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REVIEW ON CLINICAL FEATURE, PATHOPHYSIOLOGY AND MANAGEMENT OF MOTOR DECLINE IN PARKINSON DISEASE

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ABSTRACT

Parkinson's disease is one of the most common neurodegenerative Disease and characterized by the progressive loss of dopamine (DA) neurons in midbrain substantia nigra (SN) and the consequent movement malfunction. The dopaminergic neuronal degeneration and loss is closely associated with activation of caspase-3 and decrease in expression of brain-derived neurotrophic factor (BDNF). Caspase activation and decrease in BDNF expression are the early signals of dopaminergic neuronal apoptosis. Parkinson disease is one of the most common age-related brain disorders. It is defined primarily as a movement disorder, with the typical symptoms being resting tremor, rigidity, bradykinesia and postural instability, and is pathologically Characterized by degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (misfolded α-synuclein) in the surviving neurons. In addition to the defining dopamine-related motor symptoms, however, Parkinson's disease is increasingly recognized as a heterogeneous multisystem disorder involving other neurotransmitter systems, such as the serotonergic, noradrenergic and cholinergic circuits. Thus, a wide variety of nonmotor symptoms (NMS) linked with these neurotransmitters are commonly observed in patients with PD. In this review we have discussed about clinical feature, pathophysiology and management of motor decline in parkinson's disease.

KEYWORDS: Parkinson Disease, Neurodegenerative Disease, Dopamine, Motor Decline.

INTRODUCTION: Parkinson's disease (PD) is one of the most common neurodegenerative disease and characterized by the progressive loss of dopamine (DA) neurons in midbrain substantia nigra (SN) and the consequent movement malfunction.[1] Although the mechanisms

that drive the gradual nature remain elusive, to date, a great amount of evidence has documented microglia mediated neuroinflammation is implicated in PD.[2,3] Parkinson's disease is a non-hereditary disease of unknown etiology that usually appears after the age of 50 and affects both sexes equally.[4] It is well-known to be characterized by a progressive degeneration of dopaminergic (DAergic) neurons (70–75%) in the substantia nigra *pars compacta* (SNc), which results in a dopamine (DA) depletion in the striatum.[5] However, it is misleading to reduce PD to a malady of the SNc. Indeed, it has been repeatedly shown over the last 50 years that noradrenergic (NAergic) cells from the locus coeruleus (LC) also degenerate in the disease.[6,10] The neuronal loss in the LC is greater (83%) than in the SNc (78%).[11] This is in agreement with the Braak's theory.[12] that proposed a progressive caudo-rostral alteration of monoaminergic centers in the symptomatology of PD with a degeneration of LC NAergic neurons occurring before that of SNc DAergic neurons. Parkinson's symptoms usually begin gradually and get worse over time. As the disease progresses, people may have difficulty walking and talking. They may also have mental and behavioural changes, sleep problems, depression, memory difficulties, and fatigue. Both men and women can have Parkinson's disease. However, the disease affects about 50 percent more men than women. One clear risk factor for Parkinson's is age. Although most people with Parkinson's first develop the disease at about age 60, about 5 to 10 percent of people with Parkinson's have "early-onset" disease, which begins before the age of 50. Early-onset forms of Parkinson's are often, but not always, inherited, and some forms have been linked to specific gene mutations.[13]

Parkinson's disease signs and symptoms can be different for everyone. Early signs may be mild and go unnoticed. Symptoms often begin on one side of your body and usually remain worse on that side, even after symptoms begin to affect both sides.

Parkinson's signs and symptoms may include:[14]

- **Tremor.** A tremor, or shaking, usually begins in a limb, often your hand or fingers. You may rub your thumb and forefinger back and forth, known as a pill-rolling tremor. Your hand may tremble when it's at rest.
- **Slowed movement (bradykinesia).** Over time, Parkinson's disease may slow your movement, making simple tasks difficult and time-consuming. Your steps may become shorter when you walk. It may be difficult to get out of a chair. You may drag your feet as you try to walk.

