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## **The effects that secondary parkinsonian syndromes have on health status**

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## ABSTRACT

### **Introduction and purpose:**

The parkinsonian syndrome is a component of Parkinson's disease. A thorough neurological examination can detect symptoms belonging to the parkinsonian syndrome. Diagnosis using the Queen Square Brain Bank criteria is based on the presence of bradykinesia along with one additional symptom in the patient. These include muscle rigidity or resting tremors at a frequency of 4-6 Hz, or postural disturbances that cannot be explained by visual, vestibular, cerebellar, or deep sensory disorders. The parkinsonian syndrome can occur in idiopathic Parkinson's disease, hereditary disorders, secondary parkinsonism, or be part of an atypical parkinsonian syndrome.

The aim of the study was to discuss the diagnostic features and differences in the occurrence of the parkinsonian syndrome as a component of Parkinson's disease, both within the context of other neurological disorders.

### **Materials and method:**

The foundation of the research was medical articles gathered from the Google Scholar database. The studies were conducted by analyzing keywords such as "parkinsonism," "drug-induced parkinsonism," and "vascular parkinsonism."

### **Results:**

Secondary parkinsonism, or secondary parkinsonism syndrome, can be indicated by clinical features such as: disease onset below the age of 40, abrupt onset, rapid disease progression, symptoms related to medication use, and symptoms associated with the underlying condition. In addition to clinical evaluation, imaging studies are also employed.

### **Conclusions:**

Various conditions can lead to the development of secondary parkinsonism, including hydrocephalus, brain tumors, encephalitis, cerebral atherosclerosis, traumatic brain injuries, medications, and poisoning. The aforementioned conditions exert different mechanisms of influence on the central nervous system.

**Key words:** Parkinsonism; Parkinson's disease; Vascular parkinsonism; Parkinsonian syndrome; Drug-induced parkinsonism.

## **Introduction**

Among patients with secondary parkinsonism, it was found that it was most commonly caused by medications (43.4%), vascular parkinsonism (37%), normotensive hydrocephalus (5.1%), functional or psychogenic parkinsonism (3.8%) (1). However, there are causes that are less frequently described by researchers. The association of parkinsonian syndrome with brain abscess, manifestation of multiple sclerosis changes, tuberculosis, methanol, carbon monoxide, and hypoxia has been proven (2). Some studies seek a common feature for both primary and secondary parkinsonian syndromes. Infectious, neoplastic, autoimmune factors may induce the onset of the immune system response. Stimulated T lymphocytes produce proinflammatory cytokines. The result of this process may be neurodegenerative phenomena (3). Secondary parkinsonism is caused by other diseases, some of which can be cured. However, according to studies, the lack of protein accumulation in the central nervous system does not guarantee a cure after removing the cause (4). Impaired blood-brain barrier and damaged vessels associated with proteinuria may play a role in the development of secondary parkinsonism (5). However, the mechanism is still unclear.

In a retrospective study, 3663 patients with nephrotic syndrome (NS) and 14652 age- and gender-matched patients without NS were evaluated. Both Parkinson's disease (PD) and secondary parkinsonian syndrome (sPS) were considered. The analysis showed that NS patients had a higher risk of PD and sPS than patients without NS, aged 20-49 years (adjusted hazard ratio (HR) 4.75; 95% CI, 4.06-5.56) and aged 50-64 years (adjusted HR 2.00; 95% CI, 1.66-2.40) (6).

## Vascular Parkinsonism

Myocardial infarction (MI), along with other cardiovascular diseases, is the most common cause of death in developed countries. A cohort study involving 181,994 patients diagnosed with MI was conducted between 1995 and 2016. According to the authors, MI was associated with a reduced risk of secondary parkinsonism (adjusted HR=0.72, 95% CI, 0.54-0.94) (7).

