmetric in severity. The typical parkinsonian type of resting tremor is rare, although two-thirds of patients have irregular, jerky actions or postural tremor. In fact, it is this irregular, small amplitude myoclonic movements (termed polyminiomyoclonus) of the hands and/or fingers in an outstretched posture, which is sometimes touch- or stretch-sensitive, that is indicative of MSA. A quivery voice with increased pitch reminiscent of myoclonic speech is also suggestive of

MSA, as is significant dysphagia. Also, early falls (i.e. in the first year of disease) are not uncommon. Cerebellar dysfunction (limb and gait ataxia, dysarthria) are present in more than two-thirds of MSA patients, regardless of initial subtype or origin. The presence of two or more “red flags”, including early instability, rapid progression, abnormal posture, bulbar dysfunction, respiratory dysfunction and emotional incontinence in subjects with parkinsonism is indicative of MSA. Cognitive impairment, exhibited mainly as frontal system or executive dysfunction in MSA patients is considered to be ubiquitous (present in up to 75% of patients) but is not in itself diagnostic. Typical dementia features have been reported in up to 18% of patients [3]. Finally, pain is an under-recognised symptom of MSA and is more severe and common in MSA-P subjects, affecting mainly lower limbs followed by neck and back pain. As in other neurologic disorders, pain intensity has been shown to correlate more with affective function than motor severity [5].

Cerebrospinal fluid (CSF) and Imaging Biomarkers of MSA

A number of studies have recently sought to promote candidate biomarkers to aid in MSA diagnosis utilising blood and cerebrospinal fluid (CSF), but no reliable biomarkers have been validated in terms of diagnostic specificity. In addition to the prominent role of α -synuclein, the most promising biomarkers thus far include plasma norepinephrine levels [6], plasma catecholaminergic vesicular storage levels [7] and plasma and CSF neurofilament light chain protein [8]. In addition, the utility of such biomarkers as outcome measures in clinical trials is based upon the assumption that these biomarkers are valid proxies for the pathophysiologic changes associated with MSA and/or can serve as reliable surrogates that are reasonably likely to predict clinical benefit.

Although structural brain magnetic resonance imaging (MRI) may be unremarkable in the early stage of disease, two MRI abnormalities are common as the disease progresses. The first of these has been described as the “hot-cross bun” sign as seen on T2 or FLAIR MRI reflecting selective loss of myelinated transverse pontocerebellar fibres in the pontine raphe with preservation of the corticospinal tract and tegmentum. Although highly suggestive for MSA [9], this sign has also been described in other disorders such as spinocerebellar ataxias, leptomeningeal carcinomatosis, and vasculitis. The second neuroimaging abnormality described as a “putaminal slit” caused by a hyperintense signal in the dorsolateral margin of the putamen also has high positive predictive value for the diagnosis of MSA [10]. Similar to the higher sensitivity of T2*-weighted echo gradient MRI to reveal putamenal abnormalities, these imaging techniques

seem to be more sensitive for the detection of the hot-cross bun sign than classical T2-weighted MRI. Therefore, imaging protocols in MSA studies should include T2*-weighted echo gradient imaging or equivalent sequences [3]. In regards to molecular neuroimaging, a reduction in 18FDG-PET uptake in both the putamenal nuclei with a rostrocaudal gradient is the most prominent finding in MSA-P, although decreased 18FDGPET uptake can also be detected in the thalamus, brainstem and cortical areas. The current consensus diagnostic criteria [11] or MSA established hypometabolism in the putamen nucleus, mesencephalic region and cerebellum as being supportive for MSA-P. Additionally, the development of PET radiotracers that can image aggregated α -synuclein has been a development priority for a number of companies seeking not only to define disease state but promote a biomarker that can track disease progression and treatment effects of MSA therapies. Despite the fact that several chemical entities have moderate affinity for α -synuclein, their binding affinities and selectivity versus tau and beta amyloid have made them less than ideal as candidate PET radiotracers.

Diagnostic Difficulties in Multiple system atrophy (MSA)

The heterogeneity of clinical phenotype noted above and lack of diagnostic biomarkers renders the diagnosis of MSA in clinical trial settings quite challenging, particularly in patients at the early stages of the disease where a disease-modifying drug may be most likely to show benefit. Not surprisingly, the most common misdiagnosis for patients with MSA-P is idiopathic Parkinson's disease (IPD). An autonomic presentation of MSA may be confused with pure autonomic failure (PAF) which usually has Lewy body pathology, or with Parkinson's disease presenting with autonomic failure. Most patients of MSA presenting with autonomic failure develop other neurological features within five years, but in rare cases this interval can be longer. When considering cerebellar signs and symptoms, approximately 25% of patients with idiopathic late onset cerebellar ataxia (ILOCA) will ultimately turn out to have a diagnosis of MSA. The introduction of consensus diagnostic criteria [11] in 2008 was intended to improve diagnostic accuracy and aid clinical trial conduct. These criteria recognise definite, probable, and possible MSA. Definite MSA requires neuropathologic demonstration of GCIs with neurodegenerative changes in striatonigral or olivopontocerebellar structures. Probable MSA requires a sporadic, progressive adult onset disorder including rigorously defined autonomic failure and poorly levodopa responsive parkinsonism or cerebellar ataxia. Unfortunately, lack of response to L-dopa is present in less than 50% of patients and although this

response to L-dopa might be suboptimal, when present it is surprisingly sustained with a mean duration of 3 to 3.5 years, suggesting that levodopa responsiveness should be critically reconsidered as a requirement for the diagnosis of probable MSA-P. Possible MSA requires a sporadic, progressive adult onset disease including parkinsonism or cerebellar ataxia and at least one feature suggesting autonomic dysfunction, plus one other feature that may be a clinical or a neuroimaging abnormality. Despite the acceptance of the consensus criteria over the past ten years, clinical trials have not meaningfully benefited in terms of homogeneity of patient populations or signal detection. Of note, a large series of MSA patients from the Mayo Clinic Brain Bank exhibited an unexpectedly low diagnostic accuracy, suggesting further refinement of these consensus criteria may be needed. Of 134 patients with clinically diagnosed MSA, only 83 (62%) had definite MSA confirmed at autopsy [12].

Multiple system atrophy (MSA) Outcome Measures in Clinical Trials

In addition to the diagnostic difficulties with initial misclassification, the selection of experienced investigators in MSA trials is paramount toward the successful conduct of a controlled clinical trial. This is important not only for diagnostic purposes but to ensure reliable and consistent outcome measures. Due to the disease rarity, complex disease neurobiology and clinical heterogeneity, there are only a handful of clinical research sites of excellence present across a small number of countries. In fact, one of the largest countries (the United States) is the only country close to approaching double digit numbers of sites of excellence in MSA research. Even in such experienced sites, monitoring of strict adherence to diagnostic criteria is mandatory and we have found it useful to have an independent expert's supervision of diagnostic procedures to ensure appropriate patient selection. Additionally, our experience across multiple orphan and ultra-orphan neurological indications support Singer et al.'s reliance on an oligocentre model that selects the smallest number of very experienced and high-performing sites to ensure proper patient identification and to reduce outcome variability [13].

Additionally, a standardised rater training programme covering both diagnostics and assessments for site raters and clinical research monitors has been shown to reduce variability and improve signal detection via a multi-pronged training approach: assessment through audio or video recordings which must achieve at least 85-90% concordance with the score of an expert consensus panel as well as the group consensus score; applied skills assessment training through a live interview with an actor trained to portray a subject with MSA; and ongoing

ing in-study monitoring of assessment data to ensure rater consistency utilising electronic data capture “flags” to identify scoring trends, inconsistencies, and changes in scoring that may infer rater bias or drift.

The most common efficacy outcome measure in MSA trial is the Unified Multiple System Atrophy Rating Scale (UMSARS) which allows scores ranging from 0 to 104 with higher scores indicating greater impairment. This instrument consists of four parts. The first part is the UMSARS activities of daily living subscale (range 0-48), and the second is the motor examination subscale (range 0-56). The third part is measurement of autonomic function, and the fourth is a five-grade overall clinical status, similar to Hoehn and Yahr in Parkinson’s disease. UMSARS has proven to be a, reliable and valid scale for semi-quantitative assessments of MSA patients with known rates of change associated with natural history [13]. These rates can be used to power models of disease progression with the caveat that changes in slope vary with length of disease with steeper declines seen earlier in the illness (thus requiring fewer patients) while plateauing later in the illness¹³. Unlike Alzheimer’s disease, where the steepest part of the clinical decline is seen in the more moderate patients, MSA patients with the steepest declines are still in a phase of illness that is early enough to have a significant impact on disease progression.

Additionally, accelerated UMSARS progression was predicted not only by shorter symptom duration at baseline, but also by an absent levodopa response. It appears that UMSARS-related disease progression slows down as early as the second year of follow-up, which is important to consider when embarking on therapeutic trials of long duration. Of note, a minimal clinically important change using the UMSARS has not yet been established for MSA patients making it difficult to appreciate the relationship between statistical significance and clinical importance. As the scale was initially validated in Europeans, its validity and applicability across various populations requires further examination. In particular, some items regarding cutting food, handling utensils, and dressing may not apply to some rural and geographically isolated cultures. Furthermore, due to the need to design a scale that was reasonably simple, short, and user-friendly, some prominent features of MSA are not fully covered by the UMSARS and other validated scales may need to be supplemented to evaluate items not covered by the UMSARS that may have an impact on the overall function of MSA subjects, such as bradyphrenia, anhedonia, depression, sleep disorders, fatigue, and overall quality of life. Finally, the long-term follow-up of MSA patients is restricted by the rapid neurodegenerative process resulting in reduced life expectancy. This may help explain the high rate of attrition and serious ad-

verse events often seen in MSA trials. Given the rapid disease progression, survival rates might be considered as an outcome measure particularly when inclusion criteria are not restricted to early stages of the disease. In contrast, choosing patients earlier in the disease course should help improve attrition. Utilising the correct analysis that takes into account attrition patterns coupled with limiting the sites to those experienced investigators and demanding rigorous training on diagnostic and outcome measures which minimise error variance will help to ensure the chosen sample sizes will be able to detect treatment effects should they exist.

