Medicinski podmladak

Medical Youth

Review article

OLDER AGE AND PARKINSON'S DISEASE

STARIJA ŽIVOTNA DOB I PARKINSONOVA BOLEST

Igor Petrović[1,2], Aleksandra Tomić[1,2], Nataša Dragašević Mišković[1,2], Milica Ječmenica Lukić[1,2], Vladana Marković[1,2], Nikola Kresojević[1,2], Iva Stanković[1,2], Marina Svetel[1,2], Vladimir Kostić[1,2]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Univerzitetski klinički centar Srbije, Klinika za neurologiju, Beograd, Srbija

Correspondence: marinasvetel@gmail.com

Abstract

The etiology of PD remains unclear, with aging identified as the primary risk factor. Epidemiological data show an increasing prevalence of PD with age, affecting 1 - 2% of persons over 65. The incidence of PD rises rapidly with age, peaking in the eighth decade of life. Motor symptoms in older PD patients are characterized by severe hypokinetic syndrome, axial features, and postural and gait difficulties. Non-motor symptoms, including cognitive impairment, sleep disorders, and dysautonomia, significantly impact quality of life. The prevalence of dementia and frailty increases with age and PD duration. This age group faces a higher risk of side effects from antiparkinsonian therapies, thus therapeutic adjustments are necessary to address the progression of both motor and non-motor symptoms.

The differential diagnosis of PD involves distinguishing it from other Parkinsonian syndromes, which can be challenging due to overlapping symptoms and the absence of specific diagnostic tools.

The presence of mild Parkinsonian signs in the aged population predicts worse outcomes, including dementia, disability, and mortality.

This review provides a comprehensive overview of the clinical manifestations, therapeutic considerations, and differential diagnosis of PD in older adults, highlighting the importance of individualized treatment approaches.

Keywords:
Parkinson's disease,
aging,
motor and non-motor symptoms

The authors declare no conflicts of interest.

doi:10.5937/mp75-52132
Editorial board: podmladak.med.bg@gmail.com

Sažetak

Etiologija Parkinsonove bolesti (PB) ostaje nejasna, pri čemu je starenje identifikovano kao glavni faktor rizika. Epidemiološki podaci ukazuju na porast prevalencije PB sa starenjem, sa zahvatanjem 1 - 2% osoba starijih od 65 godina. Incidencija PB brzo raste sa godinama, dostižući vrhunac u osmoj deceniji života.

Motorne simptome u starijoj grupi obolelih od PB karakterišu teža forma hipokinetskog sindroma, posturalna nestabilnost, poremećaji hoda i aksijalni deformiteti. Nemotorni simptomi, uključujući kognitivno oštećenje, poremećaje spavanja i disautonomiju, značajno utiču na kvalitet života. Učestalost demencije i opšte fizičke slabosti povećava se sa starošću i trajanjem PB.

Ova starosna grupa suočava se sa većim rizikom od neželjenih efekata antiparkinsonih lekova, što zahteva prilagođavanje terapije u skladu sa progresijom motornih i nemotornih simptoma.

Diferencijalna dijagnoza PB u odnosu na druge parkinsone sindrome može biti izazov zbog preklapanja simptoma i odsustva specifičnih dijagnostičkih alata. Prisustvo blagih parkinsonih znakova kod starije populacije ukazuje na mogući lošiji ishod, uključujući demenciju, invaliditet i mortalitet.

Ovaj pregledni rad pruža sveobuhvatan uvid u kliničke manifestacije, terapijske mogućnosti i diferencijalnu dijagnozu PB kod starijih odraslih osoba, naglašavajući važnost individualnog pristupa lečenju.

Ključne reči:
Parkinsonova bolest, starenje, motorni i nemotorni simptomi

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive loss of dopaminergic neurons in the pars compacta of the substantia nigra (SNpc). However, other structures of the brainstem, autonomic nervous system and cerebral cortex are also affected by the pathological process to varying degrees, which represents the pathological basis of the heterogeneity of the clinical manifestation, both in terms of specific symptoms and the speed of disease progression. The clinical presentation of PD is characterized by a specific combination of motor (bradykinesia, rigor, rest tremor, gait disturbance, etc.) and non-motor symptoms (affective disorder, cognitive problems, orthostatic hypotension, etc.), which often remain unrecognized in the early stages of the disease and attributed to the normal aging process (1). The etiology of PD is still undefined clearly, and the traditional concept identifies age as the most important risk factor. The strongest proof for this claim is that the frequency of PD increases with aging and that aging is a necessary factor in the manifestation of even rare, hereditary, monogenetic forms of PD that are clinically manifested only after several decades of the mutation's negative impact on cellular metabolism (2). In addition to this, data from numerous studies indicate common denominators of cellular homeostasis disorders, such as mitochondrial and lysosomal dysfunctions, which are characteristic of both the normal aging process and PD patients (3). However, the relationship between aging and PD is far from linear and the view that aging is the main cause of PD is oversimplified and inaccurate. As an example, epidemiological studies show that the incidence of PD decreases after the age of 75, pointing out that PD is not a common cause of mortality in people over 85 years of age (4, 5). The recently defined entity of mild ("soft") parkinsonian symptoms in the population of elderly people who do not meet the clinical criteria for the diagnosis of PD, also speaks of the complexity of the interrelationship between PD and aging (6). This concept represents an attractive field for future research that would clarify the specificity of the relationship between aging and parkinsonism.