In the course of vascular parkinsonism (VP), gait disturbances were reported as the initial symptom in up to 90% of patients. This presents as a mixed pattern, known as atactic-parkinsonian gait, distinguishing it from the parkinsonian gait seen in Parkinson's disease (PD) (8). The features of VP have been accurately described by Levin et al. The onset of symptoms can be acute or subacute, usually bilateral, with symptoms of parkinsonian syndrome, a progressive or stable course. Cognitive impairment and dementia, as well as psychiatric disorders, may accompany VP, with an exceptionally low frequency of visual hallucinations (9). Specific features of parkinsonian syndrome in VP may vary in frequency. Resting tremor was observed in 4% of VP patients (10). Additionally, there was impaired tandem gait, gait on an expanded base, postural instability, and an increased risk of falls (10). Recent reports indicate the presence of pain preceding motor symptoms in patients with VP (11). Parkinsonian symptoms in VP may appear weeks to months after a stroke, typically not immediately (12). Cognitive processes in individuals with VP were assessed through neuropsychological studies, revealing more frequent cognitive disorders in the VP group compared to a control group of similar age (13).

In a cross-sectional study involving 15 VP patients and 30 PD patients, urinary incontinence ( $p<0.001$ ) and pyramidal symptoms ( $p=0.001$ ) were more common in the VP group. Lacunar infarctions (66.7%) were also more frequent in magnetic resonance imaging (MRI) scans (14). Presumably, pyramidal symptoms in VP patients are associated with damage to corticospinal pathways due to a past stroke or small vessel occlusion. Changes described in MRI involved bilateral subcortical and periventricular white matter areas (13). Levin et al. detected focal changes in the cortex and globus pallidus, less frequently in the substantia nigra and frontal lobe, using computed tomography (CT) and MRI (9). Karen et al. examined VP patients using DaTSCAN imaging, which illustrates presynaptic dopamine uptake. DaTSCAN results were normal in 32.5% of patients (15). Among 14 VP patients, changes were identified in MRI, including increased volume of the tail of the caudate nucleus and the presence of hyperintense

lesions in the white matter (16). This may be related to vascular dysfunction in old age. Infarctions in the basal ganglia or loss of neurons in the substantia nigra were associated with a better response to levodopa (17). A response to levodopa was observed in 29% of VP patients (17). Transcranial Doppler ultrasonography was used for the diagnosis of vascular parkinsonism and its comparison with Parkinson's disease. A higher Gosling index (PI) was observed in VP individuals compared to the PD group (median 29.1 compared to 96.0,  $p=0.013$ ) (18). This relatively inexpensive and simple test may serve in detecting vascular parkinsonism. Using MRI, patients with vascular parkinsonism and a control group were evaluated, revealing hyperintensity in the dorsolateral part of the substantia nigra in 35 out of 38 individuals in the control group and in 19 out of 34 patients with VP (19). Infarction in the striatum area may cause damage to the nigrostriatal pathway, visible through DaT-SPECT imaging as asymmetry in dopamine transporter uptake in the caudate nuclei (20).

### **Parkinsonism in the Course of Normal Pressure Hydrocephalus**

The triad of symptoms for idiopathic normal pressure hydrocephalus (iNPH) includes 1) urinary incontinence, 2) gait disturbances, and 3) cognitive impairment along with ventriculomegaly (21). There is evidence suggesting similarities between progressive supranuclear palsy (PSP) and normal pressure hydrocephalus (NPH) (21).

iNPH may present with parkinsonism, although this clinical feature is often overlooked (22). The main symptoms reported in the clinical picture are bradykinesia and postural instability, along with akinesia noted in 70% of cases (22). The hypokinetic deficit affects both upper and lower limbs and may occur asymmetrically (22). Dysfunction of gait was assessed in 35 patients with NPH, with a reassessment after a large-volume lumbar puncture (LP). Individuals with NPH had shorter and slower steps, more frequently exhibiting hypokinetic gait compared to the control group or the PD group. After LP in NPH patients, the results improved but did not reach the level of the control group (23). Patients with iNPH and symptoms resembling parkinsonism were assessed using neuropsychological tests. Cognitive function worsened in 65% of the iNPH group, and only 35% of iNPH patients performed within the normal range ( $p<0.05$ ) (24). Motor symptoms in individuals with NPH or obstructive hydrocephalus more often improved after valve surgery and less frequently with

levodopa treatment (25). According to the study authors, besides resting tremor, other parkinsonian symptoms were common in individuals with NPH (26).