- **Rigid muscles.** Muscle stiffness may occur in any part of your body. The stiff muscles can be painful and limit your range of motion.
- **Impaired posture and balance.** Your posture may become stooped, or you may have balance problems as a result of Parkinson's disease.
- **Loss of automatic movements.** You may have a decreased ability to perform unconscious movements, including blinking, smiling or swinging your arms when you walk.
- **Speech changes.** You may speak softly, quickly, slur or hesitate before talking. Your speech may be more of a monotone rather than have the usual inflections.
- **Writing changes.** It may become hard to write, and your writing may appear small.

Causes of Parkinson's Disease

Parkinson's disease is a neurological disorder that develops when changes occur in the brain. Precisely why it happens is unclear, but scientists have identified some variations that occur.

Low dopamine levels

Parkinson's disease symptoms mainly result from low or falling levels of dopamine,[15] a neurotransmitter. It happens when cells that produce dopamine die in the brain. Dopamine plays a role in sending messages to the part of the brain that controls movement and coordination. Therefore, low dopamine levels can make it harder for people to control their movement. As dopamine levels continue to fall, symptoms gradually become more severe.

Low norepinephrine levels

Parkinson's disease may also involve damage to the nerve endings that produce another neurotransmitter, norepinephrine, which contributes to blood circulation and other automatic body functions.[16] Low levels of norepinephrine in Parkinson's disease may increase the risk of both motor and nonmotor symptoms, such as: stiffness and rigidity, postural instability, tremor, anxiety, difficulty focusing, dementia, depression. This may explain why people with Parkinson's disease commonly experience orthostatic hypotension. This refers to when a person's blood pressure changes when they stand up, leading to light-headedness and a risk of falling.[17]

Lewy bodies

A person with Parkinson's disease may have clumps of protein known as alpha-synuclein, or Lewy bodies, in their brain the accumulation of Lewy bodies can cause a loss of nerve cells,

leading to changes in movement, thinking, behaviour, and mood.[18] It can also lead to dementia. Lewy body dementia is not the same as Parkinson's disease, but people may have both as the symptoms are similar.[19]

Genetic factors

Experts have identified changes in several genes that appear to have links with Parkinson's disease, but they do not consider it a hereditary condition. Genetic factors appear to cause only 10% of cases, mostly among people with early onset disease.[15]

Autoimmune factors

In a 2017 study, Aree witoelar and his team.[20] found a possible genetic link between Parkinson's disease and autoimmune conditions, such as rheumatoid arthritis. In 2018, researchers investigating health records in Taiwan found that people with autoimmune rheumatic diseases had a 1.37-higher chance of also having Parkinson's disease.[21]

Clinical Features And Diagnosis of Parkinson's Disease

Cognitive impairment of PD has been paid more attention to in recent years. However, motor symptoms and cognitive deficits in PD are heterogeneous in age of onset.[22] clinical manifestations.[23] and disease progression.[24] PD patients are mainly divided into two phenotypes based on motor symptoms: tremor-dominant (TD) and postural instability gait difficulty (PIGD) phenotypes.[25] Previous studies showed that PIGD phenotype or change from TD to PIGD phenotype served as a higher risk of cognitive decline and the development of dementia.[26] in later stage of PD.[27] However, the above studies were small size, and focused on the clinical manifestations. The current study explored the relationship between different motor phenotypes and cognitive function in PD patients and the underlying mechanisms. Microglia, the resident immune cells in the central nervous system, present a series of changes in morphology and function after activated by an acute insult to the CNS.[28,29] Upon activation by brain injury or inflammogen exposure, microglia produce and secrete a great deal of pro-inflammatory factors, such as interleukin (IL)-1b, tumor necrosis factor a (TNF-a) and nitric oxide (NO). Routine clinical evaluation of patients with PD should always include an assessment of blood pressure (lying, sitting, and 3-minute standing). Although orthostatic hypotension is diagnosed with a reduction of s-SBP of at least 20 mmHg within 3 minutes of standing, lesser drops in s-SBP may still be symptomatic, and orthostatic hypotension may not occur until beyond 3 minutes.[30,31] Heart rate should normally rise 4–6 beats per minute upon standing, with a greater increase in response to