On the other hand, the impact of aging on PD patients is more clearly defined and finds application in everyday clinical practice. Furthermore, due to a higher burden of associated diseases (diabetes mellitus, hypertension, etc.) and pathological changes in the brain (changes in small blood vessels caused by aging and/or pathological changes characteristic of Alzheimer's disease), the clinical presentation of PD in the elderly (> 70 years) is characterized by a specific combination of motor and non-motor symptoms. This combination includes a varying degree of risk for side effects from specific antiparkinsonian therapies (7, 8). Recognition of a subtype of PD ("late-onset PD") imposes specific therapeutic priorities in this population of patients, thus being an essential part of current therapeutic guidelines (9), with a significant influence in the selection of modern therapeutic procedures (deep brain stimulation and infusion therapy) (10). Finally, even in patients with a classic onset of the disease (ages 55 to 65), knowledge about the impact of the aging process and the duration of the disease on the pattern and speed of disease progression necessitates specific therapeutic adjustments to reduce the risk of negatively affecting certain, primarily non-motor symptoms of the disease (9, 10).

This review paper will cover the specific clinical manifestations of Parkinson's disease in older adults, including the differential diagnosis of parkinsonism in this age group. The authors aim to highlight the therapeutic specificities of treating Parkinson's disease in the elderly, taking into account the unique relationship between motor and non-motor symptoms in this patient category.

Epidemiology

Parkinson's disease is the second most common neurodegenerative disease with cumulative lifetime risk of 1.5%, 2% for men and 1.3% for women (11) and with an increase of prevalence with older age, hence affecting approximately 1 - 2% of persons older than 65 years (12).

It was estimated that PD affected up to 300,000 persons in the USA - which was expected to increase to 530,000 by 2030 which has significant consequences for the healthcare system (13).

Older studies showed that the prevalence of PD varies widely, from 18 to 418 per 100,000 persons in different regions and depending on methodology that was applied (14). However, when adjusted for age and including studies with similar methodology variability is reduced and estimated to be 102 to 190 per 100,000 persons in Western European countries (15). A meta-analysis of the worldwide data showed a rising prevalence of PD with age (all per 100,000): 41 in 40 to 49 years; 107 in 50 to 59 years; 173 in 55 to 64 years; 428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80. A significant difference regarding geographic location was shown in the age group 70 to 79 years old, with a prevalence of 1,601 in persons from Western culture (North America, Europe, and Australia), in contrast to 646 in Asia. A significant difference in prevalence by gender was found in the age group 50 to 59 years old, with a prevalence of 41 in women and 134 in men (16).

The incidence of Parkinson's disease is low before the age of 50 years, but it increases rapidly with age. In Rochester, a longitudinal epidemiological study incidence of idiopathic PD was shown to increase from 1.3 per 100,000 person-years in the age group 30 - 49 up to a maximum of 93.1 per 100,000 person-years in eight decade, with an observed decrease to 79,1 per 100.000 person-years in the ninth decade of life (17).

In a more recent systematic review, the overall incidence rate of PD in women 40 years and older was 37.5 per 100,000 person-years, and 61.2 in men 40 years and older. Meta-analysis of the data showed an increase in incidence for both genders with age, where in women, incidence rates rose from 3.26 per 100,000 person-years in fifth decade to 103.48 at age 80+ and peaked in eight decade in a majority of studies. In men, incidence increased steadily from 3.57 per 100,000 person-years in fifth decade to 258.47 at age 80+. In contrast to females, incidence continued to rise after age 80 according to approximately half the number of studies (18).

Average disease duration from diagnosis to death is 15 years (19). Until levodopa was introduced in the treatment of PD mortality of these patients was significantly higher than in general population, while more recent studies showed that mortality index in 1.35 (20). Cause of death is often difficult to ascertain, most commonly documented is pneumonia (21).

Motor symptoms

Since its original description, the clinical diagnosis of PD has centered on a defined motor syndrome (22). The cardinal motor signs of Parkinson's disease (PD) include bradykinesia, rigidity, tremor and postural instability. These signs are considered as dopaminergic features, with bradykinesia and rigidity being "the pure" dopaminergic signs, while tremor and postural instability are only partly dependent on dopamine. Besides cardinal motor signs, PD motor phenotype contains signs that don't respond to dopaminergic (levodopa) therapy, like axial (gait disorders, falls) and bulbar symptoms (dysphagia, dysarthria, sialorrhea), as well as postural deformities (striatal hand, camptocormia, Pisa syndrome) (23). Older adults tend to have more severe hypokinetic motor impairment and prominent axial features, with more commonly present postural and gait difficulty phenotype than tremor-dominant phenotype (24), and with significant prevalence of frailty (a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors), even in early stages (25). Furthermore, patients with a later onset of PD are prone to develop motor and non-motor complications during the first 5 years of illness (26). However, interactions between the aging process and disease progression are complex and remain to be defined.

