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Cognitive impairment and Parkinson's disease dementia

Kognitivni upad in demenca pri Parkinsonovi bolezni

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system which presents itself with motor and non-motor signs. Motor signs include tremor, rigidity and bradykinesia, while the most common non-motor sign is cognitive decline.

The results of longitudinal studies show that 80% of patients exhibiting cognitive decline progress to dementia (PDD). The impact of PDD on life is severe. If we recognise cognitive decline early enough, PDD can be slowed down, thereby improving the quality of life.

The review article summarises the most common causes of cognitive decline, describes the impact of heredity and presents a typical clinical picture. Several cognitive tests may be used to detect cognitive impairment, e.g. Montreal Cognitive Assessment Scale (MoCA), Frontal Assessment Battery (FAB), Mini-Mental State Examination (MMSE) and Test Your Memory (TYM). The article concludes with an outline of possible symptomatic treatments using available drugs as well as prospective approaches which are still in clinical trials.

Izvleček

Parkinsonova bolezen (PB) je nevrodegenerativna bolezen možganov, ki se kaže z motoričnimi in nemotoričnimi znaki. Med motorične znake prištevamo tremor, rigidnost in bradikinezijo, med nemotoričnimi pa je najpogostejši kognitivni upad.

Rezultati longitudinalnih raziskav kažejo, da pri 80 % bolnikov kognitivni upad napreduje do demence (PBD). Vpliv PBD na življenje je velik. Če kognitivni upad prepoznamo dovolj zgodaj, lahko simptome PBD olajšamo in s tem izboljšamo kakovost posameznikovega življenja.

V preglednem članku se bomo dotaknili najpogostejših vzrokov za nastanek kognitivnega upada, vpliva dednosti in prikazali značilno klinično sliko. Za prepoznavo kognitivnega upada uporabljamo kognitivne teste, npr. Montrealsko lestvico ocenjevanja spoznavnih sposobnosti (MoCA), Baterijo testov frontalnih funkcij (FAB), Kratek poskus spoznavnih sposobnosti (KPSS) in test Testiraj svoj spomin (TSS). Na koncu članka bomo prikazali možnosti simptomatskega zdravljenja z zdravili, ki jih imamo na voljo, ter z zdravili in postopki, ki so še v fazi razvoja.

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1 Introduction

Parkinson's disease (PD) is a disease of the motor system, characterized by bradykinesia, rigidity, resting tremor, and postural instability. It is considered as a heterogeneous neurodegenerative syndrome, since in addition to motor symptoms, many non-motor symptoms also occur (1,2). The latter include autonomic, psychiatric, and psychosocial disorders. The most common non-motor characteristic of PD is cognitive dysfunction. Autonomic disorders include orthostasis, slowed peristalsis, and urinary frequency or incontinence. Psychiatric disorders in patients with PD manifest themselves as depression, anxiety, psychosis, and impulse control disorders. Psychosocial disorders describe the patient's maladaptation to daily life, tasks, and interactions. In patients with PD, psychosocial performance is impaired mainly due to stereotypical behaviour and apathy (2).

The extent of cognitive dysfunction in PD varies. Patients can have PD with preserved cognition, PD with mild cognitive impairment (PD-MCI) and extreme clinical expression in the form of dementia in PD (PDD), which develops during the progression of the disease in 80% of patients with PD (3,4).

PDD together with Lewy body dementia (LBD) is classified into a heterogeneous group of dementias in which α-synuclein accumulates and Lewy bodies are formed (5). Both PDD and LBD are progressive neurodegenerative diseases that are probably two ends of the same disease spectrum. Both are characterized by diffuse cortical Lewy bodies (6). The clinical features of PDD and LBD are also similar and include hallucinations, fluctuations in consciousness, and dementia as part of extrapyramidal impairment. In clinical practice, they are distinguished mainly by an arbitrarily determined time frame. In clinical and research, the "one-year rule" applies (7). In DLB, dementia occurs before parkinsonism or one year after the onset of signs of parkinsonism. On the contrary, we talk about PDD when cognitive disorders appear after one year of already established motor signs of PD (8,9).

Lewy's bodies were first described by Frederick Lewy in connection with PD in 1912, and they were not defined in connection with dementia until 1961 (10). They were a rare finding until the 1980s, when the link between cortical Lewy bodies and LBD and PDD (11) began to be discovered with the possibility of immunostaining by labelling ubiquitin and α-synuclein. Clinical, neuropsychological, and neuropathological similarities between LBD and PDD led to the hypothesis that they are different phenotypic expressions of an otherwise identical pathological process, which remains valid today (7,12).

