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LEADING TOPIC

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Importance of non-motor symptoms in PD and atypical parkinsonism

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As a guest editor of the second Leading Topic published in the Polish Journal of Neurology and Neurosurgery, I would like to present a series of papers regarding the occurrence and influence of non-motor symptoms (NMS) on disease course in Parkinson's Disease (PD) and other parkinsonism, paying special attention to cognitive disorders.

Parkinson's Disease, the second most frequent neurodegenerative disease, is mainly recognised as a movement disorder, but some non-motor symptoms, such as sleep disturbances and gastrointestinal dysfunction, were already described by James Parkinson in his *Essay on the shaking palsy* [1]. Nowadays, we are well aware that NMS are very common and important parts of PD, being even more disabling, leading to poor health-related quality of life, and increased caregiver burden. The NMS in PD (Tab. 1) may precede motor symptoms onset, or appear alongside disease progression [2]. In advanced disease stages, neuropsychiatric disorders and autonomic dysfunction are usually present, becoming a major therapeutic difficulty [3, 4].

Familiarity with the presence of NMS in parkinsonism can help clinicians to better diagnose and treat these patients. Proper recognition of non-motor symptoms, along with adequate understanding of the factors related to their development, should be important for physicians, because patients themselves rarely mention these symptoms, thinking that they are not associated with PD. There are several scales and questionnaires that can help clinicians to recognise NMS in PD. The Movement Disorder Society-Unified Parkinsons's Disease Rating Scale (MDS-UPDRS) part I contains several questions regarding non-motor symptoms, and is validated to many languages to be easily used in a clinical practice [5]. The Non-Motor Symptoms Questionnaire (NMSQuest) is more specific to non-motor aspects of PD than the MDS-UPDRS. NMSQuest is a self-completed patient questionnaire with 30 qualitative questions covering all important non-motor symptoms of PD [6]. The last scale and questionnaire is the Non-Motor Symptoms Scale (NMSS), a grade rating scale for estimating the frequency and severity of non-motor symptoms in PD. Its revised version, MDS-NMS, was recently developed by Chaudhuri et al. This rater-completed assessment measures the frequency and severity of 13 non-motor domains over 52 items, and covers a range of key non-motor symptoms both PD- and treatment-related [7].

Among various NMS in PD, cognitive impairment is one of the most disabling symptoms. Mild cognitive impairment (MCI) may occur early in the disease course, and has been identified in 10-40% of newly diagnosed PD patients. PD-MCI can progress to dementia in 6-9% of patients annually, remain stable, or even revert to normal cognition [8]. Therefore identifying possible risk factors of cognitive decline in PD is crucial for treatment decisions and prognosis. Important risk factors related to PD dementia are elderly age at diagnosis, akinetic-rigid phenotype, severe motor impairment in advanced disease, and low education level [9]. The *APOE*, *MAPT*, *SNCA*, *GBA*, *LRRK2*, and *COMT* genes have also been found to play a role in the onset and development of PD dementia [10]. The effect of various factors on PD-related cognitive decline were assessed by Tipton et al. [11] They found that male sex and APOE ε4 allele, along with age and lower education level, are associated with poorer

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Table 1. Non-motor symptoms in parkinsonism

Domain	Symptom
Neuropsychiatric symptoms	Depression
	Apathy
	Anxiety
	Anhedonia
	Psychosis: hallucinations, illusion, delusions
	Cognitive impairment and dementia
	Confusion/delirium
	Panic attacks
Disorders of sleep and wakefulness	Restless legs and periodic limb movements Rapid eye movement sleep behaviour disorder (RBD)
	Excessive daytime sleepiness
	Vivid dreaming
	Sleep fragmentation
	Insomnia
	Sleep disordered breathing
Autonomic symptoms	Urinary dysfunction: urgency, nocturia
	Excessive sweating
	Drooling
	Orthostatic hypotension
	Sexual dysfunction: hypersexuality, erectile impotence
	Dry eyes (xerostomia)
	Gastrointestinal symptoms: gastroparesis, constipation
Sensory symptoms	Pain
	Paresthesia
	Olfactory disturbance
Other symptoms	Fatigue
	Ophthalmological dysfunction: diplopia, blurred vision
	Seborrhoea
	Weight loss/weight gain

cognitive performance among a population of predominantly non-demented PD patients early in their clinical course. APOE ε4 dose was associated with lower scores on Mini-Mental Status Evaluation (MMSE) and Dementia Rating Scale (DRS-2), but reached statistical significance only with DRS-2 total scores, suggesting that more detailed neuropsychological testing should be used in selected cases, preferably male PD patients, even in the absence of subjective complaints of cognitive decline. However, in everyday clinical practice, screening tests are more frequently used in diagnosing mild neurocognitive decline, and the Montreal Cognitive Assessment (MoCA) has been found to be more effective than the MMSE in this context [12].