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder characterized by parkinsonism and cognitive impairment but may also manifest with dysautonomia, sleep disorders, hallucinations, and cognitive fluctuations. Although first described several decades ago, DLB is still considered a diagnostic challenge because of the clinical and pathological overlap with other neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and frontotemporal lobar degeneration¹⁴. The temporal sequence distinguishes DLB from another related condition, Parkinson's disease dementia (PDD). The term DLB is used when dementia develops before, or within one year after, parkinsonism onset. The term PDD is used when dementia appears more than one year after the onset of otherwise typical Parkinson's disease. Cognitive decline and parkinsonism are insidious, so the distinction can be difficult to draw and may be influenced by the subspecialty interest of the diagnosing neurologist (for example, movement disorder versus behavioral neurology) [14,15]. Data on the relative frequency of DLB and PDD may be similarly affected by this subspecialty referral pattern. DLB and PDD share the same neuropathology, may be manifestations of the same neurodegenerative disorder, possibly related to the abnormal accumulation of α -synuclein and it is often impossible to differentiate DLB from PDD at autopsy [16]. However, there is a frequent coexistence of AD pathology with DLB [17,18] which tends to be modest in typical PDD [19]. The overlap between DLB and AD these two diseases is so extensive that "pure" Lewy body disease (without any Alzheimer-type pathology beyond that attributable to normal ageing) is relatively uncommon, accounting for no more than a third of all cases of Lewy body disease and at perhaps 10% of all cases of clinical dementia [20].

DLB is an under-recognized disease. The diagnostic criteria have low sensitivity (12 to 32 %) and high specificity (>95 %) [14] so many cases are not diagnosed. Therefore, meta-analytic studies suggesting that DLB accounts for 4 % of

dementia diagnoses [21] underestimate the true prevalence [22], which may be closer to 20 % of dementia [23]. PDD accounts for a further 3 to 5 % of dementia cases [24]. Many symptoms of DLB are noncognitive in nature, and many are under-recognized [25,26,27]. It can be helpful to divide the array of symptoms into five symptom categories: cognitive, neuropsychiatric, movement, autonomic, and sleep. Patients often view DLB as a purely cognitive disease, and consequently will not volunteer non-cognitive symptoms since they do not believe they are a consequence of the disease. Directed questions in each of the five categories can form the basis of a comprehensive drug research strategy that can improve the patient's quality of life. The disease course can be rapid, although prognosis varies between individuals. In one study, life expectancy at diagnosis is 2.3 years shorter for DLB compared with Alzheimer's disease [27].

Designing the study protocol for Dementia with Lewy bodies (DLB) and Pervasive developmental disorders (PDD)

DLB and PDD are very complex diseases and both have identical clinical and neuropathological phenotypes [28,29]. During early stages DLB and PDD might be differentiated by the predominance of dementia in DLB and of parkinsonian motor features in PD [28], but there is no single sign, symptom or biomarker, that definitively distinguishes PDD from DLB [29]. The management of both is replete with quandaries: in choosing to treat one symptom, we often produce complications in other facets of the disease. For example, dopamine replacement for motor symptoms frequently exacerbates a patient's neuropsychiatric symptoms, antipsychotic treatment of hallucinations worsens parkinsonism and risks a potentially fatal adverse reaction, while cholinesterase inhibitor treatment of cognitive symptoms can complicate cardiac and gastrointestinal dysautonomia. Due to aforementioned similarities, an ideal patient population for clinical study in patients with dementia with Lewy body will be those aged 50-85 years with diagnosis of "all cause dementia" [30] specifically due to probable DLB [31], or PDD [32]. One of the unique features of both PDD and DLB, but not of AD, are cognitive fluctuations, with episodes of confusion, hypersomnolence, incoherent speech, and staring spells. These are seen in 15% to 80% of patients with DLB [33] and are also as common in patients with PDD [34]. Visual hallucinations occur in 60 to 70 % of DLB patients, whereas auditory hallucinations are present in 40-50% of subjects with DLB. Delusion and misidentifications have been observed in 40-60% of DLB subjects [35].

The clinical presentation at that stage is difficult to distinguish from delirium which can be seen in severe Alzheimer's Disease, and it should be seriously

considered during the clinical assessment, (avoiding testing at that time, for instance) particularly cognition and behavioural symptoms. The inclusion MMSE range should be fairly wide 12-24.

DLB and PPD are conditions where falls are very common, and potential preventive effect on falls might be ideally investigated in these patients populations. Typically, all studies in DLB and PPD would have a randomised, parallel placebo-controlled design with drug exposure at least 12, preferably 24 weeks, to capture clinically important efficacy signal.

Endpoints selection

Regardless of what will be selected as primary efficacy endpoint, the intensity of cognitive and non-cognitive symptoms/syndromes (neuropsychiatric, movement, autonomic, and sleep) should be assessed either as an efficacy or safety endpoints in all protocols. Unfortunately, there is no unified scale which will be used as comprehensive assessment of symptoms or disease progression in DLB as we have been used in other neurodegenerative disorders (UPDRS in PD or UMSARS in MSA). Therefore, the changes within each of the syndromes should be assessed with specific scale (i.e UPDRS-3 in motor syndromes, NPI in neuropsychiatric syndromes). For instance, if treatment of psychosis will be selected as an efficacy objective, the Scale of the Assessment of Positive Symptoms (SAPS) might be used. It provides coverage of hallucination, delusions, and behavioural changes associated with psychosis and was developed for schizophrenia. Information is acquired from both the patient and an informant. If cognition will be selected as primary efficacy endpoint, DLB and PDD have prominent visuospatial, executive and attention dysfunctions, and selection of specific assessment instruments should be done accordingly.

If psychosis and/or cognition have been selected as an efficacy endpoint, the assessment of autonomic features, sleep and motor symptoms should be done as a safety endpoint.

Conclusion

Although DLB has been considered as the second the most common dementia, number of therapeutic clinical studies so far is very low, mimicking the DLB as an orphan disease. In spite of some lessons learnt, there are plenty of methodological issues affecting patient's selection and assessment. We have already addressed some of them, but the greatest challenge of these studies is to create clinically feasible, state of art protocols, which will be able to capture signals in this multi domain complex neurodegenerative synucleinopathy.

References

- [1] Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). *J Neurol Sci.* 1989;94(1/3):79–100.
- [2] New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study. *J Neurol Neurosurg Psychiatry.* 2016;87(5):554–61.
- [3] Laurens B, Vergnet S, Lopez MC et al. Multiple System Atrophy – State of Art. *Curr Neurol Neurosci Rep* 2017;17:41
- [4] Gilman S, May SJ, Shults CW et al. North American Multiple System Atrophy Study, The north American multiple system atrophy study group. *J. Neural Transm. (Vienna)* 2005: 112, 1687–1694.
- [5] Kass-Iliyya L, Kobylecki C, McDonald KR, Gerhard A, Silverdale MA. Pain in multiple system atrophy and progressive supranuclear palsy compared to Parkinson's disease. *Brain Behav.* 2015;5(5), e00320.
- [6] Kaufmann H, Norcliffe-Kaufmann L, Palma JA et al. Autonomic Disorders, Natural history of pure autonomic failure: a United States prospective cohort. *Ann. Neurol.* 2017b;81, 287–297.
- [7] Goldstein DS, Kopin IJ, Sharabi Y, Holmes C. Plasma biomarkers of decreased vesicular storage distinguish Parkinson disease with orthostatic hypotension from the parkinsonian form of multiple system atrophy. *Clin. Auton. Res. Off. J. Clin. Auton. Res. Soc.* 2015;25, 61–67.
- [8] Blood-based NfL: a biomarker for differential diagnosis of parkinsonian disorder. *Neurology* 2017; 88, 930–937.
- [9] Lee YC, Liu CS, Wu HM, Wang PS, Chang MH, Soong BW. The “hot cross bun” sign in the patients with spinocerebellar ataxia. *Eur J Neurol.* 2009;16(4):513–6.
- [10] Longitudinal MRI study of multiple system atrophy - when do the findings appear, and what is the course? *J. Neurol.* 2002; 249, 847–854.
- [11] Gilman S, Wenning GK, Low PA et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* 2008;71(9):670–6.
- [12] Koga S, Aoki N, Uitti RJ et al. When DLB, PD, and PSP masquerade as MSA: an autopsy study of 134 patients. *Neurology* 2015;85:404–12.)
- [13] Singer W and Low P. Optimizing clinical trial design for multiple system atrophy: lessons from the rifampicin study. *Clin Auton Res.* 2015 February; 25(1): 47–52.
- [14] Nelson PT, Jicha GA, Kryscio RJ, Abner EL, Schmitt FA, Cooper G, et al. Low sensitivity in clinical diagnoses of dementia with Lewy bodies. *J Neurol.* 2010;257:359–66.
- [15] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007;69:2197–204.