Although PDD represents a smaller share of all dementias, due to the aging population and successful treatment of PD, we can expect an increase in its prevalence (2,13). It is also important to be aware of its impact on the patient's quality of life, as it is associated with a higher risk of falls, a higher burden on carers, early entry into retirement homes that offer adequate care and a shortened life by 4 years on average (14,15).

The purpose of this review article is to present current concepts in the field of PDD with an emphasis on understanding the pathophysiological processes and genetic background of the disease, to distinguish identified risk factors and to present new, individualized treatments in accordance with current recommendations. The overview of the articles is summarized in Appendix 1.

2 Epidemiology

PD is the second most common neurodegenerative disease in the world, affecting 0.4–1% of the population between the ages of 60 and 79 and 1.9% of the population over the age of 80 (16). PDD accounts

for 3–4% of all dementias (2). The annual incidence is about 10%, the prevalence depends on the incidence among patients with PD and their survival after the development of dementia (13,17). According to various studies, the prevalence of PDD is expected to be 30–40%, which represents a 4- to 6 times higher incidence than in healthy individuals (17,18).

At the time of diagnosis of PD, 15–40% of patients have MCI (19). Half of all patients with PD develop MCI within 6 years after the diagnosis of PD (20). Researchers in Norway found that 19% of people were diagnosed with cognitive impairment when they were diagnosed with PD, and over the next 8 years, 75% developed dementia (18). Similar conclusions were reached in an administrative study by the US health insurance programme US Medicare, which found that dementia developed with 69.9% of newly diagnosed individuals with PD (21) within 6 years of diagnosis. A longitudinal study conducted in Australia found that after 20 years, dementia occurs in 83% of patients with PD (22,23). A study conducted among patients who were still cognitively preserved at the time of diagnosis of PD showed a rapid decline in function; 47% of patients developed PD-MCI after 6 years, and after 5 years all of them transitioned to PDD (20). Such data suggest that the prevalence of PDD is relatively low for the first 10 years after PD is diagnosed, and then increases dramatically. The period without dementia depends almost exclusively on the age at which PD is diagnosed - in younger patients this period is longer, as dementia usually occurs around the age of 70, regardless of the previous duration or stage of the disease (24).

Prevalence studies depend to a large extent on geographical areas, and differences are also observed over time. In Spain, a prevalence of 16% of patients with PD was recorded in 1994, and in 2005, the percentage rose to 31.3% (25,26). We do not have data collected for Slovenia. A high prevalence in patients with PD, for example, has been noted in Thailand (39.4%), Mexico (39%) and Korea (38.3%), while in Germany, this percentage is lower (29%) (27-30).

PD is the most common among white men (31). Research in the United States has shown that we have unsatisfactory data in tracking the course of the disease in women and other racial communities, as these two groups are included in the tertiary stage in smaller numbers. A review of the US Medicare program, used by 98% of Americans over the age of 65, showed demographic differences among patients 6 years after being diagnosed with PD. 78.2% of black people and 73.1% of Hispanic people developed PDD during this time (compared with 69.6% in the general population of PD patients). Using a regression model, they found that the likelihood of developing dementia was higher in black people, Hispanic people, and women, and lower in Asian people. The data may point to a specific pattern of PD progression, but it may only be a sign of inconsistencies in the provision of quality co-morbidity care in the United States – unbalanced arterial hypertension and diabetes contribute significantly to the development of vascular dementia (2,21,32).

3 Genetic background

Genetic risk factors are most evident in familial parkinsonism, but may also affect cognitive decline in sporadic forms of PD (3). There is an increased risk of PDD in patients with genetic mutations of GBA, SNCA, APOE4 allele and MAPT H1 haplotype (33). A mutation in the PARK2 gene that encodes Parkin has been linked to the autosomal recessive form of PD. Carriers of this mutation have a more benign course of the disease and rarely reach end-stage dementia (34).