orthostatic hypotension; with autonomic dysfunction, this cardioacceleratory response is typically blunted.[30] Symptomatic nOH may not always correlate with isolated measurements of s-SBP, due to the diurnal circadian rhythm of blood pressure and also to the marked fluctuations in blood pressure that occur throughout the day. Twenty-four-hour ambulatory blood pressure monitoring can be helpful in the evaluation of patients with symptomatic nOH to better understand temporal fluctuations in blood pressure, especially when clinical symptoms do not regularly correlate with sporadic blood pressure measurements.[32]

Currently, positron emission tomography has an important value for the early diagnosis of PD, however, its limitations of high price, time-consuming, strict technical requirements and exposure to the tracer highly restrict its wide application clinically. Transcranial ultrasound (TCS), a non-invasive neuroimaging technique, is a useful tool for providing the evidences for the early diagnosis and differential diagnosis of PD. Although investigations on PD patients with TCS is increasing, however, most of them mainly focused on the relationship between hyper echogenicity in SN and disease duration or severity of MS.[33-37]

Neuropathology of Parkinson's Disease

Although our appreciation for the breadth of systems affected by PD is growing,[38] PD still is characterized by prominent loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc) in relatively early stages of the disease, depletion of striatal dopamine (DA), and the presence of intraneuronal inclusions called Lewy bodies (LBs).[39,40] PD is the most common idiopathic cause of parkinsonism. Other diseases involving the nigrostriatal DAergic system, which also produce Parkinsonism, include progressive supranuclear palsy, multiple system atrophy (a syndrome consisting of extrapyramidal, cerebellar, and/or autonomic features), corticobasal degeneration, and Dementia with Lewy Bodies. The neuropathological hallmark of PD is accumulation of LBs in the SNpc or locus ceruleus (LC).[41,42] This association is so strong that incidental LB disease, which occurs in about 7–10% of older individuals,[43] is regarded by many investigators as a preclinical stage of PD. However, autopsy findings in individuals who die of PD not only include LB accumulation in SNpc and LC with extensive neurodegeneration at these sites, but also degenerative changes in other regions of the brain including the dorsal motor nucleus of the glossopharyngeal and vagal nerves, some subnuclei of the reticular formation and the raphe system, the magnocellular nuclei of the basal forebrain, and many subnuclei of the thalamus and amygdala.[44] In addition, cases with severe damage usually show neurodegeneration and LBs

in neocortical regions.[45,46] Braak and colleagues conducted elegant studies using autopsied brain from PD patients and neurologically normal controls.[44,47] They concluded that pathological changes in PD follow a stereotypical course as the disease progresses. Braak Stages 1 and 2 show LB pathology and associated neuronal degeneration confined to the medulla oblongata and olfactory bulb, where many nuclei are involved, including the spindle-shaped projection neurons of the dorsal IX/X motor nucleus and, in some instances, in projection cells of the intermediate reticular zone. Braak Stages 3 and 4 define PD cases with involvement chiefly confined to the lower and upper brain stem, e.g., SNpc, in the absence of cortical lesions or with initial involvement of the anteromedial temporal mesocortex. Finally, Braak Stages 5 and 6 indicate severe involvement of brain, including neocortical areas such as parietal and frontal cortex. Others have largely confirmed these studies in patients with PD.[48] Numerous clinico-pathologic studies have sought the structural bases of cognitive impairment The hallmark of any neurodegenerative disease is a selective neuronal loss, and loss in PD is most marked in the substantia nigra pars compacta. It has been known for many years, however, that Lewy bodies in PD extend well beyond the substantia nigra. Based on the distribution of alpha-synuclein pathology, Braak and coworkers have proposed a staging scheme for PD. In this scheme, neuronal pathology occurs early in the dorsal motor nucleus of the vagus in the medulla and the anterior olfactory nucleus in the olfactory bulb. As the disease progresses, locus ceruleus neurons in the pons and then dopaminergic neurons in the substantia nigra are affected. In later stages, pathology extends to the basal forebrain, amygdala, and the medial temporal lobe structures, with convexity cortical areas affected in the last stages. Subsequently, there have been proposals that autonomic neurons in the peripheral nervous system may be affected by the involvement of the central nervous system (CNS), which has prompted recognition that PD is a multiorgan disease process, not merely a disorder of the CNS. Moreover, it has fed the debate on cell-to-cell transmission of unknown transmissible agents, from the gut onwards to the brain through retrograde transmission in the vagus nerve.[15]