The binding of the dopamine transporter in the striatum was evaluated in 50 individuals with iNPH. Reduced transporter binding was demonstrated in 62% of iNPH patients, correlating with the severity of parkinsonism, with no correlation found with white matter changes or ventriculomegaly features (27). Scientific reports indicate characteristic features of iNPH in MRI examinations. The narrow cerebellopontine angle (less than 71 degrees, 95% CI 0.88-0.93,  $p < 0.001$ ), larger or equal to 7mm temporal horns (95% CI 1.57-2.45,  $p < 0.001$ ), Evans index greater than 0.37 (95% CI 1.40-1.85,  $p < 0.001$ ), and iNPH Radscale greater than 9 (95% CI 1.92-3.22,  $p < 0.001$ ) were associated with iNPH (28). In the future, the identification of diagnostic markers may facilitate the discovery of the underlying cause of symptoms.

Normal values of striatal binding ratios (SBR) [<sup>123</sup>I]FP-CIT SPECT were associated with the diagnosis of iNPH, even after adjusting for changes in white matter and coexisting diseases (adjusted odds ratio (OR): 4.17; 95% CI, 1.26-13.80) (29).

### **Parkinsonism in the Course of Brain Tumors**

Brain tumors are considered rare causes of secondary parkinsonism. Movement disorders due to brain tumors more often manifest as hyperkinetic rather than hypokinetic (30). Parkinsonism is very rare in individuals with brain tumors, especially those located in the basal ganglia, brainstem, or posterior fossa of the skull (30). A case has been described in the literature involving a patient with a frontal skull base meningioma who presented with symptoms of Parkinson's disease. The clinical picture showed an acute onset of bradykinesia, cogwheel rigidity, and resting tremor. The MRI revealed a moderate mass effect with edema, and both frontal horns were distorted bilaterally (31). After resection, there was an improvement in muscle rigidity and a reduction in resting tremor, which persisted at a mild level (31).

According to reports, compression of the nigrostriatal pathway in the brainstem caused by tumors may lead to parkinsonism (32). Patients with leucine-rich glioblastoma and present antibodies, without significant abnormalities in MRI, exhibited asymmetric parkinsonian

features (33). Individuals showed bradykinesia and vocalization-related falls, most of which resolved after immunotherapy was administered (33).

### **Post-Traumatic Parkinsonism**

Head injuries, especially repetitive ones, can be a cause of post-traumatic parkinsonism. Severe head trauma is associated with post-traumatic movement disorders reported in about 20% of patients (34). The presence of tremors is most commonly associated with damage to the cerebellum and interbrain. Frequent head injuries in athletes may lead to encephalopathy with parkinsonian features (34). Chronic Traumatic Encephalopathy (CTE) caused by repeated head injuries in athletes is characterized by cognitive decline, mood changes, motor disturbances, including parkinsonism. CTE is characterized by the accumulation of tau protein in the brain (35). According to McKee, a single brain injury due to trauma can accelerate the process of neurodegeneration or increase the risk of Alzheimer's and Parkinson's diseases (36). Chronic head injuries can cause neuronal loss in the extrapyramidal system. Another rare cause of secondary parkinsonism is chronic subdural hematoma (CSDH). A systematic review of case descriptions found that the most common symptoms of parkinsonism due to CSDH were bradykinesia, stiffness, and gait disturbances (75%) (37).

A comparison of brain structures between a group of amateur boxers and a control group using MRI showed a 5.5% decrease in cortical gray matter volume ( $p=0.038$ ) and an 8.4% decrease in white matter volume ( $p=0.009$ ) in amateur boxers. Additionally, there was an 11.1% decrease in gray matter volume of the caudate nucleus ( $p=0.004$ ), an 8.1% decrease in thalamic volume ( $p=0.011$ ), and a 9.6% decrease in the volume of the globus pallidus ( $p=0.017$ ) compared to the control group (38).