- [16] McKeith I, Mintzer J, Aarsland D, et al. Dementia with Lewy bodies. *Lancet Neurol.* Jan; 2004 3(1):19–28
- [17] Lippa CF, McKeith I. Dementia with Lewy bodies: improving diagnostic criteria. *Neurology.* 2003 60(10):1571–1572.
- [18] Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. *Neurology.*; 2003 60(10):1586–1590.
- [19] Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. *Archives of neurology.* 2002 59(1):102–112.
- [20] Mrazek RE, Griffin S. Dementia with Lewy body: Definition, diagnosis and pathogenic relationship to Alzheimer's disease. *Neuropsychiatric Disease and Treatment* 2007;3(5) 619–625
- [21] Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med.* 2013;44:673–83.
- [22] Boot B. The incidence and prevalence of dementia with Lewy bodies is underestimated. *Psychol Med.* 2013;43:2687–8.
- [23] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005;65:1863–72.
- [24] Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. *Mov Disord.* 2005;20:1255–63.
- [25] Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry.* 1999;156:1039–45.
- [26] Ballard C, O'Brien J, Gray A, Cormack F, Ayre G, Rowan E, et al. Attention and fluctuating attention in patients with dementia with Lewy bodies and Alzheimer disease. *Arch Neurol.* 2001;58:977–82.
- [27] Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. *Neurology.* 2013;81:833–40.
- [28] Johnson DK, Galvin JE. Longitudinal changes in cognition in Parkinson's disease with and without dementia. *Dement Geriatr Cogn Disord* 2011;31:98-108.
- [29] Aarsland D, Ballard CG, Halliday G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? *J Geriatr Psychiatry Neurol* 2004;17:137-145.
- [30] McKhann GM, Knopman DS, Chertkow et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 7 (2011) 263–269
- [31] McKeith et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005;65:1863-72.

- [32] Emre M, Arslan D, Brown R et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007 Sep 15;22(12):1689-707;
- [33] Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. *Neurology* 2004;62:181-187.
- [34] Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. *Neurology* 2002;59:1714-1720.
- [35] Ballard C, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry*. 1999;156:1039-45.

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EFFECTS OF THE NOVEL CORONAVIRUS DISEASE (COVID-19) ON COGNITION

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Summary

Coronavirus disease 2019 (COVID-19) is a highly contagious viral disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent research shows that SARS-CoV-2 enters the host cells by binding its spike protein to angiotensin-converting enzyme 2 receptors, which are also present on cells in the central nervous system. The cognitive changes that occur during the acute SARS-CoV2 infection encompass mild and severe deficits that happen in all ages. Research from the COVID-19 rehabilitation units show that as high as 80% of patients had deficits on Montreal Cognitive Assessment and Mini Mental State Evaluation tests. The cognitive deficits present in the post-COVID-19 chronic period encompass a variety of cognitive domains, and it is unclear what will be the rate of permanence. It is clear that COVID-19 had a profound effect on cognition both directly and indirectly. The challenges that we face now encompass both acute and chronic cognitive impairments with uncertainty on the length of symptoms. Previous viral pandemics have taught us that the battles we face today may just be the beginning of further challenges in patients that can occur years after initial infection. A major focus in the future will be to better define the cognitive changes that occur due to COVID-19 infections and how to treat them.

Key words: COVID-19, SARS-CoV-2, cognitive impairment, dementia

Introduction to COVID-19

Coronavirus disease 2019 (COVID-19) is a highly contagious viral disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. The speed at which the pandemic spread was staggering and has changed the world and society significantly since the start. At the time of writing, there have been upwards of two-hundred million cases and more than four million deaths [2]. For example, COVID-19 was the third leading cause of death in the United States in 2020 after heart disease and cancer [3]. The advent of vaccinations has brought hope that the pandemic would be soon over, but the virus is prone to rapid genetic evolution and multiple variants, which makes it unclear whether there will be newfound resistances to vaccination [4]. Classically, respiratory symptoms have been given the primary focus as they are the cause of death in patients and the respiratory system is the main target of the virus; however, it has quickly become clear that neurological symptoms can have a significant impact in the acute and post-COVID periods [5].

SARS-CoV-2 enters the host cells by binding its spike protein to angiotensin-converting enzyme 2 (ACE2) receptors that are present on the respiratory epithelium, among multiple other cell types in the gastrointestinal tract and kidneys [6]. Recent research has shown that ACE2 receptors are present in the central nervous system as well, which creates a potential target for infection [7]. ACE2 receptors are present on most cells, and include neurons, microglia, astrocytes and oligodendrocytes [8]. Most expression was found in the motor cortex, posterior cingulate cortex, ventricles, substantia nigra, olfactory bulb, middle temporal gyrus and widely in the brainstem including cardiorespiratory nuclei [9]. The later one opens the possibility that pathological change due to the SARS-CoV-2 can affect the respiratory center in the medulla oblongata [10] thus leading to the failure of respiratory system in the early period of infection [11].

There are three ways that SARS-CoV-2 can invade the central nervous system and include retrograde transsynaptic transfer through the olfactory nerve, vascular endothelial cell infection or through the leukocyte migration [12]. The most common neurologic symptoms in COVID-19 are headache, anosmia, ageusia, but there are numerous reports of encephalopathy, encephalitis, consciousness impairment, and even peripheral nerve disorders [13]. The pathophysiological mechanism to these symptoms is heterogenous, but can be linked to the excessive cytokine release that can be present in COVID-19, both in and out of the central nervous system [14] and direct cytopathogenic effects of the virus [12]. It is becoming increasingly clear that these mechanisms could be the cause in acute and chronic cognitive impairment as well, which is becoming a key symp-

tom of the post-COVID or long-COVID period [15]. Taken together, it is clear that SARS-CoV-2 can influence changes in the central and peripheral nervous system directly and indirectly and presents a challenge in clinical practice [16].

Effects of COVID-19 on cognition

Viral infections can affect cognition in both acute and chronic periods of infections. Previous research of SARS-CoV and MERS-CoV indicates that a third of patients develop cognitive symptoms in the acute period, with a fifth retaining cognitive impairments for an extended period of time [17]. Furthermore, there are theories that infections with herpes viruses can increase dementia risk later in life [18], while neurodegeneration was seen years after infections with the Spanish influenza [19]. Early research is unequivocal that COVID-19 can cause cognitive impairments in the acute period, and there is indication that this can persist and even influence patients with existing cognitive impairment.

Cognitive impairment during acute infection period

The cognitive changes that occur during the acute SARS-CoV2 infection encompass mild and severe deficits that happen in all ages [20]. Research from the COVID-19 rehabilitation unit at the San Raffaele Hospital (Milan, Italy) shows that as high as 80% of patients had deficits on Montreal Cognitive Assessment (MoCA) and Mini Mental State Evaluation (MMSE), with indications of depression, as measured by the Hamilton's scale for depression [21]. Importantly, a significant portion of patients retained cognitive deficits in the one month follow-up [21]. The incidence of cognitive impairment correlated with age, while cognitive impairments were dominantly present in patients requiring oxygen therapy. Importantly, the severity of cognitive deficits was less pronounced in patients who required orotracheal intubation, indicating that the cognitive disturbance cannot be attributed directly to symptom severity. However, a study by Beaud et al., focusing on severe COVID-19, revealed that the majority of patients presented with agitation and confusion, with a major proportion exhibiting dysexecutive syndrome [22]. This pattern of cognitive impairment is consistent with those previously described during ARDS [23], and could mean that the acute cognitive deficits in severe COVID-19 could be attributed to the already known systemic inflammatory patterns [24]. In general, it is known that any intensive care unit treatment often leads to cognitive deficits on its own, as most of the patients have critical severity of symptoms, regardless of cause [25]. Furthermore, delirium and encephalopathy was present in more than 80% of patients treated in the ICU due to COVID-19, which in line with other respiratory illness [26].

Persistent cognitive impairments were found in the sub-acute COVID-19 periods [27]. A research by Pistarini et al. clearly shows impaired executive function, short and long term memory, abstraction and orientation in up to 70% of patients who suffered from COVID-19 [28]. MoCA was found to be a more sensitive test to detect cognitive impairment than MMSE in this study, considering it encompasses more cognitive domains [28]. The early period after active infection could be the time when cognitive rehabilitation should be initiated, as previous research in other neurological disorders has shown that this could be warranted [29, 30]. Overall, there is a need for further research with regards to cognitive impairment directly at the bedside, during the acute period, as the current literature is scarce.

Cognitive impairment during the chronic period

Effects of COVID-19 on cognition have been extensively studied in the early post-COVID-19 and long-COVID-19 periods, with multiple studies and reports discussing the adverse effects of the infection. A large retrospective study with more than two-hundred thousand participants by Taquet et al. found that dementia is was present in 0.67% of all patients, with the percentage increasing to 1.46% in the hospitalized patients [31]. Interestingly, it is unclear whether acute cognitive changes, such as delirium, lead to chronic problems as a McLoughlin et al. did not find an association between acute and chronic cognitive symptoms [32]. This is further corroborated by a study that found a higher degree of cognitive deficits in the post-COVID-19 period than in the acute phases, indicating a different pathophysiological mechanism between the two phases of the disease [16, 33]. In studies assessing global cognitive function, we can see that the impairment can be present in nearly 15% of patients three months after infection [34]. The severity of impairment one month after hospitalization, as measured by MoCA scores, is highest in patients who were more dependent on oxygen (15.90 ± 6.97) [21], while patients without hospitalization has scores close to mild cognitive impairment (26.50 ± 2.90) [35]. Residual cognitive deficits after ICU discharge are present in as high as 25% [36], and importantly, the same can be seen in COVID-19 patients who were not treated in the ICU [37]. On the other hand, a study by Raman et al. found that while cognitive impairment was profound in COVID-19 patients, the results did not significantly differ from the healthy control groups, indicating the need for further studies in the field [38].