Management of Motor Decline In Parkinson's Disease

Parkinson's disease (PD) is a degenerative disorder of the central nervous system that impairs motor skills, cognitive processes, and other functions. Motor symptoms are characterized by tremor, rigidity, bradykinesia, and postural instability. Among non-motor symptoms are autonomic dysfunction, sensory and sleep difficulties, cognitive, and neurobehavioral problems, including dementia and depression. There is growing evidence that additional loss

of noradrenaline (NA) neurons of the locus coeruleus, the principal source of NA in the brain, could be involved in the clinical expression of motor as well as in non-motor deficits. Several studies revealed the existence of a correlation between the severity of DA and noradrenaline depletions with the severity of PD neurological symptoms.[49,50] While the DAergic system is the main target of the pharmacological approaches to PD, corrections of the NA alterations inherent to the disease could improve the efficacy of current therapies. Noradrenaline release exerts potent neuromodulatory effects on synaptic transmission, changing the membrane potential, excit-ability of neurons and synaptic plasticity *via* adrenergic receptors (ARs). Two subtypes of ARs have been described: alpha ARs (α1 and α2) and beta ARs (β1, β2, and β3). These ARs are found throughout the brain including the striatum and substantia nigra. α2ARs are distributed widely within the basal ganglia, including the substantia nigra.[51] Mavridis et al. (1991) have suggested that the activation of α1ARs, which results in an increase in NAergic tone, facilitates locomotor activity, and inversely, α2ARs activation, by decreasing NAergic tone, inhibits locomotor activity.[52] In PD, hypoactivation of NAergic tone may be involved in the manifestation of tremor and rigidity. In the reserpine rat, yohim-bine, an α2ARs antagonist blocked tremor and improved rigidity but not hypokinesia.[53] In the 6-OHDA rat and MPTP monkey models of PD, blockade of α2ARs by idazoxan improved motor disabilities,[54,55] in a manner comparable to that induced by a minimal dose of l-Dopa.[56] Although these findings provide support for the therapeutic potential of α2ARs in the treatment of PD, idazoxan as a monotherapy in PD patients did not display anti-parkinsonian actions.[57,58] However, co-administra-tion of idazoxan with l-Dopa can provide an anti-parkinsonian action lasting more than twice the duration obtained with l-Dopa alone. Interestingly, the α2AR agonist clonidine and βARs blockers like propranolol are effective in treating akathisia and tardive dyskinesia.[59] However, clonidine is more often used to treat attention deficit in PD. Attention accuracy was not affected by withdrawal of DAergic drugs in mild or severe PD patients. Clonidine retarded accuracy of performance in a difficult attention test in PD patients.[60] It seems that the NAergic system via α2AR may act differentially on the manifestation of motor and non-motor symptoms in PD. α2AR antagonism would lead to motor amelioration whereas α2ARs agonism would have non-motor benefits. Non-motor symptoms are also improved by the use of selective α1AR agonists. For example, naphtoxazine may improve performance in some cognitive tests of "frontal functions," including the Stroop and the odd-man-out tests, which have been previously found to be affected in PD.[61]

Conflict of Interest

There is no conflict of interest.

ABBREVIATIONS

PD: Parkinson's Disease.

ARs: Adrenergic Receptors.

CNS: Central Nervous System.

DA: Dopamine.

IL: Interleukin.

TNF-a: Tumor necrosis factor a.

NO: Nitric oxide.

SNc: Substantia nigra pars compacta.

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