The first links between DLB and genetic defects were established by studying the GBA gene that encodes β-glucocerebrosidase. Homozygous GBA mutations cause autosomal recessive Gaucher disease, and

heterozygous mutations are associated with PD with as much as a 5.8-fold risk for MCI and PDD and DLB (35). This has led to the idea that both LBD and PDD have the same lysosomal dysfunction in the background, but genetic differences between the two have not been investigated in detail to date (36). In patients with GBA and SNCA mutations, sleep disorders are more common in the REM phase, which is a risk factor for PDD (37). Gaucher disease can be manifested by parkinsonism and the presence of Lewy bodies in the brainstem. Relatives of these patients develop PD more often than the general population (38).

PD is an α-synucleinopathy. It is therefore not surprising that mutations in the SNCA gene (39) are also associated with familial and sporadic forms of parkinsonism. Mutation or duplication of the SNCA gene encoding α-synuclein results in autosomal dominant PD; triplications, however, are often associated with parkinsonism and dementia (40). The effects of α-synuclein have not yet been fully elucidated. It is thought to play a role in synaptic vesicle function and regulate dopamine release (39).

Newly diagnosed patients with PD who carry the APOE4 allele have reduced medial temporal lobe activity when performing memory tasks, and carriers of the homozygous MAPT H1 mutation show reduced activity of the posterior visual networks while solving visual-spatial tasks (41). Apolipoprotein (APOE) encodes a cholesterol transporter and has 3 allelic forms: APOE2, APOE3 and APOE4. The influence of mutations of these three alleles on cognitive decline is not yet completely clear (3). The MAPT gene encodes the protein tau, and its variations affect the incidence of PDD. H1/H1 homozygotes have an increased risk of PD with cognitive decline and for early development of dementia (42).

Not all genes associated with PD are also necessarily associated with an increased risk of cognitive impairment. This is the case, for example, with mutations in the PARK8 gene, which encodes LRRK2. These cause autosomal dominant PD with late onset without associated cognitive impairments (43). PARK6, a mutation in the PINK1 gene, is associated with autosomal recessive PD with associated psychiatric disorders. Mutations in the PARK7 gene are not associated with dementia. PARK9 and PARK14 are associated with an atypical juvenile form of parkinsonism and with cognitive decline (3).

Genetic counselling and tests (5) are recommended for patients who conclude that a positive family history suggests that it may be a genetic component of the disease. However, genetic testing is not routinely recommended (3).

4 Clinical picture

4.1 Decline in cognitive abilities

Cognitive disorders are most often manifested as problems with daily activities, e.g., when taking medication or managing finances. Cognitive impairment can be evaluated by psychological tests to determine fluctuating attention in patients, nominal aphasia with otherwise preserved language ability, bradyphrenia, and impaired recall (5).

In a patient with PDD, executive functions are typically impaired. They cover problem solving, planning, mental flexibility, working memory, and inhibition. Some also include directing attention under its auspices (33,44). Impairment of executive functions is encountered by patients from the onset of the disease. They can also be observed in the context of premotor prodromal syndrome. As the disease progresses, executive functions deteriorate. The patient will complain about problems with concentration, information retention, planning and organization, and as a result with social and occupational problems (3,33).

Attention deficit disorder is also pronounced. Sohlberg and Mateer categorised

the attention into several levels. The most basic is wakefulness, or vigilance. Focused attention is the ability to respond to a stimulus from the environment. Shared attention (vigilance) is the ability to respond to multiple stimuli simultaneously. Selective attention is the ability to select relevant information, which is then maintained for a longer period of time with maintained attention (vigilance). We switch between tasks with alternating attention (45).

Attention deficit disorders are encountered at an early stage of the disease at the level of divided and alternating attention. The impairment is detected by tests of executive functions. As the disease progresses, the symptoms worsen. Disorders of sustained and directed attention are also associated (33). It is these disorders that limit the patient the most. They find themselves worse off in everyday activities, lose the train of thought and fail to follow the conversation, which significantly affects their quality of life (46).

Memory involves all the cognitive processes involved in encoding, storage, and retrieval of information. It depends on the individual's ability to focus attention on the stimulus (this allows for coding) and to use executive processes (to enable recall). Memory disorders are one of the most common disorders in PDD. All aspects of memory are affected (33). Spontaneous recall is impaired, which is improved by hinting (47). Recognition memory is not affected at first, then the impairment becomes increasingly apparent due to associated temporal lobe dysfunction and storage disturbances in the presence of an existing recall impairment. Over time, the naming of objects in particular is severely affected. Patients have difficulty understanding the meaning of words and phrases (semantics) and forming different words on the same letter (voice - phoneme).