In advanced disease, PD patients frequently suffer from dysautonomia. This comprises orthostatic hypotension (OH), supine hypertension, and the absence of a decrease of blood pressure (BP) during the night. There is also some data suggesting that PD might even predispose to heart failure and sudden cardiac death by severe QTc prolongation frequently associated with medications used for treatment of different motor and non-motor symptoms present in PD [13].

Dysautonomia, especially BP fluctuations, could be an important co-factor for the development of vascular brain changes and can trigger neurodegeneration resulting in cognitive impairment progression to dementia. As in other neurodegenerative diseases, cognitive deterioration in PD most probably develops as a result of multiple underlying processes [14]. Thus, disturbances to the circadian BP rhythm may contribute to cognitive decline in PD through many different and independent mechanisms. A possible relationship between cardiovascular risk factors, especially OH, and cognition in PD has been discussed in a review paper by Kwaśniak-Butowska et al. [15]. Several pathological mechanisms are considered: cerebral hypoperfusion as a result of recurrent episodic hypotension, widespread neurodegeneration, or central and peripheral noradrenergic dysfunction. A positive correlation between OH and cognitive deterioration has been observed, where executive and visuospatial functions were more impaired among PD patients with orthostatic hypotension. Literature data suggests that older age, male sex, and the presence of RBD and OH are predictors of dementia development in PD. In approximately 50% of PD patients, orthostatic hypotension often coexists with supine hypertension, and this combination leads to more severe cognitive impairment. An abnormal nocturnal blood pressure profile presenting as either loss of nocturnal BP fall, or even an increase of BP values during the night, has also been linked to cognitive impairment in the elderly. The correlation between abnormal nocturnal BP and dementia has been shown to be independent of age, gender, Hoehn and Yahr score, diabetes, history of stroke and white matter hyperintensities (WMHs).

Non-motor symptoms, including cognitive impairment, frequently accompany not only PD, but also atypical parkinsonism, making a differential diagnosis and therapeutic approach challenging [16]. Detailed neuropsychological assessment shows differences in the cognitive profiles of PDD and dementia features in atypical parkinsonism, e.g. greater memory impairment is present in dementia with Lewy bodies, while in PDD there is greater and faster decline in visuospatial and executive domains [17]. In rare cases, patients with dementia with Lewy bodies develop focal cortical syndromes, such as cortico-basal syndrome (CBS) and primary progressive aphasia. An interesting manifestation of Lewy body disease could be Capgras syndrome (CS), one of the presentations of a delusional misidentification syndrome characterised by the recurrent and transient belief that a person, usually the spouse or a sibling, has been replaced

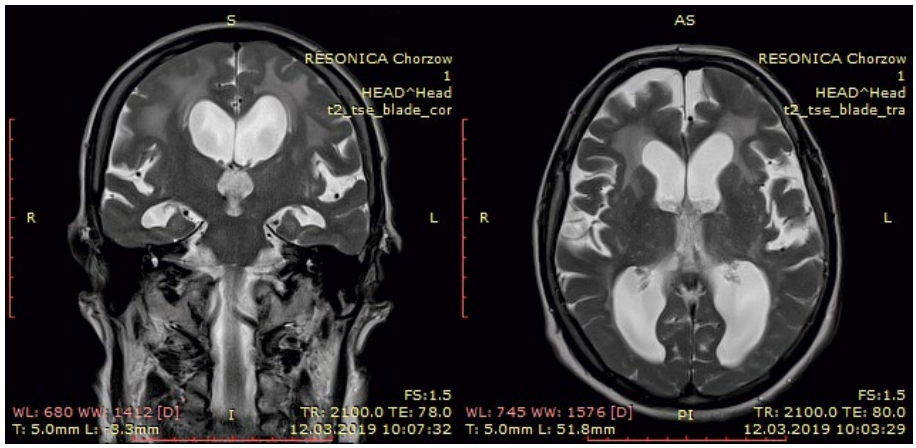

Figure 1. Normal preassure hydrocephalus with narrow sulci and subarachnoid spaces at vertex

by an imposter. CS occurs in neurodegenerative diseases where dementia and hallucinations are already present. A clinico-pathological case study of a patient with dementia with Lewy bodies, who developed Capgras syndrome four years after the onset of parkinsonism, has been presented by Koga et al. [18]. The authors carried out a detailed pathological evaluation showing that CS is likely to be associated with greater cortical Lewy body pathology burden.

Cognitive impairment and dementia is also present in about 30% of patients with multi system atrophy, where the cognitive profile is predominantly characterised by a dysexecutive syndrome [19]. Another example of concurrent parkinsonism and executive dysfunction is progressive supranuclear palsy (PSP), where profound language dysfunctions are also present. PSP can have substantial phenotypic overlap with CBS [20]. CBS symptoms localise in the cerebral cortex and basal ganglia, clinically presenting as asymmetric parkinsonism with higher brain functions impairment, e.g. cognitive impairment, apraxia, cortical sensory loss. Therefore, CBS can be misdiagnosed not only as PSP, but also as Alzheimer's Disease and frontotemporal dementia [21]. Besides differences in cognitive profile, parkinsonism may manifest with a variety of gait disturbances, and the ability to recognise and interpret these disturbances is valuable for clinicians. Parkinsonian gait disorders universally cause reduced gait velocity, reduced step length and height during the swing period, as well as reduced arm swing but increased cadence. Various cognitive and gait manifestations of the most common causes of parkinsonism are nicely described, and the possible connections between these two conditions discussed, in a review paper by Dr. Tipton published in this issue [22].