The cognitive deficits present in the post-COVID-19 period encompass a variety of cognitive domains. Research has shown that the cognitive domain of attention, executive function and visuospatial function is most affected in CO-

VID-19 related cognitive impairment in MoCA testing [38], with further corroboration of changes in fluency, inhibition and conceptualization using the Frontal Assessment Battery [22, 39, 40]. Deficits in memory have also been noted in several studies, mostly in short-term memory [21, 40], while language was not affected to a significant degree [41].

Finally, it is still unclear whether the deficits are temporary or long-lasting despite that some meta-analysis data suggest that multiple effects after COVID-19 persist [42]. A study by Lu et al. has shown that the incidence of cognitive deficits increases from the acute period [33], while a study by Sykes et al. has shown that the burden of cognitive impairment lessens during time [43]. It is a question that will only be answered as time passes and our experience with COVID-19 grows; however, current research on viral infections shows that multiple virus types, such as Herpes simplex virus or Varicella zoster virus can all cause long lasting cognitive impairment that significantly affects the quality of life [44].

Indirect effects of COVID-19 on concurrent cognitive diseases

An important aspect of COVID-19 is the pandemic itself, that changed our society greatly, and can negatively impact the health of patients with dementia without infection [45]. We can speak about an epidemic of dementia, with more than 50 million worldwide living with dementia, all of which could be impacted negatively by social isolation restrictions due to COVID-19 [46]. Studies focused on the community based effect of lockdowns in Europe and Latin America reveal a significant worsening of cognitive and behavioral symptoms, with an increase of prescribed medications in the period [47]. Studies by Tsapanous et al. and Borelli et al. revealed that cognitive worsening was present in more than a half of patients during the brief pandemic period, with a significant strain on the caregivers as well, due to a disruption of daily routines and social isolation [48, 49]. Neuropsychiatric and behavioral symptoms worsened even more during the pandemic, with an immense increase of depression, anxiety and agitation [50]. An interesting study by Lara et al. compared the effects of the lockdown by applying The Neuropsychiatric Inventory and EuroQol-5D questionnaire scores before and 5 weeks into the lockdown, which revealed worsening of agitation and apathy in both patients and caregivers in a short amount of time [51]. This is quite concerning, especially as we know that these symptoms are related with lower quality of life in dementia patients [52, 53].

The possible reasons of such rapid worsening are imposed changes in the daily life habits of dementia patients, as there was a sudden stop in social and leisure activities that fill a significant period of their routine [54]. Furthermore,

separation from family members and loved ones induce significant stress, which dementia patients deal with less successfully than healthy adults [55]. One way to help would be to address the issue by raising it to the patients and caregivers, inform them of the risks isolation and social changes hold [56], while organizing educations on coping mechanisms to reduce the induced stress [57].

Conclusion and future directions

It is clear that COVID-19 had a profound effect on cognition both directly and indirectly. The challenges that we face now encompass both acute and chronic cognitive impairments with uncertainty on the length of symptoms. Previous viral pandemics have taught us that the battles we face today may just be the beginning of further challenges in patients that can occur years after initial infection. A major focus in the future will be to better define the cognitive changes that occur due to COVID-19 infections and how to treat them.

Furthermore, current dementia patients face a significant burden due to major changes in our society, and their impaired abilities to cope with them. A large portion of our efforts should be turned towards assisting the patients and their caregivers in empowering their ability to deal with stress, to reduce the cognitive and behavioral worsening that happens rapidly during the pandemic.

References

- [1] Hu B, Guo H, Zhou P, Shi ZL (2021) Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 19:141–154. doi: 10.1038/s41579-020-00459-7
- [2] WHO (2021) Bangladesh: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. World Heal Organ 1–5.
- [3] Ahmad FB, Cisewski JA, Miniño A, Anderson RN (2021) Provisional Mortality Data — United States, 2020. *MMWR Surveill Summ* 70:519–522. doi: 10.15585/mmwr.mm7014e1
- [4] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, Evaluation and Treatment Coronavirus (COVID-19). *StatPearls*
- [5] Mao L, Jin H, Wang M, et al (2020) Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 77:683–690. doi: 10.1001/jamaneurol.2020.1127
- [6] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int. J. Oral Sci.* 12:

- [7] Ni W, Yang X, Yang D, et al (2020) Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit. Care* 24:
- [8] Chen R, Wang K, Yu J, Howard D, French L, Chen Z, Wen C, Xu Z (2021) The Spatial and Cell-Type Distribution of SARS-CoV-2 Receptor ACE2 in the Human and Mouse Brains. *Front Neurol* 11:1860. doi: 10.3389/fneur.2020.573095
- [9] Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E (2007) Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 292:
- [10] Lee M-H, Perl DP, Nair G, et al (2021) Microvascular Injury in the Brains of Patients with Covid-19. *N Engl J Med* 384:481–483. doi: 10.1056/nejmc2033369
- [11] Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN (2020) The pathophysiology of “happy” hypoxemia in COVID-19. *Respir Res* 21:1–9. doi: 10.1186/s12931-020-01462-5
- [12] Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S (2020) Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. *JAMA Neurol* 77:1018–1027. doi: 10.1001/jamaneurol.2020.2065
- [13] Helms J, Kremer S, Merdji H, et al (2020) Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 382:2268–2270. doi: 10.1056/nejmc2008597
- [14] Ye Q, Wang B, Mao J (2020) The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *J Infect* 80:607–613. doi: 10.1016/j.jinf.2020.03.037
- [15] Heneka MT, Golenbock D, Latz E, Morgan D, Brown R (2020) Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer’s Res. Ther.* 12:
- [16] Yong SJ (2021) Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. *ACS Chem Neurosci* 12:573–580. doi: 10.1021/acschemneuro.0c00793
- [17] Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G, David AS (2020) Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry* 7:611–627. doi: 10.1016/S2215-0366(20)30203-0
- [18] Warren-Gash C, Forbes HJ, Williamson E, Breuer J, Hayward AC, Mavrodaris A, Ridha BH, Rossor MN, Thomas SL, Smeeth L (2019) Human herpesvirus infections and dementia or mild cognitive impairment: a systematic review and meta-analysis. *Sci. Rep.* 9:
- [19] McCall S, Vilensky JA, Gilman S, Taubenberger JK (2008) The relationship between encephalitis lethargica and influenza: A critical analysis. *J Neurovirol* 14:177–185. doi: 10.1080/13550280801995445
- [20] Daroische R, Hemminghyth MS, Eilertsen TH, Breivte MH, Chwiszczuk LJ (2021) Cognitive Impairment After COVID-19—A Review on Objective Test Data. *Front Neurol* 12:1238. doi: 10.3389/fneur.2021.699582

- [21] Alemanno F, Houdayer E, Parma A, et al (2021) COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID rehabilitation unit experience. *PLoS One* 16:
- [22] Beaud V, Crottaz-Herbette S, Dunet V, Vaucher J, Bernard-Valnet R, Du Pasquier R, Bart PA, Clarke S (2021) Pattern of cognitive deficits in severe COVID-19. *J Neurol Neurosurg Psychiatry* 92:567–568. doi: 10.1136/jnnp-2020-325173
- [23] Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF (2005) Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 171:340–347. doi: 10.1164/rccm.200406-763OC
- [24] Solomon T (2021) Neurological infection with SARS-CoV-2 — the story so far. *Nat Rev Neurol* 17:65–66. doi: 10.1038/s41582-020-00453-w
- [25] Elizabeth Wilcox M, Brummel NE, Archer K, Wesley Ely E, Jackson JC, Hopkins RO (2013) Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Crit. Care Med.* 41:
- [26] Helms J, Kremer S, Merdji H, et al (2020) Delirium and encephalopathy in severe COVID-19: A cohort analysis of ICU patients. *Crit. Care* 24:
- [27] Hosp JA, Dressing A, Blazhenets G, et al (2021) Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain* 144:1263–1276. doi: 10.1093/brain/awab009
- [28] Pistarini C, Fiabane E, Houdayer E, Vassallo C, Manera MR, Alemanno F (2021) Cognitive and Emotional Disturbances Due to COVID-19: An Exploratory Study in the Rehabilitation Setting. *Front Neurol* 12:643646. doi: 10.3389/fneur.2021.643646
- [29] Xuefang L, Guihua W, Fengru M (2021) The effect of early cognitive training and rehabilitation for patients with cognitive dysfunction in stroke. *Int J Methods Psychiatr Res* 30:e1882. doi: 10.1002/mpr.1882
- [30] Fuke R, Hifumi T, Kondo Y, Hatakeyama J, Takei T, Yamakawa K, Inoue S, Nishida O (2018) Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: A systematic review and meta-analysis. *BMJ Open* 8:
- [31] Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ (2021) 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry* 8:416–427. doi: 10.1016/S2215-0366(21)00084-5
- [32] Mcloughlin BC, Miles A, Webb TE, Knopp P, Eyres C, Fabbri A, Humphries F, Davis D (2020) Functional and cognitive outcomes after COVID-19 delirium. *Eur Geriatr Med* 11:857–862. doi: 10.1007/s41999-020-00353-8
- [33] Lu Y, Li X, Geng D, et al (2020) Cerebral Micro-Structural Changes in COVID-19 Patients – An MRI-based 3-month Follow-up Study: A brief title: Cerebral Changes in COVID-19. *EClinicalMedicine* 25:
- [34] van den Borst B, Peters JB, Brink M, et al (2021) Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 73:e1089–e1098. doi: 10.1093/cid/ciaa1750