With the word fluency test, we test semantics and phonemics. With the test of semantic fluency, we introduce the subject to a hypernym and ask them to list as many hyponyms as possible. In the phonemic fluency of the subject, we encourage them to list as many words as possible, starting with a certain letter/voice. PDD is characterized by a poorer result in semantic fluency testing, as it is largely dependent on the temporal lobe function (33).

Visual disturbances, which include both visuospatial and visuoperceptual disturbances, are often observed in the clinical picture. Visuospatial disturbances are manifested by disturbances in the perception of extrapersonal space, and visuoperceptual with difficult recognition of objects on the basis of their shape (3). They can appear early in the disease. As they progress, they become more and more pronounced (33).

4.2 Neuropsychiatric and autonomic disfunctions in the advanced stage of PDD

In patients with PDD, cognitive decline may be further exacerbated by signs of autonomic dysfunction and neuropsychiatric symptoms.

Patients also often exhibit neuropsychiatric symptoms (15). As many as 64% of patients have at least one neuropsychiatric symptom (2). Depression affects 20-50% of patients with PDD, and apathy and anxiety are common (2,48,49). These symptoms are particularly pronounced in younger patients with an advanced form of the disease (49). Patients may suffer from psychosocial disorders, among which stereotypies are most commonly encountered.

Patients in the advanced stage of PDD have visible hallucinations that are scenic, unimodal, and only occasionally frightening. They usually occur in the later stages of the disease. Both hallucinations and attention fluctuations may be due to medications, especially dopamine agonists (3,5,33). Rarely, a patient has delusions (5). Insight is initially present, but after three years, 81% of patients lose this ability (50). Patients also report sleep disturbanc-

es (49). Autonomic nervous system disorders also occur, manifested by orthostasis, urinary urgency or frequency, and slowed peristalsis (2). Due to the increased risk of falls, patients break their bones more often (15).

The impact of PDD on quality of life is considerable. Predictors of poorer quality of life in patients with PDD are the presence of severe motor impairment, depression, neuropsychiatric symptoms, PD-MCI, and lower age and awareness of their disorder. Younger patients, unlike older ones, find it harder to come to terms with their disease because they have higher expectations for their life (15) at the time of diagnosis.

5 Diagnosis

Regular monitoring of the patient's cognitive status is the minimum standard in the treatment of patients with PD and is recommended at least once a year. At each visit, we ask the patient about their memory problems (2). For the global assessment of cognitive ability, we use two screening tests in the outpatient clinics: Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). MoCA (51) showed greater sensitivity for the assessment of executive dysfunction and thereby for PDD. MoCA is comprised of 30 questions to evaluate eight cognitive domains. Memory testing involves five words, and a longer time is used to test the recall. Testing of language, executive functions and visuospatial functions takes place at a higher level than in MMSE, as it indicates mainly frontostriatal dysfunction (3,52).

Neuropsychiatric symptoms of PDD are assessed by the Neuropsychiatric Inventory (NPI), which checks for the presence of hallucinations, delusions, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritation, motor disorders and sleep and appetite disorders (49). The clinical criteria for PD-MCI and PDD are shown in Table 1.

It is important to perform tests that rule out possible reversible causes of dementia (5). The latter include e.g., toxicity of dopaminergic drugs or a state of withdrawal after their discontinuation, toxicity of anticholinergics and other drugs acting on the central nervous system (CNS), depression, vitamin B12 or folic acid deficiency, thyroid disease, CNS disorders, acute inflammation, and other metabolic diseases (53). Laboratory and imaging examinations are performed to distinguish between PDD and reversible causes of dementia (5).

5.1 Imaging biomarkers and electroencephalography (EEG)

MRI is undiagnostic and shows only symmetrical global atrophy. It can exclude the presence of possible changes of other aetiologies (vascular causes, etc.) (5).