In a classic form of Parkinson's Disease with good response to levodopa, it is not recommended to perform a neuroimaging study [23]. Nonetheless, patients with early parkinsonian symptoms or presenting with additional symptoms such as cognitive impairment, should be referred to a brain magnetic resonance imaging (MRI) to rule out secondary, possibly -old treatable, causes of disease. An example could be a 75-year-old female patient with a 6-months history of mild dementia and parkinsonian gait disorder. Her brain MRI showed severe cortico-subcortical atrophy, and the diagnosis of Alzheimer's Disease was made. In spite of acetylcholinesterase inhibitor treatment, the patient quickly deteriorated. A second neuroradiological opinion was performed, describing: moderately dilated supratentorial ventricular system (Evans ratio 0.39), acute callosal angle measured on coronal images at the level of the posterior commissure, and narrow sulci and subarachnoid spaces at the vertex and medial/parafalcine region. The brain MRI was consistent with radiological diagnosis of normal pressure hydrocephalus. What was missed before was a disproportion of cortical atrophy between temporal lobes and brain vertex (Fig. 1). The diagnosis was changed to normal pressure hydrocephalus, and ventriculoperitoneal shunting, as a treatment of choice, was proposed to the patient. Ventriculoperitoneal shunting can be associated with some complications, and thus the initial valve opening pressure should be set close to the patient's lumbar puncture opening pressure to decrease overdrainage without compromising symptom improvement [24].

Neuroimaging studies may also have a value in a differential diagnosis of PD versus atypical neurodegenerative parkinsonian syndromes, especially in more advanced stages of disease, when substantial phenotypic overlap is common [23, 25]. Figure 2 shows a brain MRI of a 64-year-old male patient who presented with an initial diagnosis of PD dementia. His neuropsychological and neurological examination showed ideomotor apraxia, right side visual agnosia, and right side parkinsonism, along with the evaluation of brain imaging, showing asymmetrical cortical atrophy especially in the left parietal lobe. The diagnosis was changed to a CBS. Some brainstem measurements could also be very helpful in the differential diagnosis of atypical parkinsonism, PSP, and multi system atrophy versus PD. Several neuroimaging techniques, conventional MRI and functional imaging, are described, and

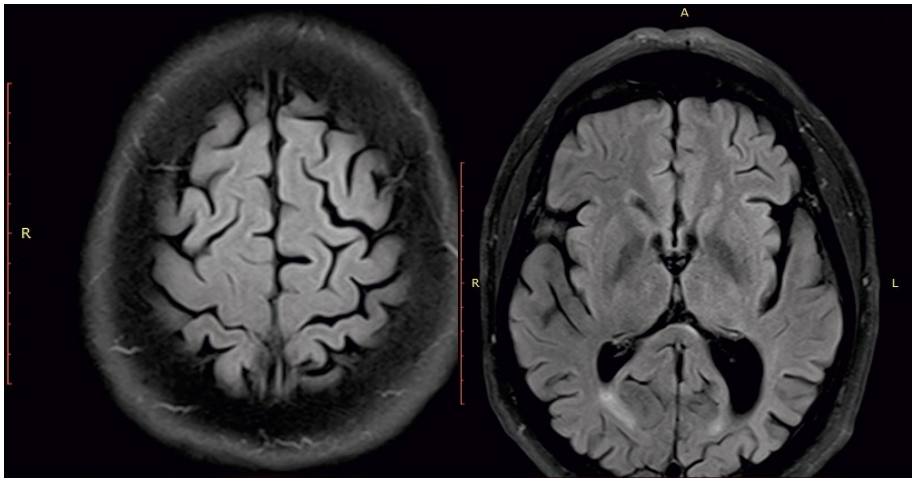

Figure 2. Cortico-basal syndrome with asymmetrical cortio-subcortical atrophy of left hemisphere

their clinical usefulness critically discussed, by Śmiłowska et al. [26]. In this review paper one can also find case studies presenting examples of unusual, surprising imaging results in patients with clinically typical parkinsonian syndromes.

In conclusion, I would like to stress the importance of non-motor symptoms in parkinsonian disorders. NMS are common in both Parkinson's Disease and atypical parkinsonism, and they strongly influence the patient's quality of life, especially in more advanced stages.

I must emphasise that comprehensive examination of non-motor symptoms may not only help clinicians in differential diagnosis, but could also allow the introduction of more effective symptomatic treatment.

I do hope the readership of the Polish Journal of Neurology and Neurosurgery will find this second Leading Topic instructive, interesting, and useful in clinical practice.

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