Dopamine-dependent motor signs

Bradykinesia is the core symptom for defining parkinsonism and diagnosing PD. It is characterized by slowness of movement and a decrease in amplitude or speed, or progressive hesitations and halts as movements continue (23). In clinical practice, hypokinesia (abnormally reduced movement amplitude) and akinesia (a decrease in automatic movements, or a failure or delay in the initiation of voluntary movements) are often included under the umbrella term of bradykinesia (27,28). Rigidity refers to the velocity-independent resistance to passive movement, unselectively affecting both agonistic and antagonistic muscles ("lead pipe" and cogwheel resistance) (22). It was shown that bradykinesia and rigidity were more pronounced in older onset PD patients (29), possibly due to age-related nigral and extranigral changes that could modify the presentation of these symptoms (30,31).

Rest tremor, which is characterized by a 4 - 6-Hz tremor occurring in a fully resting limb and typical suppression when movement is initiated (22) wasn't linked to faster progression of PD in the older group of patients (26).

Even though postural instability, characterized by impaired protective reflexes that prevent falling, is a cardinal symptom of PD, it usually manifests later in the disease course. If postural instability is present early in the presentation of PD, it may indicate atypical parkinsonism (23). On the other hand, higher age at onset predicts an advanced impairment in balance and ambulatory functions (26).

Non-dopaminergic motor signs

Gait disorder in Parkinson's disease is characterized by a slow, shuffling gait, increased variability in gait parameters, start hesitation, freezing of gait, and compromised postural control. Gait slowness is typically associated with reduced stride length and decreased amplitude of automatic arm movements (23). Patients with old age at onset PD have a higher burden of axial symptoms, including gait and posture variables after 5 years of disease duration (29). Gait and balance dysfunction coupled with cognitive impairment contributes to the propensity of older PD patients to fall, resulting in "fear-of-falling" (24).

Bulbar dysfunction is common in PD, with more than 80% of affected individuals developing dysphagia over the course of the disease. It is particularly significant in older PD patients, as oesophageal motility disorders are quite common in the healthy older population. Dysphagia contributes to the development of aspiration pneumonia, which is the leading cause of death in PD (32). Furthermore, due to dysphagia and impaired intraoral clearance of saliva, drooling (an excessive pooling and spillover of saliva out of the oral cavity) can occur (33).

Speech impairment in PD can manifest as hypophonia, dysphonia, hypoprosody (monotonous speech), hypokinetic articulation, tachyphemia (oral festination), and palilalia (34). It was shown that older PD patients with hypokinetic dysarthria have receptive prosodic skills inferior to those of the younger patients, suggesting that age is a significant factor for prosody impairment (35).

Postural deformities are frequent and disabling complications of PD (36) that develop in > 30% of patients during the first 4 - 6 years (37). These deformities include camptocormia (marked flexion in the sagittal plane originating in the thoracolumbar spine), antecollis (marked forward flexion of the head and neck), Pisa syndrome (marked lateral flexion of the trunk, which is typically mobile) (36). Older age at onset is associated with higher incidence of postural abnormalities (37).

Non-motor symptoms

Beyond the classical motor signs numerous non-motor symptoms (NMS) characterize PD and their absence in the first five years from symptom onset is a red flag against PD diagnosis (**figure 1**). A long list of NMS in PD includes psychiatric symptoms, cognitive impairment, sleep disorders, reduced olfaction, dysautonomia symptoms, pain, and fatigue, among others (**table 1**). They have a significant negative impact on quality of life throughout the entire PD course. These symptoms are present from prodromal to advanced stages, significantly contributing to disability (38). Frequency and severity of NMS vary across the disease stages and they are an important determinant for PD subtyping together with motor symptoms and biomarkers. The REM sleep behavior disorder, hyposmia, constipation and depression are characteristic of the prodromal disease stage, a number

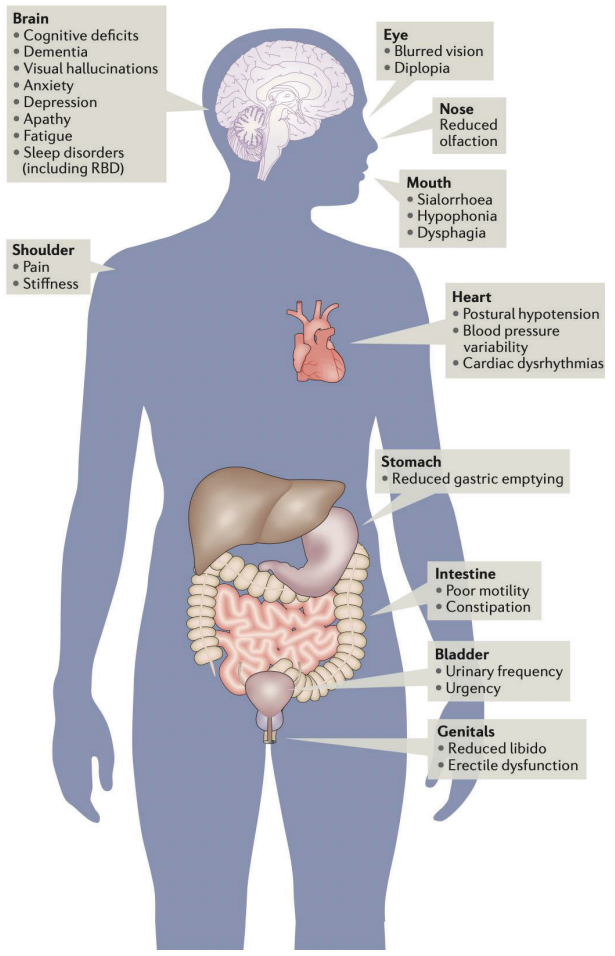

Figure 1. Multi-organ dysfunction in PD. Reprinted from Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017; 18(8):509.

of NMS are present in early and moderate disease stages whereas psychosis and dementia are classical features of the advanced disease.