Fluorodeoxyglucose (^{18}F) (FDG-PET) imaging, which is more sensitive and more specific than single-photon emission computed tomography (FDG-SPECT), is informative. FDG-PET in patients with PDD shows symmetrical hypometabolism not only of the parietal and temporal lobes found in Alzheimer's dementia but also of the occipital lobes (54). At the same time, the signal in the cerebellar dentate nuclei increases (3). Clinical presentation of the patient is also important in the interpretation of images, as occipital hypometabolism also occurs in PD without cognitive dysfunction, PD-MCI, and posterior cortical atrophy (5). In addition to the above, fewer dopamine transporters (DAT) are observed in PET and 123FP-CIT-SPECT images, which, due to their high sensitivity and specificity, helps to differentiate it from Alzheimer's dementia (54). Imaging also shows a reduction in the volume of the hippocampus, medial temporal lobe, parahippocampus, frontal association areas, and cingulate gyrus (55). PET with amyloid markers shows the presence of amyloid plaques, which is higher in LBD than in PDD (6). Compared to LBD, the

main differences observed with functional imaging in PDD are less pronounced atrophy of the temporal, occipital and parietal lobes, more pronounced bilateral frontal atrophy, and less infiltration with amyloid plaques (54).

The EEG excludes epileptic activity, which is suspected mainly in patients with obvious fluctuations in attention or cognition. Generalized wave deceleration can be seen in the images. Polysomnography (3) is used to diagnose sleep disorders in the REM phase. In a prospective study, Postuma et al. found that sleep disorders in the REM phase are an independent risk factor for developing PD. Neurodegenerative processes were observed in the majority of included patients with sleep disorders in the REM phase (56). Sleep disturbances in the REM phase can occur in patients with PD at any time during the course of the disease, but are significantly more pronounced with disease progression and in the PDD phase (5).

5.2 Neuropathological results

The neuropathology is remarkably similar in LBD and PDD. An autopsy alone cannot determine whether a patient had LBD or PDD in their lifetime. In both, we observe widespread Lewy bodies in the limbic system and cortex, Lewy neurites in the brainstem, limbic system, and neocortex, loss of dopaminergic neurons in the mesencephalon, and loss of cholinergic neurons in the basal telencephalon. In addition, senile plaques and neurofibrillary tangles are present (5,6).

6 Treatment

6.1 Treatment of cognitive decline

We have no causal drugs to treat cognitive decline caused by PDD. The acetylcholinesterase inhibitor (AChEi) rivastigmine, which is also used in the treatment of Alzheimer's disease, has been registered for symptomatic treatment (33,57).

Rivastigmine significantly improves attention disorders, and also affects cognitive fluctuations and wakefulness disorders (58). Based on the research conducted so far, it is not possible to conclude whether the improvement in cognitive function in AChEi treatment is due to the actual improvement in cholinergic deficits or if it is influenced by improved attention. AChEi function is better in PDD than in AD, probably due to the smaller extent of degeneration of the Meynert nucleus in the latter (33). Side effects include nausea, which is most often due to the "highest dose" phenomenon and can be reduced by delivering the drug via the skin (5).

In smaller studies, memantine, a mixed antagonist of N-Methyl-D-aspartate and nicotinic receptors, has also been shown to be effective (5,33). Treatment results showed a slight improvement in executive control attention tests (3,33). Smaller studies have also investigated the effect of atomoxetine, a norepinephrine reuptake inhibitor that increases excitability and alertness and improves inhibition (59).

If the cognitive decline is due to dopamine agonists used to treat PD, they are gradually discontinued and levodopa is introduced (5). Levodopa also improves executive functions associated with mental flexibility, while worsening some other aspects of executive functions, e.g., feedback-based learning. This phenomenon is probably due to hyperactivation of relatively flawless limbic and orbitofrontal networks (33).

6.2 Treatment of other non-motor symptoms affecting cognitive decline

Depression and anxiety are treated with selective serotonin reuptake inhibitors (SSRIs), e.g., with escitalopram, citalopram, fluoxetine and sertraline. Selective serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, may also be used. Exacerbation of tremor

may occur at high doses. Tricyclic antidepressants (TCAs) are not used because they impair cognitive function (60) due to their action on acetylcholine receptors.

A side effect of discontinuation of dopamine agonists or switching to levodopa may also be an exacerbation of psychosis. When this occurs in the clinical picture, we decide on treatment based on the severity of the problem. In non-urgent hallucinations, antipsychotics are avoided due to Parkinson's disease-specific hypersensitivity (61). Before prescribing therapy, discontinue medications that could cause hallucinations, namely anticholinergics, amantadine, dopamine agonists, monoamine oxidase inhibitors, and levodopa, in this order (3).

With mild hallucinations, acetylcholinesterase (AChEi) inhibitors, which also have fewer cardiovascular side effects, can be used. AChEi action reduces the activation of acetylcholine receptors in the ventral visual system, which contributes to the onset of psychotic symptoms (5).