- [35] Soldati AB, Almeida C, Lima M, Araujo A, Araujo-Leite MA, Silva MTT (2021) Telephone Screening of Cognitive Status (TICS) in severe COVID-19 patients: Utility in the era of social isolation. *eNeurologicalSci* 22:
- [36] De Lorenzo R, Conte C, Lanzani C, et al (2020) Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study. *PLoS One* 15:
- [37] Ortelli P, Ferrazzoli D, Sebastianelli L, et al (2021) Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J. Neurol. Sci.* 420:
- [38] Raman B, Cassar MP, Tunnicliffe EM, et al (2021) Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 31:
- [39] Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J (2020) Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. *Brain, Behav Immun - Heal* 9:100163. doi: 10.1016/j.bbih.2020.100163
- [40] Negrini F, Ferrario I, Mazziotti D, Berchicci M, Bonazzi M, de Sire A, Negrini S, Zapparoli L (2021) Neuropsychological Features of Severe Hospitalized Coronavirus Disease 2019 Patients at Clinical Stability and Clues for Postacute Rehabilitation. *Arch Phys Med Rehabil* 102:155–158. doi: 10.1016/j.apmr.2020.09.376
- [41] Woo MS, Malsy J, Pöttgen J, et al (2020) Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun.* 2:
- [42] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S (2021) More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 11:1–12. doi: 10.1038/s41598-021-95565-8
- [43] Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG (2021) Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 199:113–119. doi: 10.1007/s00408-021-00423-z
- [44] Damiano RF, Guedes BF, de Rocca CC, et al (2021) Cognitive decline following acute viral infections: literature review and projections for post-COVID-19. *Eur Arch Psychiatry Clin Neurosci* 1:1–16. doi: 10.1007/s00406-021-01286-4
- [45] Mok VCT, Pendlebury S, Wong A, et al (2020) Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimer's Dement* 16:1571–1581. doi: 10.1002/alz.12143
- [46] Wittenberg R, Hu B, Jagger C, Kingston A, Knapp M, Comas-Herrera A, King D, Rehill A, Banerjee S (2020) Projections of care for older people with dementia in England: 2015 to 2040. *Age Ageing* 49:264–269. doi: 10.1093/ageing/afz154
- [47] Suárez-González A, Rajagopalan J, Livingston G, Alladi S (2021) The effect of COVID-19 isolation measures on the cognition and mental health of people living with dementia: A rapid systematic review of one year of quantitative evidence. *EClinicalMedicine* 39:
- [48] Tsapanou A, Papatranta-fyllou JD, Yiannopoulou K, et al (2021) The impact of COVID-19 pandemic on people with mild cognitive impairment/dementia and on their caregivers. *Int J Geriatr Psychiatry* 36:583–587. doi: 10.1002/gps.5457

- [49] Borelli WV, Augustin MC, De Oliveira PBF, Reggiani LC, Bandeira-De-Mello RG, Schumacher-Schuh AF, Chaves MLF, Castilhos RM (2021) Neuropsychiatric Symptoms in Patients with Dementia Associated with Increased Psychological Distress in Caregivers during the COVID-19 Pandemic. *J Alzheimer's Dis* 80:1705–1712. doi: 10.3233/JAD-201513
- [50] Canevelli M, Valletta M, Toccaceli Blasi M, Remoli G, Sarti G, Nuti F, Sciancalepore F, Ruberti E, Cesari M, Bruno G (2020) Facing Dementia During the COVID-19 Outbreak. *J Am Geriatr Soc* 68:1673–1676. doi: 10.1111/jgs.16644
- [51] Lara B, Carnes A, Dakterzada F, Benitez I, Piñol-Ripoll G (2020) Neuropsychiatric symptoms and quality of life in Spanish patients with Alzheimer's disease during the COVID-19 lockdown. *Eur J Neurol* 27:1744–1747. doi: 10.1111/ene.14339
- [52] Gomez-Gallego M, Gomez-Garcia J, Ato-Lozano E (2015) Addressing the bias problem in the assessment of the quality of life of patients with dementia: Determinants of the accuracy and precision of the proxy ratings. *J Nutr Heal Aging* 19:365–372. doi: 10.1007/s12603-014-0564-7
- [53] Springate BA, Tremont G (2014) Dimensions of caregiver burden in dementia: Impact of demographic, mood, and care recipient variables. *Am J Geriatr Psychiatry* 22:294–300. doi: 10.1016/j.jagp.2012.09.006
- [54] Iodice F, Cassano V, Rossini PM (2021) Direct and indirect neurological, cognitive, and behavioral effects of COVID-19 on the healthy elderly, mild-cognitive-impairment, and Alzheimer's disease populations. *Neurol Sci* 42:455–465. doi: 10.1007/s10072-020-04902-8
- [55] Meléndez JC, Satorres E, Redondo R, Escudero J, Pitarque A (2018) Wellbeing, resilience, and coping: Are there differences between healthy older adults, adults with mild cognitive impairment, and adults with Alzheimer-type dementia? *Arch Gerontol Geriatr* 77:38–43. doi: 10.1016/j.archger.2018.04.004
- [56] Tsatali M, Moraitou D, Poptsi E, et al (2021) Are there any cognitive and behavioral changes potentially related to quarantine due to the COVID-19 pandemic in people with mild cognitive impairment and AD dementia? A longitudinal study. *Brain Sci* 11:1165. doi: 10.3390/brainsci11091165
- [57] Bavel JJV, Baicker K, Boggio PS, et al (2020) Using social and behavioural science to support COVID-19 pandemic response. *Nat Hum Behav* 4:460–471. doi: 10.1038/s41562-020-0884-z

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MANAGEMENT OF MOVEMENT DISORDERS AND DEEP BRAIN STIMULATIONS' PATIENTS IN COVID 19 PANDEMIC

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Summary

The COVID-19 pandemic has major consequences on our society and way of life and has changed the way we practice neurology. Studies have observed that patients with COVID 19 infections can develop other movement disorders symptoms like myoclonus or confusion and encephalic symptoms. Individuals with Parkinson's disease (PD), the most often movement disorders, are particularly vulnerable to experiencing the negative sequelae, not only because of changed lifestyle, which causes an increased stress and reduction in physical exercise, but also because of compromised respiratory system that put them at higher risk of COVID-19 pneumonia: rigidity of respiratory muscles, common dyspnoea and reduced cough reflex. Also, less capability to adapt to new circumstances is a big issue in PD patients. People with PD demonstrated more anxiety and depression as well as decreased levels of quality of life and physical activity as compared to controls during the COVID-19 lockdown. Since PD affects elderly population the risk factors for a more severe COVID-19 presentation in general population. According to the current literature in advanced PD, a rapid worsening of PD could mean onset of COVID-19 infection. Recent studies have shown higher risk for a worse course and outcome. The common risk factors for higher mortality are older age, longer disease duration, use of advanced therapies, dementia, and hypertension. In the last year we have developed telemedicine-based communication with our patients. Also, elective interventions including new implantations of deep brain stimulation (DBS) and initial programming were postponed in first wave but not so much in the second and third. Since public health guidelines and bed capacity vary across countries and rapidly change, each medical, movement

disorders (MD) and DBS center needed to develop quickly strategies and clear recommendations how to care for MD and DBS patients.

We will give in this paper an overview of challenging experiences on management of movement disorders' patients and DBS implanted patients in COVID-19 pandemic time.

Key words: Movement disorders; COVID 19 pandemic; Deep brain stimulation

Introduction

The new coronavirus (SARS-CoV-2) that originated in China spread rapidly around the world, so in March 2020 a pandemic was declared. In the last years we have witnessed the impact of the COVID-19 pandemic on the lives of particularly affected families, on health systems, the economy and the world economy.

The COVID-19 pandemic has major consequences on our society and way of life and has changed the way we practice neurology. Studies have observed that patients with COVID 19 infections can develop other movement disorders symptoms like myoclonus or confusion and encephalic symptoms [1]. Individuals with Parkinson's disease (PD, the most often movement disorders, are particularly vulnerable to experiencing the negative squeals, not only because of changed lifestyle, which causes an increased stress and reduction in physical exercise, but also because of compromised respiratory system that put them at higher risk of COVID-19 pneumonia: rigidity of respiratory muscles, common dyspnea and reduced cough reflex. Also, less capability to adopt to new circumstances is a big issue in PD patients. People with PD demonstrated more anxiety and depression as well as decreased levels of quality of life and physical activity as compared to controls during the COVID-19 lockdown [2]. Since PD affects elderly population the risk factors for a more severe COVID-19 presentation in general population. According to the current literature in advanced PD, a rapid worsening of PD could mean onset of COVID-19 infection. Recent studies have shown higher risk for a worse course and outcome. The common risk factors for higher mortality are older age, longer disease duration, use of advanced therapies, dementia, and hypertension. In the last year we have developed telemedicine-based communication with our patients [3,4]. Similar is with other disabling neurological conditions especially neurodegenerative diseases like Alzheimer disease, multiple sclerosis etc.

Deep Brain Stimulation

Deep brain stimulation (DBS) is a well-established, safe, and effective treatment for the management of patients with advanced Parkinson's disease and

other movement disorders [5]. Patients with DBS require often visiting DBS centers and life-long management of the medical device as well as medications. Such management is depending on geography, socioeconomic factors, and support systems. The COVID-19 pandemic has changed the way we practice

neurology, especially movement disorders and, nevertheless, our management of patients with deep brain stimulation implanted for movement disorders worldwide. The global lockdown has forced movement disorders patients (Parkinson's disease, essential tremor, dystonia) to stay at home or they became infected by virus or became worse due to interruption of therapy due to neurostimulator battery reaching end of life, device malfunction or infection. They can develop due to COVID 19 infections other movement disorders symptoms like myoclonus or confusion and encephalic symptoms [6].