Elderly patients with PD commonly encounter clinical features associated with their advanced age such as frequent falls, cognitive impairment, frailty, and sarcopenia. They have an age-related neuronal loss in substantia nigra, and an increased burden of cortical beta-amyloid deposition and white matter lesions compared to younger patients with PD which may underlie differences in NMS in this population (30,31). Orthostatic hypotension arises from the neurodegenerative process affecting the autonomic nervous system, and its link to falls particularly in elderly subjects has been established (39,40). The prevalence of cognitive impairment and dementia increases with aging and PD duration. Dementia is very prevalent in advanced PD, found in 60% of patients after 10 years and 80% after 20 years of disease (41). In elderly PD patients, there is an overlap of PD symptoms with frailty. One of the aspects of frailty is a physical aspect which includes slow gait speed, weight loss, decreased muscle strength, fatigue and diminished physical activities. Sarcopenia is another syndrome significantly associated with both frailty and PD characterized by the loss of muscle mass, strength and function. Polypharmacy in elderly patients negatively affects cognition, and may aggravate OH as well as frailty and sarcopenia symptoms (25).

Table 1. Summary of common non-motor symptoms in PD.

Non-motor symptom domain	Non-motor features
Psychiatric	Depression
	Anxiety
	Apathy
	Psychosis
Cognitive	Subjective cognitive impairment
	Mild cognitive impairment
	Dementia
Impulse control disorder	Pathological gambling
	Compulsive buying
	Pathological hypersexuality
	Compulsive eating
	Punding
	Dopamine dysregulation syndrome
Sleep disorders	Insomnia
	Restless leg syndrome
	Excessive daytime somnolence
	REM sleep behavior disorder
Pain	
Fatigue	
Vision impairment	Blurred vision
	Diplopia
Dysautonomia	Orthostatic hypotension
	Delayed gastric emptying
	Constipation
	Overactive bladder symptoms
	Decreased libido
	Erectile dysfunction
	Sweating dysregulation
Skin problems	Seborrheic dermatitis

Age at symptom onset is a well-recognized determinant of the clinical presentation in PD. A peculiar group of PD patients are those with onset after the age of 70 or 75 years (late-onset PD; LOPD). LOPD patients were more frequently diagnosed with dementia and had more gastrointestinal symptoms compared to patients with symptom onset in middle age (29). A faster progression of cardiovascular, cognitive and neuropsychiatric symptoms in early disease was observed in the LOPD patients compared to patients with onset before the age of 50 years (26).

Therapy

The prevalence of PD increases with age and treatment in older people is complicated with comorbidities and polypharmacy. Besides that, the disease progresses faster in older people and falls, fractures, and orthostatic hypotension are more common and there is a higher risk for delirium during hospitalization. In general, the treatment of PD in the elderly must be considered very carefully and multidisciplinary, taking into account drug interactions and drug side effects, that are more common than in younger patients (42). Older patients have fewer motor fluctuations and dyskinesias, but they develop non-dopaminergic signs of the disease, such as gait problems, falls, impaired cognition, and other non-motor symptoms, faster and more frequently (8, 43).

The treatment of older PD patients must be individualized based on stage of the disease, severity of motor signs, presence of motor fluctuations and non-motor signs (42).

The initial treatment in elderly with PD is usually levodopa, starting with small doses, with slowly titrated based on clinical response and side effects. Orthostatic hypotension, confusion, hallucinations and nausea are more common in this group of patients which limits fast up-titration of drugs (24).

Dopamine agonists are rarely used in older patients since they can cause hallucinations and somnolence. Catechol-O-methyltransferase (COMT) inhibitors (entacapone, opicapone) can be used to increase the central availability of dopamine in cases with wearing off motor fluctuations. It has been shown that entacapone has significant improvement in the frequency and severity of OFF periods without significant adverse events in patients older than 70 years but it can cause worsening of dyskinesias. Amantadine can be used for dyskinesias but tends to worsen cognitive impairment and hallucinations (44).

Monoamine-oxidase (MAO-B) inhibitors (rasagilline and selegiline) are better tolerated than dopamine agonist in older patients and may significantly improve the motor symptoms. They are usually used in combination with levodopa and it has been shown that there is no statistical relationship between adverse effects of rasagilline and age (45).

Duodenal infusion pump (duodopa) and subcutaneous apomorphine infusion are systems for continuous drag delivery, effective for reducing motor fluctuations. There is no clear age cut-off for continuous drug infusions but adverse events are less tolerated in older patients due to comorbidities. Deep brain stimulation can also improve motor fluctuations in older patients but the presence of cognitive, psychiatric manifestations and other comorbidities limits the applications of this method in the elderly (44).

Considering that dementia and hallucinations are more common in elderly people with PD, there is a frequent need for the use of neuroleptics. Dopamine antagonists are generally contraindicated as they can cause worsening of PD symptoms. Atypical neuroleptics such as clozapine and quetiapine are preferentially used as antipsychotics in PD to avoid the worsening of parkinsonism. In older people, we have to be careful with drugs that have anticholinergic properties even benzodiazepines (46).