With severe hallucinations, second-generation antipsychotics are used in a minimal still effective dose. The intensity of extrapyramidal symptoms is the least affected by quetiapine and clozapine. Their use, less frequently than with other antipsychotics, results in neuroleptic malignant syndrome. Clozapine requires weekly blood tests due to the risk of agranulocytosis. The QT interval should also be monitored on the ECG, as cardiac arrest, congestive heart failure and pneumonia are more common in those treated with antipsychotics. The risk of death also increases (5). A new drug in the treatment of hallucinations is pimavanserin, which is an inverse agonist of 5HT-2A receptors (62).

Treatment for a sleep disorder in the REM phase is not necessary unless patients are harming themselves or their caregivers. It is important to remove sharp objects from the sleeping environment, upholster the floor, and separate the bed of such patient from roommates. Benzodiazepines are not used despite their effectiveness as they exacerbate confusion. Melatonin treatment is effective and not dangerous for patients (5).

Table 1: Clinical criteria for mild cognitive impairment and for PDD. Summarized from Safarpour et al., 2016 (2).

Criteria for diagnosing PD-MCI
PD diagnosis
Cognitive decline, based on neuropsychological evaluation
Deterioration of cognitive abilities compared to the previous condition
Cognitive deficits does not affect daily living
Practical clinical criteria for diagnosing PDD
PD diagnosis
PD developed prior to the onset of dementia
MMSE < 26 points
Cognitive deficits severe enough to affect daily living
Impairment in ≥2 of the following: attention, executive function, visuospatial function and memorymemory

Legend: PD – Parkinson's disease; PD-MCI – Parkinson's disease with a mild cognitive impairment; PDD – dementia in Parkinson's disease; MMSE – Mini-Mental State Examination.

6.3 Non-pharmacological treatments

One possible method of nonpharmacological treatment is repetitive transcranial magnetic brain stimulation (rTMS). rTMS has been tested to treat migraines, mood disorders and strokes. A larger number of studies (63) will be needed to make a definitive assessment of PDD performance. Smaller-scale studies have shown improved results on the Stroop test after stimulation of the lower frontal gyrus and improved problem-solving after stimulation of the dorsolateral prefrontal cortex (64).

The importance of cognitive rehabilitation, which involves solving complex tasks (e.g., sudoku), is increasingly emphasized. Smaller-scale studies have concluded that this form of therapy improves mental performance in patients with PD-MCI and PDD. Particular progress can be seen in executive function tests (65). Cognitive exercise combined with physical activity can reduce the likelihood of a mild cognitive decline by 80% (66). Social support for patients and relatives also plays an important role in treatment (3). Patients also benefit from physical and occupational therapy, which have a positive effect on everyday functions (5).

6.4 Drugs in research

In the future, we can expect drugs that will act on several neurotransmitter systems (33). Treatment for cognitive decline with deep brain stimulation has also been developed, which has been shown to improve motor signs of PD. Treatment is based on changes in the processing of motor signals at the level of the neural network. Such an effect is caused by a change in structural and functional connections through the mechanism of brain plasticity and therefore returns dysfunctional motor signals to their natural state (67,68). The same principle is being developed for neuromodulation of cognitive networks, using the Meynert nucleus (69) as the main target structure. In attempts to treat Alzheimer's disease, results have been mixed with varying degrees of success, which does not necessarily indicate much success in the treatment of PDD, which involves a greater cholinergic deficit (33).

Another treatment option is offered by intrahippocampal transplantation of stem cells, which prevents neurodegeneration in specific cognitive networks. Stem cells that convert to cholinergic neurons or form nerve growth factor have improved learning deficits in rodents and could in the future serve as a counterbalance to medial temporal lobe damage (33).

7 Conclusion

As the population ages, more and more patients with various forms of dementia, including PDD, can be expected. According to a number of preclinical and clinical studies, causal drugs, most likely of the biological variety, can be expected in the future (70). Based on the results of research in patients with Alzheimer's dementia, we know that treatment will be successful if we recognize the disease and start treatment at the earliest possible stage.

The same is true for PDD. It is important to perform regular cognition examinations in patients with PD, and then treat the cognitive decline appropriately symptomatically.

8 Online appendix

Appendix 1: Review of research on dementia in Parkinson's disease, included in the review article. The file is available at the website: https://doi.org/10.6016/ZdravVestn.3003.

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