In first wave of COVID-19 pandemic, the most medical centers were postponing elective procedures and prevent spread of COVID-19 what presented unique challenges for management of DBS patients and transitioning to predominantly telemedicine or remotely by smartphone consultations for outpatient care [7]. Urgent intervention to maintain or restore stimulation were required mostly for patients with Parkinson's disease who could develop a rare but potentially life-threatening complication known as DBS-withdrawal syndrome and patients with generalized dystonia with potential developing status dystonicus. Also, DBS system infection required urgent, and rarely emergent surgery (like lead fractures, electrical malfunction). Elective interventions including new implantations and initial programming were postponed in first wave but not so much in the second and we will observe the consequences in the future. Since public health guidelines and bad capacity vary across countries and rapidly change, each medical and DBS center needed to develop quickly strategies and clear recommendations how to care for DBS patients.

Parkinson's disease and COVID 19 pandemic

Recently, due to the difficult situation with the coronavirus, all public attention has been focused on combating the infection. Many activities had to adapt to the emerging pandemic, including neurology (7). In many Institutions, neurology accommodation facilities have been reduced, or relocated to the COVID department. Many doctors and nurses were withdrawn to COVID wards. In the first wave, only emergency activities and more urgent outpatients worked. Patients themselves avoided visiting a neurologist for fear of infection despite significant exacerbations. Even in emergencies such as acute stroke, it has been observed that 25% of patients did not even seek help in the emergency neuro-

logical service, despite the symptoms of stroke [8]. These were usually milder symptoms. Many movement disorders services have had telephone, telemedicine, zoom, email and other virtual consultations and examinations of patients in order to avoid unnecessary patient arrivals if possible and to receive an appropriate recommendation. Behind the first wave, we all had a rush of patients with significant exacerbations and complications in our clinics, multidisciplinary teams, and wards. In the other two waves, however, they came in larger numbers to both clinics and wards, especially in acute conditions and worsening of movement disorders.

Patients with chronic progressive neurodegenerative diseases, regardless of whether they had COVID 19 infection, had exacerbations. Isolation and social distancing that should be adhered due to coronavirus, are behaviors that do not contribute to the good condition of patients with chronic neurodegenerative diseases, including Parkinson's disease, with a lack of physical activity. Thus, in a study conducted in the spring of 2020, 7,209 people with Parkinson's disease were found to be infected with COVID 19 with new symptoms or worsening of motor and non-motor symptoms of 63% (similar in post covid 19 time) and 75% and those without COVID 19 infection with worsening motor skills, and nonmotor symptoms 43-52% [9].

We know that Parkinson's disease is more common in the elderly population and can cause respiratory disorders especially in the advanced stage such as more frequent aspiration pneumonia and, among other things, reduced lung breathing capacity due to bent posture and muscle rigors. According to some studies, prolonged stress can reveal many latent clinical pictures of Parkinson's disease so there is a possibility that during and after this pandemic we are witnessing a greater number of diagnosed patients with Parkinson's disease. This state of pandemic, which changes the routine of all citizens with increased stress, anxiety and depression, leads to worsening of control and motor (tremor, blockage, gait, dyskinesia) and non-motor symptoms (cognitive problems, anxiety, depression, digestive problems, sleep, etc.) with Parkinson's disease. One should be aware that due to the pathophysiology of the disease itself, the reduced adaptive capacity to cope with such situations, which is associated with the dopamine system, puts patients in an even more unenviable position and increases psychological stress, hopelessness and feelings of loss of control. Otherwise, we know that any infection, even respiratory, can worsen the symptoms of Parkinson's disease and reduce the effect of antiparkinsonian drugs, which has been described in the last year [2,4]. Parkinson's disease does not increase the risk of infection with COVID-19, but older patients are known to have a more

severe clinical picture and a higher risk of poor outcome. Common risk factors for higher mortality are older age, longer disease duration, application of advanced therapies, dementia, and hypertension [3].

We often had to do reevaluations of therapy and most often increase the doses of antiparkinsonian drugs or introduce new groups, especially those groups of drugs that reduce OFF and prolong the action of drugs. Patients with Parkinson's disease that is chronic and progressive are predominantly elderly with comorbidities such as high blood pressure and diabetes present and therefore are likely to have a higher risk of a poor outcome. That is why prevention and vaccination are the best, and those suffering from all neurodegenerative diseases must be especially careful and protect themselves - hand washing, social distancing, not touching the face, nose, mouth and eyes with unwashed hands. We already know that hyposmia is both a symptom of COVID-19 infection and a prodromal symptom of Parkinson's disease, so researchers are trying to find a link, whether the same mechanism of occurrence or just sharing is the same symptom of the two diseases. Mostly after 8 months the sense of smell returns with COVID 19 infection. There are 3 reported cases of transient parkinsonism in COVID 19 infection that had both a positive DAT scan and little or no response to antiparkinsonian therapy. Although we know that the Spanish flu was caused by a completely different virus, it is also known for delayed parkinsonism as a neurological consequence. Viral parkinsonism is known but it is clinically and pathologically different from Parkinson's disease. The proposed mechanisms have always been considered such as structural and functional damage to the basal ganglia, inflammatory (neuroinflammatory) processes, hypoxic brain injuries due to encephalopathy, the occurrence of latent Parkinson's disease and the hypothetical possibility of viral infection triggering (as a trigger) long-term development of Parkinson's disease with a genetic predisposition [10]. For now, the causal link between SARS-CoV-2 infection and the development of Parkinson's disease is not supported by solid evidence and it is up to scientists to find out if there is a link or not and what the real mechanisms underlie all these developments. Prospective well-planned and coordinated studies and long-term follow-up of patients with COVID-19 infection are needed, as possible neurological consequences should not be ignored.

The same is true for other neurological diseases such as multiple sclerosis, Alzheimer's disease, etc., in which we record many exacerbations with and without COVID-19 infection, as well as in Parkinson's disease. As we learned, observationally and in basic and clinical research, COVID 19 infection, recommendations of world, European and national bodies / societies for the care of

patients with various neurological diseases were issued, which facilitated daily work. It is certainly necessary to monitor all neurological patients and those who had COVID 19 infection and who are not, so that in the event of a significant increase in the incidence of some of these diseases, the health system and society are ready and organized for it and respond in a timely manner [11,12].

Post Covid neurological symptoms in Parkinson disease patients

Beside the respiratory symptoms, the virus is also neurotropic. It could enter a nerve cell. The SARS-COV-2 virus enters the cell via the angiotensin receptor by converting enzyme 2. Regardless of the severity of respiratory symptoms, 85% of patients with SARS-CoV-2 had acute and subacute symptoms and complications of the peripheral and central nervous systems. The most common are headache, dizziness, hyposmia, hypogeusia, stroke, encephalopathy, meningoencephalitis, and acute polyradiculoneuritis (Guillain Barre syndrome) [13]

Also, there are studies that recognize the increasing numbers of ex-patients with Post COVID Neurological Syndrome (PCNS). A small number of people who recovered from COVID-19 are reporting neurological concerns such as headache, dizziness, lingering loss of smell or taste, sleep problems, fatigue, muscle weakness, nerve damage, and trouble thinking or concentrating — sometimes called “COVID fog” or “brain fog”. In the United Kingdom, the National Institute for Health and Care Excellence has defined the “post-COVID-19 syndrome” as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis [11].” In everyday practice it was recognized that some of the post-COVID-19 symptoms may be part of the PD clinical phenomenolog. It was very hard to study post covid in PD so researcher considered symptoms as part of the clinical manifestations of a post-COVID-19 syndrome only if these occurred after a confirmed SARS-CoV-2 infection or in case of an acute or subacute worsening of a preexisting symptom that had been previously stable. In multicenter case series investigating the occurrence of post-COVID-19 syndrome in patients with PD were reported motor worsening and increased levodopa equivalent daily dose requirements within the long-COVID spectrum. In one study, 85.2% patients with PD developed post-COVID 19 symptoms . They founded that the most common long-term effects of COVID-19 were worsening of motor function (51.9%) and increased levodopa daily dose requirements (48.2%) followed by fatigue (40.7%); cognitive disturbances (22.2%), including “brain fog”, loss of concentration and memory deficits; and sleep disturbances (22.2%), such as insomnia (9). Broadly these symptom complexes concur with

the existing literature on long COVID in the general population [12-17]. Nevertheless, post-COVID clinical manifestations may result from a combination of new symptoms and lockdown as well as viral illness-related worsening of preexisting PD features. So, PD patients had in post COVID period, beside this classical PCNS symptoms, appearance of new PD symptoms or worsening of previous motor and non-motor symptoms

Conclusions

In conclusion, we had to adopt MD out-patients' clinics and Units and introduce remote consultations in this COVID-19 pandemics. The guidelines for invasive treatment like DBS were needed. For now, the causal association of SARS-CoV-2 infection with the development of Parkinson's disease is not supported by robust evidence yet. But, the potential neurological sequelae of this novel coronavirus should not be underestimated and must be carefully monitored in the future. A coordinated international effort to investigate viral effects is essential and should be based on well-designed prospective studies. Undoubtedly, we need additional studies to confirm/refute the trigger effect of SARS-CoV-2 on the neuroinflammatory and neurodegenerative processes leading to the development of parkinsonian symptoms. It remains unclear therefore, whether the COVID-19 and PD are related or merely share a symptom. Although the Spanish flu was caused by an entirely different virus from SARS-CoV2, it does stand as an example of a primarily respiratory infection associated with delayed parkinsonism as a neurological consequence. We need further neurological and cognitive/affective monitoring of all cases of COVID19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS and patients with movement disorders too. Global clinical registries MD patients with a meticulous systems-based approach to the assessment, management and reporting of post-COVID patients will help us.