The risk of dementia is doubled in PD and rivastigmine is approved for PD dementia although donepezil and memantine are also used. Cholinesterase inhibitors such as rivastigmine and donepezil are effective for cognitive dysfunction in PD and are widely used in demented PD patients. Several large studies favoured the use of rivastigmine in patients with PD and dementia (44).

Elderly people often take a large number of medications, which is why we have to take care of interactions. These drugs can have interactions with cytochrome P450 metabolised medications. For example, entacapone can elevate CYP2C9 metabolised drugs (warfarin, angiotensin-converting enzyme 2 inhibitors). Dopamine agonist apomorphine can prolong Qt interval and should not be used with other medications that have similar side effects (24).

Differential diagnosis

Differentiating idiopathic PD from other parkinsonian syndromes is neither easy nor always possible. Large pathological studies of patients with parkinsonism have shown that we often misdiagnose PD, even if we belong to neurologists with special training in this field, and that the most frequent misdiagnoses are progressive supranuclear palsy (PSP), multiple system atrophy (MSA), vascular parkinsonism (VP), essential tremor, etc (47-49).

The diagnosis of these diseases is still based on "old fashion" methods that rely on the skills of a neurological examination and the skills of taking an adequate history, which requires experience and a good knowledge of the clinical characteristics of a large number of diseases from the parkinsonism spectrum. "New fashion" diagnostic tools such as neurovisualization methods, specific analyses of blood and cerebrospinal fluid, and neurophysiology methods are still missing, which makes the process of establishing a reliable diagnosis even more difficult. Additionally, with the breakthrough of new genetic methods, it becomes clear that the concept of "one gene-one phenotype" is unsustainable, which further complicates the problem of differential diagnosis of parkinsonism. By identifying new paraneoplastic and auto-antibodies, the field of immunology begins to overflow into the field of neurodegeneration, thus opening a new chapter in the differential diagnosis of parkinsonism.

As a result of our current understanding of what is "atypical" within the spectrum of parkinsonism, neurologists are faced with a complex classification of these diseases, which implies a complex differential diagnostic task (**figure 2**, Adapted from Scholz and Bras, 2015) (50).

The most common neurodegenerative parkinsonisms after PD include PSP and MSA. Their main feature is the rapid progression of parkinsonian symptoms and signs, with the absence of a positive response to dopaminemimetic therapy, which is often the first moment that makes us suspect that we are dealing with "ordinary", idiopathic PD. However, the key moment in establishing the diagnosis of atypical parkinsonism and moving away from the diagnosis of PD is the appearance of additional, "plus" symptoms and signs. Some of them are never encountered in idiopathic PD, such as downward vertical gaze palsy. Others may be part of the clinical spectrum of PD, but the timeframe of their occurrence is not typical for PD, for example, early onset of autonomic dysfunction. Thus, vertical gaze palsy, early postural instability with backward falls, and early onset of frontal cognitive and behavioral changes, along with rapidly progressive, predominantly axial, and levodopa-unresponsive parkinsonism, are part

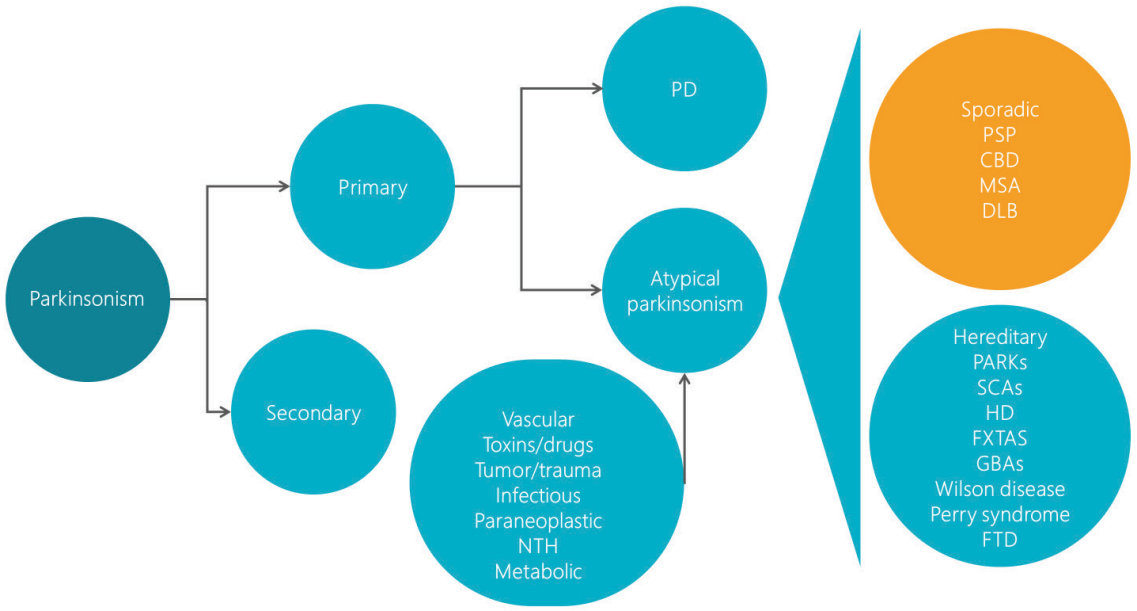

Figure 2. Classification of parkinsonisms. PD - Parkinson's disease; PSP - progressive supranuclear palsy; CBD - corticobasal degeneration; MSA - multiple system atrophy; DLB - dementia with Lewy bodies; SCAs - spinocerebellar ataxias; Huntington's disease; FXTAS - fragile X tremor ataxia syndrome; FTD - frontotemporal dementia; NTH - normotensive hydrocephalus (Adapted from Scholz and Bras, 2015) (50).

