Acta Neurophysiologica

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Editorial *Volume 4 Issue 4*

Non-Motor Symptoms of Parkinson's Disease

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Received Date: April 18, 2023; **Published Date:** May 17, 2023

Abbreviations: PD: Parkinson's Disease; SNPc: Substantia Nigra Pars Compacta; GP: Globus Pallidus; SNPr: Substantia Nigra Pars Reticulate; MSNs: Medium-Sized Spiny Neurons; ENS: Enteric Nervous System.

Editorial

Parkinson's disease (PD) is the second most neurodegenerative disease, initially described by James Parkinson in 1817. This disease is primarily observed in aged people, characterized by defective motor functions, cognitive failure, and non-motor symptoms. The common motor deficits are tremors at rest, slowness of movement (bradykinesia), rigidity of the extremities and neck, and minimal facial expressions. Despite motor problems, many of the non-motor symptoms, including sleep disorder, depression, anxiety, dementia, hyposmia, impaired color vision, and constipation are associated with PD that decrease the quality of life of the patients. The non-motor symptoms arise much earlier than motor deficits, which are not getting priority for the early detection of PD.

Classically, the loss of dopaminergic neurons of the substantia nigra pars compacta (SNPc) affects the inhibitory signal of the GABAergic pathway of the internuclear connections, causing impaired motor activity from the subthalamic and thalamic areas. Mutations of three distinct genes, α -*synuclein*, *Parkin*, and *DJ-1*, have been implicated in PD. Deposition of parkin, ubiquitin carboxyterminal hydrolase L1, and a-synuclein promote the occurrence of PD. Defective or misfolded α -*synuclein* protein increases their deposition in Lewy bodies, leading to the progression of apoptosis of dopaminergic neurons in the SNPc and intensification of PD pathogenesis [1].

The basal ganglia are the regulatory hub of hub of both motor and non-motor functions. Primarily, the basal ganglia regulate motor movements, but it makes several loops for modulating non-motor activity. The basal ganglia and thalamus make complex connections with the prefrontal, dorsolateral prefrontal, somatosensory and parietal cortex, oculomotor area, limbic system, and superior colliculus. These loops control the different non-motor functions. The prefrontal circuit involves in the regulation of cognitive function. Limbic connection is responsible for maintaining emotion, behavior, and motivation. Oculomotor circuit, prefrontal circuit, and connection with the superior colliculus control movement of eyelids and visual effects. The internal segment of the *globus pallidus* (GPi) and the *substantia nigra* pars reticulate (SNPr) receive two different types of inputs. Striatal medium-sized spiny neurons (MSNs) project a direct connection through excitatory dopamine receptor 1 (D1R) to the GPi and SNPr that exerts major inhibition by activating GABAergic neurons, while excitatory glutamatergic projection forms an indirect pathway. GABAergic and glutamatergic projection controls the activity of output neurons to the thalamic and brainstem areas. A group of striatal MSNs innervates the inhibitory D2R expressing external segment of the *globus pallidus* (GPe) that makes an indirect connection to the GPi and SNPr [2]. Intrneuronal excitatory and inhibitory connections regulate the functions of different output circuits. Therefore, loss of dopaminergic neurons in PD exhibit both motor and non-motor symptoms.

Many of the non-motor symptoms are neurological problems. Basal ganglia are associated with behavioral and memory functions. PD patients exhibit different neuropsychiatric problems, including anxiety, depression, psychosis, dementia, cognitive impairment, hedonistic and homeostatic

dysfunction [3]. Alterations in brain monoamines levels in the different brain regions are associated with depression. An imaging study revealed that loss of white matter in cortico-limbic regions causes weak dopaminergic signaling for the regulation of mood, motivation, and reward, leading to the advancement of PD-related depression [4]. Raphe nuclei are the site of major serotonergic outflows that are also connected with the basal ganglia. Loss of serotonin in the interneuronal connections promotes depression. Degenerated raphe nuclei were observed in postmortem brain tissue of PD patients [5]. Anxiety disorders are prevalent in female PD patients. Both anxiety and depression occur before the onset of motor problems, indicating extra nigrostriatal pathologies. The presence of Lewy bodies in the frontal, temporal, parietal, and visual cortex and the limbic area (amygdala) promotes dementia, psychotic disorders, and visual and auditory problem [6].