References

- [1] Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology*. 2020;95(6):e767-e772.
- [2] Fearon C, Fasano A. Parkinson's disease and the COVID-19 pandemic. *J Parkinsons Dis* 2021;11(2):431–444.
- [3] Fasano A, Elia AE, Dallochio C, et al. Predictors of COVID-19 outcome in Parkinson's disease. *Parkinsonism & Related Disorders* 2020;78:134-137
- [4] Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord* 2020;35(6):905–908
- [5] Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinski MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J; German Parkinson Study Group, Neurostimulation Section. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;31:355(9):896-908.
- [6] Myoclonus in Patients With Coronavirus Disease 2019: A Multicenter Case Series. *Crit Care Med*. 2020;48(11):1664-1669.
- [7] Moro E, Fernandez HH. Adaptive neurology in COVID-19 times. *Parkinsonism Relat Disord*. 2020;75:124-125.
- [8] Dula AN, Gealogo Brown G, Aggarwal A, Clark KL. Decrease in Stroke Diagnoses During the COVID-19 Pandemic: Where Did All Our Stroke Patients Go?. *JMIR Aging*. 2020;3(2):e21608.
- [9] Leta V, Rodríguez-Violante M, Abundes A, Rukavina K, Teo JT, Falup-Pecurariu C, Irincu L, Rota S, Bhidayasiri R, Storch A, Odin P, Antonini A, Ray Chaudhuri K. Parkinson's Disease and Post-COVID-19 Syndrome: The Parkinson's Long-COVID Spectrum. *Mov Disord*. 2021 Jun;36(6):1287-1289
- [10] Merello M, Bhatia KP, Obeso JA. SARS-CoV-2 and the risk of Parkinson's disease: facts and fantasy. *Lancet Neurol*. 2021 Feb;20(2):94-95
- [11] National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. <https://www.nice.org.uk/guidance/NG188>. Accessed February 1, 2021.
- [12] Davis HE, Assaf GA, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *medRxiv* 2020. <https://doi.org/10.1101/2020.12.24.20248802>
- [13] Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci* 2020;417
- [14] Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. *J Neurol Sci* 2020;419

- [15] Tabacof L., Tosto-Mancuso J., Wood J., Cortes M., Kontorovich A., McCarthy D., Rizk D., Mohammadi N., Breyman E., Nasr L., et al. Post-Acute COVID-19 Syndrome Negatively Impacts Health and Wellbeing despite Less Severe Acute Infection. *medRxiv*. 2020:20226126
- [16] Taquet, Maxime et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry* 2021;8: 416 – 427
- [17] Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C. et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 11, 16144 (2021)

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POST COVID NEUROLOGICAL SYNDROME – A NEW CHALLENGE TO THE NEUROLOGICAL PROFESSION

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Summary

The new coronavirus (SARS-CoV-2) that originated in China spread rapidly around the world, so in March 2020 a pandemic was declared. We have witnessed the impact of the COVID-19 pandemic on the lives of particularly affected families, on health systems, the economy, and the world economy. Beside the respiratory symptoms, the virus is also neurotropic. It can enter a nerve cell. The SARS-COV-2 virus enters the cell via the angiotensin receptor by converting enzyme 2. Regardless of the severity of respiratory symptoms, 85% of patients with SARS-CoV-2 had acute and subacute symptoms and complications of the peripheral and central nervous systems. The most common are headache, dizziness, hyposmia, hypogeusia, stroke, encephalopathy, meningoencephalitis, and acute polyradiculoneuritis (Guillain Barre syndrome). There are studies that recognize the increasing numbers of ex-patients with Post COVID Neurological Syndrome (PCNS). A small number of people who recovered from COVID-19 are reporting neurological concerns such as headache, dizziness, lingering loss of smell or taste, sleep problems, fatigue, muscle weakness, nerve damage, and trouble thinking or concentrating — sometimes called “COVID fog” or “brain fog”. We need further neurological and cognitive/affective monitoring of all cases of COVID19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS. Global clinical registries with a meticulous systems-based approach to the assessment, management and reporting of post-COVID patients will help us.

Key words: Neurological diseases; COVID 19 pandemics; post Covid neurological syndrom

Introduction

The new coronavirus (SARS-CoV-2) that originated in China spread rapidly around the world, so in March 2020 a pandemic was declared. Since then, more than 175 million people worldwide have been infected after a year, and over 3.8 million people have died from the coronavirus disease 2019 (COVID-19) [1]. In the last years we have witnessed the impact of the COVID-19 pandemic on the lives of particularly affected families, on health systems, the economy, and the world economy.

For the past years all efforts from the scientific and medical community have been directed to sequence, diagnose, treat, and prevent COVID-19 in acute phase. Since acute respiratory syndrome is the main feature of severe COVID-19, most initial studies on COVID-19 have focused on its impact on the respiratory system. But SARS-CoV-2 can also cause neurological complications [2].

Many previous viruses' studies have shown that central nervous system could be affected. It is also hypothesized that SARS-CoV-2 infection could promote or enhance susceptibility to different forms of CNS changes that may lead to neurodegeneration as a long-term effect, especially in individuals already at risk [2]. Moreover, other viral infections suggest that systemic inflammatory mediators may access the CNS and trigger damage via impaired BBB function. More investigation of post-mortem brain and spinal cord tissue from deceased COVID-19 individuals are needed and may provide evidence for parenchymal infection. The hypothesis of direct neuroinvasion of COVID-19 is based on involvement and role of angiotensin-converting enzyme-2 (ACE-2) [3]. It is a potential receptor for SARS-CoV-2 entry. ACE-2 is expressed on various brain cells and cerebral parts, i.e., subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, and rostral ventrolateral medulla, as well as in non-cardiovascular areas such as the motor cortex and nuclei raphe. The hematogenic pathway is an additional probable route of virus entry into the nervous system that includes the vagus nerve, the olfactory nerve, or the enteric nervous system [4].

Beside the global dimension and effect of the current pandemic, we could recognize a possible long-term impact of COVID-19. As we could see in the past years, persistent symptoms following COVID-19 infection are prevalent, debilitating and appear to affect individuals regardless of acute infection severity or prior health status [4].

Especially in the beginning the terminology of this prolonged symptoms has been confusing and not standardized. Different authors have used several terms to describe prolonged symptoms following COVID-19 illness, such as "Long COVID-19", "post-acute COVID-19", "persistent COVID-19 symptoms", "chronic

COVID-19”, “post-COVID-19 manifestations”, “long-term COVID19 effects”, “post COVID-19 syndrome”, “ongoing COVID-19”, “long-term sequelae”, or “long-haulers” as synonyms. Most recently, the term “post-acute sequelae of SARS-CoV-2 infection” (PASC), “long-COVID-19”, and “post-acute COVID-19”, has been used (5). In the United Kingdom, the National Institute for Health and Care Excellence has defined the “post-COVID-19 syndrome” as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis [6].

Furthermore, a cytokine storm is seen in COVID-19 cases with higher levels of different cytokines where some of them can cross the blood-brain barrier and activate the brain’s immune cells to produce neural cytokines, leading to neuronal dysfunctions, delirium and neurodegeneration as a late long-term effect [7]. Nevertheless, the serious worsening of clinical pictures have been observed in many neurodegenerative diseases like Alzheimer dementia, Parkinson disease and Lewy body dementia who survive COVID-19 infection [8,9]. The most common impairment reported was delirium, non-motor and motor symptoms [8-10]. Influence on working memory and attention have been recorded [8,9].

In patients who develop neurological complications long clinical follow up and investigation of CSF samples for the presence of viral antigen/RNA and inflammatory mediators should be provided to determine direct CNS infection. Careful follow up of COVID-19 patients with neurological complications in the long term is mandatory.

Regardless of the severity of respiratory symptoms, 85% of patients with SARS-CoV-2 had acute and subacute symptoms and complications of the peripheral and central nervous systems [5]. The most common are headache, dizziness, hyposmia, hypogeusia, stroke, encephalopathy, meningoencephalitis, and acute polyradiculoneuritis (Guillain Barre syndrome). Recently, due to the difficult situation with the coronavirus, all public attention has been focused on combating the infection. Many activities had to adapt to the emerging pandemic, including neurology. In many Institutions, neurology accommodation facilities have been reduced, or relocated to the COVID department. In the first wave, only emergency activities and more urgent outpatients worked. Patients themselves avoided visiting a neurologist for fear of infection despite significant exacerbations. Many neurological services have had telephone, telemedicine, zoom, email and other virtual consultations and examinations of patients. Behind the first wave, we all had a rush of patients with significant exacerbations and complications in our clinics, multidisciplinary teams, and wards. In the other two waves, however, they came in larger numbers to both clinics and wards, especially in acute conditions and worsening of chronic diseases.

Patients with chronic progressive neurodegenerative diseases, regardless of whether they had COVID 19 infection, had exacerbations. Isolation and social distancing that should be adhered due to coronavirus, are behaviors that do not contribute to the good condition of patients with chronic neurodegenerative diseases, including Parkinson's disease, with a lack of physical activity.