of the clinical continuum of PSP (51). Symptoms of autonomic dysfunction, predominantly in the form of orthostatic hypotension and urogenital dysfunction, are characteristic of advanced PD. Their appearance early in the disease course or even before the appearance of the first motor symptoms strongly supports the diagnosis of MSA (52).

It is important to point out that not only the absence of a positive response to dopaminergic therapy is a warning criterion for atypical parkinsonism, but also the side effects of this therapy provide us with important information for the differential diagnosis of parkinsonism. Levodopa-induced dyskinesias, most often of the choreic type, predominantly on the extremities, in the interdose intervals (so-called peak of dose dyskinesias), speak strongly in favor of PD and reduce the probability of atypical parkinsonism (22, 53). On the other hand, dyskinesias in MSA most often involve the oro-bucco-lingual region, are more often dystonic, and occur even in the absence of a therapeutic response to levodopa (54). while dyskinesias in PSP are reduced to rare reports of individual cases (55).

In the group of symptomatic, secondary parkinsonisms, the differential diagnosis in contrast to PD is sometimes significantly facilitated by "new fashion" methods. Thus, the basis of the hemiparkinsonian syndrome, which is a common finding in the early stages of PD, can also be a basal ganglia cavernoma, or a subdural hematoma, which is visible on computer tomography as a widely available diagnostic method. Among symptomatic parkinsonism, the most common mimics of PD are VP and drug-induced parkinsonism (DIP) (56). In addition, the appearance of pyramidal signs, cognitive decline, and sphincter affection speaks more in favour of VP than idiopathic PD (57).

When considering DIP, information about the use of neuroleptics or other drugs that may be responsible for the development of symptoms is often missing. The most common scenario is the subacute development of symmetrical parkinsonism, which is more often reversible after stopping the drug. On the other hand, the gradual development of chronic parkinsonism tends to be more permanent (tardive parkinsonism) and often accompanied by other tardive dyskinesias (58). Given that the differential diagnosis in these patients is often difficult due to unreliable history data, the only helpful diagnostic tool could be DaT SPECT, which indicates the preservation of nigrostriatal pathways in DIP, as opposed to the reduced accumulation of specific ligands in neurodegenerative parkinsonisms (59).

Considering all the facts mentioned above, it becomes clear that the differential diagnosis of PD cannot be seen as a momentum in which an accurate diagnosis is established at the first patient's visit to the doctor. Establishing the accurate diagnosis within the spectrum of parkinsonism is rather a process that takes time, repeated examinations of the patient, monitoring of the treatment efficacy and adverse effects, and planning of diagnostic procedures, which will all lead to greater reliability of the diagnosis.

Mild parkinsonian signs in elderly

The aged population frequently exhibits some of the hallmark symptoms of Parkinson's disease, such as bradykinesia or tremor, or gait disruption alone. However, the mere existence of these isolated symptoms is not sufficient to establish a diagnosis of PD or other neurodegenerative diseases (6). In that case, we are talking about a special entity of "mild signs of parkinsonism" that does not have a defined diagnostic criterion for now. About 4 - 52% of elderly people have mild parkinsonian signs, and this great variability is due to the different age of populations that were studied; what is consistent, however, is that the prevalence of mild parkinsonian signs increases with age (6, 60, 61). This clinical finding may be accidental, and except in the case of tremors, mild parkinsonian symptoms are usually not a reason for bringing patients to see a doctor. From the etiological aspect, it remains insufficiently clarified whether mild parkinsonian signs are a reflection of a decrease in nigrostriatal activity during aging, or the development of Alzheimer's pathology or subcortical vascular disease (62).

People with mild parkinsonian signs may have associated other, non-motor symptoms, which are also found in PD, such as hyposmia, depression, mild cognitive impairment or dementia. Some of these patients will eventually develop additional signs and meet the criteria for PD, in which case we speak of prodromal PD. (6). However, some people will develop other forms of Lewy body pathology, or dementia of the Alzheimer's type or vascular dementia (63). It is a particularly interesting observation that in some people mild parkinsonian signs can disappear over time (64). The presence of mild parkinsonian signs is a predictor of a worse outcome in terms of dementia, disability and mortality (6).

Conclusion

Parkinson's disease is common in the elderly and it seems inevitable that physicians of any specialty will not encounter such patients in their careers. The coexistence of non-motor symptoms of PD, with non-neurological comorbidities common at this age, requires a multidisciplinary approach and intensive communication among different physicians. The guidelines given here were intended to draw the attention of young doctors to the early recognition and treatment of PD. Only this approach can improve the well-being of such patients and their families.