A deficiency of dopaminergic signals and reduction in cortical cholinergic activity create impairments in frontostriatal functions that intensify the cognitive disorder. Sleep disorder in PD patients is influenced by PD-induced circadian rhythm dysfunction. Drowsiness, insomnia, low-duration REM sleep, and fragmented sleep are common problems in PD patients [7]. The interneuronal connections among the hypothalamus, basal ganglia, reticular formation, and locus coeruleus are affected by impaired dopaminergic and serotonergic signaling, suggesting nighttime insomnia and daytime drowsiness and sleepiness [8]. Many patients feel olfactory deficits, specifically hyposmia. This symptom appears at the initial stage of dopamine deficiency and can be treated as a biomarker of PD. Lewy bodies and Lewy neuritis spread in the olfactory bulb and olfactory cortex, leading to the progression of hyposmia. Moreover, the numbers of mitral cells, substance-P-containing cells, and the levels of calcium-binding protein also tend to decrease in the olfactory bulb in PD. PD patients suffer from visual disturbance [9]. Deposition of Lewy bodies in the occipital cortex and the retinal neurons potentiate visual disturbance, like diplomia, poor visual acuity, and visual hallucination.

Several peripheral disorders are the common non-motor symptoms in PD. PD patients have been suffering from the pain-related problems. Degeneration of dopaminergic neurons alters sensory perceptions and decreases pain thresholds for pain perception. PD affects serotonergic raphe nuclei and the noradrenergic locus coeruleus, which can intensify pain sensation. PD patients show increased frequency and urgency of urination. Basal ganglia maintain a balance between inhibitory and facilitatory reflex of micturition. The D1 receptor exerts an inhibitory response, while the D2 receptor facilitates the process. Loss of dopaminergic activity causes bladder dysfunction and deregulates the micturition reflex [10]. Excessive salivation, dysphagia, early satiety, and constipation-like abnormalities are common problems in PD patients. Constipation may arise a decade before the onset of motor deficit [11]. Basal ganglia have some association with the brainstem, particularly with the superior and inferior colliculi, pedunculopontine nucleus, parabrachial complex, various pontine and medullary reticular nuclei, and enteric nervous system (ENS) via the vagus nerve [2].

The problem in this circuit in PD may cause different systemic disorders. Approximately 80% of PD patients suffer from cardiac problems and orthostatic hypotension. Nocturnal hypertension in PD patients increases the risk of stroke and cardiovascular disorders. Asymptomatic tachycardia may consider a marker of early PD detection [12]. Gut microbiota modulates the functions of ENS and the brain via the gut-brain axis. It is suggested that the formation of α-synuclein starts in the gut before deposition in the brain. Moreover, gut microbiota modulates the metabolism of monoamine neurotransmitters, specifically serotonin. Collectively, the gut-brain axis has a deep impact on brain functions and the detection of α-synuclein in the GI system implicates PD development.

Although non-motor symptoms arise earlier than the appearance of motor deficit, still, motor disorders, like bradykinesia, tremor, and rigidity are considered during the diagnosis of PD. Consideration of different non-motor symptoms will be helpful for the detection of PD at the initial stage. Different strategies of treatment, like gene therapy, stem cell therapy, grafting of dopaminergic cells, and deep brain stimulation have been implicated, but administration of levodopa is the common treatment regimen. Certain symptomatic treatments for non-motor problems can increase the quality of life of PD patients. Antidepressant drugs, such as tricyclic compounds, monoamine oxidase, and selective serotonin reuptake inhibitors inhibitor can be used for the treatment of PD-related depression. Finally, it can say that PD is not a specific motor disorder but can be considered a systemic disease, where different systems are affected; thus, multiple approaches in the treatment schedule will give more benefits to PD patients.

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