There are hypothesis about increasing number of patients with Parkinson's disease in the future due to this COVID 19 pandemic [11]. The proposed mechanisms have always been considered such as structural and functional damage to the basal ganglia, inflammatory (neuroinflammatory) processes, hypoxic brain injuries due to encephalopathy, the occurrence of latent Parkinson's disease and the hypothetical possibility of viral infection triggering (as a trigger) long-term development of Parkinson's disease with a genetic predisposition [12]. Prospective well-planned and coordinated studies and long-term follow-up of patients with COVID-19 infection are needed, as possible neurological consequences should not be ignored. It is certainly necessary to monitor all neurological patients and those who had COVID 19 infection and who had not. We have to prepare our health systems and societies on possible pandemic of neurodegenerative diseases in the future and if patients with post covid consequences will be added to those possible pandemics, the health systems have to be organized for it, and respond in a timely manner [13].

Post COVID-19 neurological syndrome

There are already studies recognizing an increasing number of patients with neurological manifestations not only in the acute phase but also long after overcoming the infection. These manifestations are present regardless of the severity of the clinical picture of COVID-19 infection. A new term and a new challenge for the neurological profession is post COVID-19 neurological syndrome. It is described in 30-40% of patients and 6 months after COVID-19 infection [14,15]. In one study of over 236,000 survivors of COVID 19 infection, 33.6% had neurological and psychiatric manifestations 6 months after infection and 13% had such disorders for the first time [16]. It is a post-viral syndrome caused by the response of the brain and body to infection with the SARS-CoV-2 virus. In general, the medical profession has observed post COVID-19 syndrome, which includes many specialist activities (cardiological, pulmonary, psychiatric, psychological, neurological, etc.). Although not known for sure but post COVID neurological syndrome is thought to be due to abnormalities in the nervous, metabolic, and immune systems. It is characterized by prolonged depression, various neuromuscular diseases from muscle weakness and myopathy and further, anxiety,

fatigue, sleep disorders, various cognitive problems from problems with concentration, attention, memory and further, “brain fog” dizziness, headache, loss of smell, disease movement, epilepsy, cerebrovascular disease, etc. Severe symptoms were present in severe acute infections (mechanical ventilation, ICU stay, encephalopathy, etc.) [17,18]. In another study of neurological symptoms lasting more than 6 weeks after COVID infection, the presence of most fatigue (92%), loss of concentration and memory (74%), weakness (68%), headache (65%) and dizziness (64%). At least one neurological symptom was reported by 87.4% of patients and the quality of life was affected in 44.1% of patients [19]. In one meta-analysis the prevalence of long-term effects in COVID-19 patients is a rather high. A total of 55 long-term effects we identified as associated with COVID-19, mostly the fatigue, headache, joint pain, anosmia, ageusia, etc. In addition, diseases such as stroke and diabetes mellitus were also present. One long-term symptom or more were reported in 80% patients with COVID-19. The 5 most common manifestations were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), dyspnea (24%). Other symptoms were related to lung disease (cough, chest discomfort, reduced pulmonary diffusing capacity, sleep apnea, and pulmonary fibrosis), cardiovascular (arrhythmias, myocarditis), neurological (dementia, depression, anxiety, attention disorder, obsessive–compulsive disorders), and others were unspecific such as hair loss, tinnitus, and night sweat. A couple of studies reported that fatigue was more common in females [5].

The post of COVID-19 in Parkinson’s disease was also described, where the most common long - term effects of COVID 19 infection in the post - infection period: deterioration of motor function present in 51.9%, increase in daily levodopa dose in 48.2%, new fatigue (40, 7%), cognitive disorders, “brain fog”, memory and concentration disorders (22.2%), sleep disorders (22.2%) [10].

Acute and long-term neurological complications caused by COVID-19 are frequent and represent a risk that compromises the functional capacity and the life of patients. The suspicion of these conditions, the strict control of metabolic alterations and cardiovascular risk factors, the effective and safe treatment of these entities, and prompt and effective neurorehabilitation are a current challenge throughout the pandemic.

Post-COVID Syndrome can include symptoms related to residual inflammation, organ damage, impact on pre-existing health conditions or non-specific effects due to hospitalization or prolonged ventilation (post-intensive care syndrome) [20].

Further monitoring of the entire multidisciplinary team (neurologist, psychiatrist, psychiatrist, physiatrist, etc.) is required for all cases of COVID 19 in-

fection regardless of severity from asymptomatic, mild to severe form of the disease. They would also use clinical registries to monitor, evaluate and report on post-COVID patients.

Given the large number of requested consultations for neurological manifestations long after the infection, the neurological departments had to organize out-patients clinics where they can monitor, diagnose and treat these manifestations, the so-called post COVID- 19 neurological clinics with the possibility of processing and treatment, and monitoring. The short-term and long-term neurological effects of COVID 19 are still being investigated and monitored. In this way, we make it easier for patients to search and process, which is more accessible to them in this way. We could process and direct them faster with respect to peripheral and central nervous system disorders and our available diagnostic processing (from serum analysis, cerebrospinal fluid, cognitive tests, electromyoneurography, electroencephalogram, evoked potentials, polysomnography, ultrasound and neuroradiological imaging methods). Also, we could faster provide appropriate therapy and rehabilitation, and monitor them for a longer period. This way of organizing is also a good platform for translational investigations bringing together preclinicians and clinicians.

Conclusions

The potential neurological sequelae of this novel coronavirus should not be underestimated and must be carefully monitored in the future. A coordinated international effort to investigate viral effects is essential and should be based on well-designed prospective studies. Undoubtedly, we need additional studies (pathological, translational, clinical etc.) to confirm/refute the trigger effect of SARS-CoV-2 on the neuroinflammatory and neurodegenerative processes leading to the development of many neurological (acute and post COVID-19) symptoms. The prognosis of recovery from post-COVID neurological syndrome must be evaluated in a personalized way, depending on target organ damage, especially brain, lungs, and heart, which intervene in the process of physical activity and maintenance of daily life activities. It is also necessary to design a specific protocol for patients with PCNS, as well as to establish guidelines for treatment and neurorehabilitation of PCNS patients.

In conclusion, we need further neurological and cognitive/affective monitoring of all cases of COVID19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS. Global clinical registries with a meticulous systems-based approach to the assessment, management and reporting of post-COVID patients will help us.

References

- [1] Ritchie, H., Ortiz-Ospina, E., Beltekian, D., Mathieu, E., Hasell, J., Macdonald, B., Giattino, C., Appel, C., Rodés-Guirao, L., & Roser, M. Coronavirus Pandemic (COVID-19), 2021.
- [2] Sharifian-Dorche M, Huot P, Osharov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci* 2020;417
- [3] Ni, W., Yang, X., Yang, D. et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* 2020;24:422.
- [4] Burks SM, Rosas-Hernandez H, Alejandro Ramirez-Lee M, Cuevas E, Talpos JC. Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the blood-brain barrier? *Brain Behav Immun.* 2021;95:7-14.
- [5] Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C. et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021; 11:16144
- [6] National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. <https://www.nice.org.uk/guidance/NG188>. Accessed February 1, 2021.
- [7] Liu, YH., Wang, YR., Wang, QH. et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol Neurodegeneration* 2021;16:48.
- [8] M. Fathi, F. Taghizadeh, H. Mojtahedi, S. Zargar Balaye Jame, N. Markazi Moghaddam, The effects of Alzheimer's and Parkinson's disease on 28-day mortality of COVID-19, *Revue Neurologique*, 2021
- [9] Killen A, Olsen K, McKeith IG, et al. The challenges of COVID-19 for people with dementia with Lewy bodies and family caregivers. *Int J Geriatr Psychiatry* 2020;35(12):1431-1436. doi:10.1002/gps.5393
- [10] Leta V, Rodríguez-Violante M, Abundes A, Rukavina K, Teo JT, Falup-Pecurariu C, Irincu L, Rota S, Bhidayasiri R, Storch A, Odin P, Antonini A, Ray Chaudhuri K. Parkinson's Disease and Post-COVID-19 Syndrome: The Parkinson's Long-COVID Spectrum. *Mov Disord.* 2021 Jun;36(6):1287-1289
- [11] Fearon C, Fasano A. Parkinson's disease and the COVID-19 pandemic. *J Parkinsons Dis* 2021;11(2):431-444.
- [12] Merello M, Bhatia KP, Obeso JA. SARS-CoV-2 and the risk of Parkinson's disease: facts and fantasy. *Lancet Neurol.* 2021 Feb;20(2):94-95
- [13] McAlpine LS, Fesharaki-Zadeh A, Spudich S. Coronavirus disease 2019 and neurodegenerative disease: what will the future bring?. *Curr Opin Psychiatry.* 2021;34(2):177-185.
- [14] Rubin, R. As their numbers grow, COVID-19 "long haulers" stump experts. *JAMA* 2020;324: 1381-1383.
- [15] Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. *J Neurol Sci* 2020;419

- [16] Taquet, Maxime et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry* 2021;8: 416 - 427
- [17] Nuzzo, D.; Vasto, S.; Scalisi, L.; Cottone, S.; Cambula, G.; Rizzo, M.; Giacomazza, D.; Picone, P. Post-Acute COVID-19 Neurological Syndrome: A New Medical Challenge. *J. Clin. Med.* 2021;10:1947.
- [18] Davis HE, Assaf GA, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *medRxiv* 2020. <https://doi.org/10.1101/2020.12.24.20248802>
- [19] Tabacof L., Tosto-Mancuso J., Wood J., Cortes M., Kontorovich A., McCarthy D., Rizk D., Mohammadi N., Breyman E., Nasr L., et al. Post-Acute COVID-19 Syndrome Negatively Impacts Health and Wellbeing despite Less Severe Acute Infection. *medRxiv*. 2020:20226126
- [20] Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, Navarro-Coronado A, Moscote-Salazar L, Pacheco-Hernández A, Janjua T, Bosque-Varela P. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. *J Clin Neurosci.* 2021;88:219-225.

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