### **Drug-Induced Parkinsonism**

Drug-induced parkinsonism is mentioned as the second most common cause of parkinsonian syndrome after Parkinson's disease (39). Drug-induced parkinsonism is not associated with neurodegenerative processes and is usually reversible (40).



Among the medications most commonly causing drug-induced parkinsonism, antipsychotics (neuroleptics) and antidepressants can be distinguished (41).

Typical (first-generation) neuroleptics bind more strongly to D2 receptors in the nigrostriatal pathway than atypical (second-generation) neuroleptics, blocking them in the striatum. In contrast, atypical antipsychotics bind to receptors less strongly and dissociate more rapidly. Additionally, atypical antipsychotics act on various subtypes of serotonin 5-HT receptors, indirectly modulating dopamine release in different brain regions. As a result, atypical neuroleptics exhibit fewer side effects in the form of extrapyramidal symptoms. The first symptoms can appear within a few days of starting treatment, up to even 3 months. About 20% of patients develop drug-induced parkinsonism symptoms (42). Symptoms typically subside within a few weeks to several months after discontinuing the medication. In a cohort study involving over 60,000 patients aged 65 and older, the occurrence of parkinsonism was compared depending on whether these individuals were taking typical or atypical neuroleptics or not taking neuroleptics at all. A slightly increased frequency of parkinsonism was shown in patients taking typical neuroleptics compared to atypical ones (HR 1.30; 95% CI, 1.04-1.58). In the group not taking neuroleptics, the frequency of parkinsonism was 60% lower than that of atypical neuroleptics (HR 0.40; 95% CI, 0.29-0.43) (43).

SSRI and SNRI antidepressants block serotonin reuptake through the SERT receptor, increasing its concentration in the postsynaptic cleft. Despite numerous reports of extrapyramidal symptoms during their use, these drugs do not have a direct impact on dopamine receptors, except for sertraline, which blocks dopamine transport through DAT receptors (44). For other drugs in this group, it is believed that extrapyramidal symptoms are caused by increased stimulation of 5-HT<sub>2</sub> receptors, which indirectly inhibits dopamine secretion in the striatum (45). There is debate about drugs that do not have an affinity for 5-HT<sub>2</sub> or SERT receptors, or block them, such as mirtazapine (46). The most commonly described symptom induced by antidepressant drugs is tremor (47) and muscle stiffness (48).

Other less commonly mentioned drugs that can induce symptoms of parkinsonian syndrome include antidepressants, calcium channel blockers, H<sub>1</sub> histamine receptor blockers, antiepileptic drugs, lithium, antiarrhythmics, antibiotics (48).

## **Conclusion**

In the course of vascular parkinsonism (VP), bilateral symptoms and gait disturbances are observed, which include features of cerebellar ataxia. This may be accompanied by a history of stroke or focal changes in the basal ganglia. Levodopa in patients with VP does not always reduce the severity of clinical symptoms.

Chronic head injuries lead to the atrophy of neural tissue in the extrapyramidal system and likely increase the risk of Parkinson's disease.

Antidepressant drugs from the SSRI group may also indirectly affect the functioning of the extrapyramidal system, causing some symptoms of parkinsonian syndrome.

## **DISCLOSURE**

### **Author's contribution**

Conceptualization, Michał Urbaś, and Miłosz Ojdana; methodology, Martyna Kępczyk.; software, Oliwia Czekaj; check, Michał Urbaś, Jakub Misiak and Yehor Demianenko; formal analysis, Kaja Surowiecka.; investigation, Oliwia Kwaśniewska; resources, Aleksandra Kościółek; data curation, Yehor Demianenko; writing - rough preparation, Kaja Surowiecka and Dawid Kościółek; writing - review and editing, Miłosz Ojdana and Jakub Misiak; visualization, Jakub Misiak; supervision, Oliwia Kwaśniewska; project administration, Michał Urbaś; receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

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Informed consent was obtained from all subjects involved in the study.

## Data Availability Statement

Not applicable

## Conflict of interest

The authors deny any conflict of interest

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