Literature

1. Kouli A, Torsney KM, Kuan WL. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects. Brisbane, QLD, Australia: Exon Publications; 2018.
2. Collier TJ, Kanaan NM, Kordower JH. Aging and Parkinson's disease: Different sides of the same coin? Mov Disord. 2017; 32(7):983–90.
3. Buchman AS, Shulman JM, Nag S, Leurgans SE, Arnold SE, Morris MC, Schneider JA, Bennett DA. Nigral pathology and

Parkinsonian signs in elders without Parkinson's disease. Ann Neurol. 2012; 71(2):258–66.
4. Koller W, O'Hara R, Weiner W, Lang A, Nutt J, Agid Y, et al. Relationship of aging to Parkinson's disease. Adv Neurol. 1987; 45:317–21.
5. Aevarsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol. 1988; 55(9):1226–32.
6. Buchanan SM, Richards M, Schott JM, Schrag A. Mild Parkinsonian Signs: A Systematic Review of Clinical, Imaging, and Pathological Associations. Mov Disord. 2021; 36(11):2481-93.
7. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. Neurology. 2016; 86(15):1400–7.
8. Diederich NJ, Moore CG, Leurgans SE, Chmura TA, Goetz CG. Parkinson disease with old-age onset: a comparative study with subjects with middle-age onset. Arch Neurol. 2003; 60(4):529-33.
9. Ferreira JJ, Katzenschlager R, Bloem BR, Bonuccelli U, Burn D, Deuschl G, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol. 2013; 20(1):5–15.
10. Phokaewvarangkul O, Auffret M, Groppa S, Markovic V, Petrovic I, Bhidayasiri R. What was first and what is next in selecting device-aided therapy in Parkinson's disease? Balancing evidence and experience. J Neural Transm (Vienna). 2024; 131(11):1307-20.
11. de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meché FG, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology. 1995; 45(12):2143–6.
12. Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP. Epidemiology of Parkinson's disease. J Neurol. 2008; 255(Suppl 5):18–32.
13. Dorsey ER, George BP, Leff B, Willis AW. The coming crisis: obtaining care for the growing burden of neurodegenerative conditions. Neurology. 2013; 80(21):1989–96.
14. Zhang ZX, Roman GC. Worldwide occurrence of Parkinsons disease: an updated review. Neuroepidemiology. 1993; 12(4):195–208.
15. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, et al. Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts-Neuroloic Diseases in Elderly Research Group. Neurology. 2000; 54 (11 Suppl 5):s21-3.
16. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014; 29(13):1583–90.
17. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology. 1999; 52(6):1214–20.
18. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology. 2016; 46(2):292-300.
19. Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. Neurology. 2008; 71(7):474–80.
20. Herlofson K, Lie SA, Arsland D, Larsen JP. Mortality and Parkinson disease-A community based study. Neurology. 2004; 62(6):937-45.
21. Morgante L, Salemi G, Meneghini F, Di Rosa AE, Epifanio A, Grigoletto F, et al. Parkinson's disease survival: a population-based study. Arch Neurol. 2000; 57(4):507-12.
22. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015; 30(12):1591–601.
23. Hess CW, Hallett M. The Phenomenology of Parkinson's Disease. Semin Neurol. 2017; 37(2):109–17.
24. Banford A, Henderson E. Parkinson's disease in older people. Medicine, 2020; 49(1):56-61.
25. Ebina J, Ebihara S, Kano O. Similarities, differences and overlaps between frailty and Parkinson's disease. Geriatr Gerontol Int. 2022; 22(4):259-70.
26. De Carolis L, Galli S, Bianchini E, Rinaldi D, Raju M, Caliò B, et al. Age at Onset Influences Progression of Motor and Non-Motor Symptoms during the Early Stage of Parkinson's Disease: A Monocentric Retrospective Study. Brain Sci. 2023; 13(2):157.
27. Hess CW, Okun MS. Diagnosing Parkinson Disease. Continuum (Minneap Minn). 2016; 22(4):1047–63.
28. Bologna M, Espay AJ, Fasano A, Paparella G, Hallett M, Berardelli A. Redefining Bradykinesia. Mov Disord. 2023; 38(4):551–7.
29. Mendonça MD, Lampreia T, Miguel R, Caetano A, Barbosa R, Bugalho P. Motor and non-motor symptoms in old-age onset Parkinson's disease patients. J Neural Transm (Vienna). 2017; 124(7):863–7.
30. Bohnen NI, Müller ML, Zarzhevsky N, Koeppe RA, Bogan CW, Kilbourn MR, et al. Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease. Brain. 2011; 134(8):2358–65.
31. Huang Y, Potter R, Sigurdson W, Santacruz A, Shih S, Ju YE, et al. Effects of age and amyloid deposition on Ab dynamics in the human central nervous system. Arch Neurol. 2012; 69(1):51–8.
32. Legacy J, Herndon NE, Wheeler-hegland K, Okun MS, Patel B. A comprehensive review of the diagnosis and treatment of Parkinson's disease dysphagia and aspiration. Expert Rev Gastroenterol Hepatol. 2020; 14(6):411–24.
33. Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's Disease: a review. Park Relat Disord. 2014; 20(11):1109–18.
34. Dashtipour K, Tafreshi A, Lee J, Crawley B. Speech disorders in Parkinson's disease : pathophysiology, medical management and surgical approaches. Neurodegener Dis Manag. 2018; 8(5):337–48.
35. Martens H, Van Nuffelen G, Wouters K, De Bodt M. Reception of Communicative Functions of Prosody in Hypokinetic Dysarthria due to Parkinson's Disease. J Park Dis. 2016; 6(1):219-29.
36. Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanik OS, et al. Postural deformities in Parkinson's disease. Lancet Neurol. 2011; 10(6):538-49.
37. Fabbri M, Campisi C, Ledda C, Rinaldi D, Tsukita K, Romagnolo A, et al. Incidence and predictors of postural abnormalities in Parkinson's disease: a PPMI cohort study. J Neurol. 2024; 271(7):4628-34.
38. Stankovic Tutus I. Prospektivna studija napredovanja Parkinsonove bolesti u ranom motornom stadijumu- doktorska disertacija. Med Fak Univ u Beogradu 2021.
39. LeWitt PA, Kymes S, Hauser RA. Parkinson Disease and Orthostatic Hypotension in the Elderly: Recognition and Management of Risk Factors for Falls. Aging Dis. 2020; 11(3):679–91.
40. De Pablo-Fernandez E, Tur C, Revesz T, Lees AJ, Holton JL, Warner TT. Association of autonomic dysfunction with disease progression and survival in Parkinson disease. JAMA. 2017; 74(8):970-76.
41. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008; 23(6):837-44.
42. Ryden LE, Lewis SJG. Parkinson's Disease in the Era of Personalised Medicine: One Size Does Not Fit All. Drugs Aging. 2019; 36(2):103-13.
43. Levy G, Louis ED, Cote L, Perez M, Mejia-Santana H, Andrews H, et al. Contribution of aging to the severity of different motor signs in Parkinson disease. Arch Neurol. 2005; 62(3):467-72.
44. Lenka A, Padmakumar C, Pal PK. Treatment of Older Parkinson's Disease. Int Rev Neurobiol. 2017; 132:381-405.
45. Goetz CG, Schwid SR, Eberly SW, Oakes D, Shoulson I. Parkinson Study Group TEMPO and PRESTO Investigators. Safety of rasagiline in elderly patients with Parkinson disease. Neurology. 2006; 66(9):1427-9.
46. Sheu JJ, Tsai MT, Erickson SR, Wu CH. Association between Anticholinergic Medication Use and Risk of Dementia among Patients with Parkinson's Disease. Pharmacotherapy. 2019; 39(8):798-808.
47. Joutsa J, Gardberg M, Röyttä M, Kaasinen V. Diagnostic accuracy of parkinsonism syndromes by general neurologists. Park Relat Disord. 2014; 20(8):840–4.
48. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of

diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002; 125(4):861–70.
49. Meola G. Myotonic dystrophy type 2: the 2020 update. Acta Myol. 2020; 39(4):222-34.
50. Scholz SW, Bras J. Genetics underlying atypical parkinsonism and related neurodegenerative disorders. Int J Mol Sci. 2015; 16(10):24629–55.
51. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017; 32(6):853–64.
52. Wenning GK, Stankovic I, Vignatelli L, Fanciulli A, Calandra-Buonaura G, Seppi K, et al. The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. 2022; 37(6):1131–48.
53. Gibb WR. Accuracy in the clinical diagnosis of parkinsonian syndromes. Postgrad Med J. 1988; 64(751):345–51.
54. Köllensperger M, Geser F, Seppi K, Stampfer-Kountchev M, Sawires M, Scherfler C, et al. Red flags for multiple system atrophy. Mov Disord. 2008; 23(8):1093–9.
55. Respondek G, Höglinger GU. The phenotypic spectrum of progressive supranuclear palsy. Parkinsonism Relat Disord. 2016; 22 (Suppl 1):S34-6.
56. Hussein M, Del Toro-Pérez C, Guevara-Sánchez E, Martínez-Sánchez P. Treatment of Vascular Parkinsonism: A Systematic Review. Brain Sci. 2023; 13(3):489.
57. Kalra S, Grosset DG, Benamer HTS. Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. Mov Disord. 2010; 25(2):149–56.
58. Anand R, Pandey S, Garg RK, Singh Malhotra H, Shrivastava S, Kar SK, et al. Phenomenology, quality of life, and predictors of reversibility in patients with drug-induced movement disorders: a prospective study. CNS Spectr. 2023; 28(5):534–6.
59. Saeed U, Lang AE, Masellis M. Neuroimaging Advances in Parkinson's Disease and Atypical Parkinsonian Syndromes. Front Neurol. 2020; 11:572976.
60. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med. 1996; 334(2):71-6.
61. Louis ED, Tang MX, Schupf N, Mayeux R. Functional correlates and prevalence of mild parkinsonian signs in a community population of older people. Arch Neurol. 2005; 62(2):297-302.
62. Yamanouchi H, Nagura H. Neurological Signs and Frontal White Matter Lesions in Vascular Parkinsonism. Stroke. 1997; 28(5):965–9.
63. Lerche S, Hobert M, Brockmann K, Wurster I, Gaenslen A, Hasmann S, et al. Mild parkinsonian signs in the elderly-is there an association with PD? Crossectional findings in 992 individuals. PLoS One. 2014; 9(3):e92878.
64. Mahoney JR, Verghese J, Holtzer R, Allali G. The evolution of mild parkinsonian signs in aging. J Neurol. 2014; 261(10):1922–28.