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Parkinson's Disease: A Review of Motor and Nonmotor Symptoms

Abstract: Although Parkinson's disease (PD) is considered a motor system disorder caused by the degeneration of dopaminergic neurons in the substantia nigra, it is also associated with a wide range of nonmotor symptoms. Some of these symptoms include sensory dysfunction, depression, and dementia. Because the exact biochemical pathways for these nonmotor symptoms are not yet completely understood, current treatment options for PD focus primarily on relieving motor symptoms of the disease and leave the nonmotor symptoms inadequately treated. It is important to better understand nonmotor symptoms not only because these symptoms are associated with the rapid progression of PD, but also because they often precede the more obvious motor symptoms such as bradykinesia, tremors, and rigidity. Thus non-motor symptoms could be used for early diagnosis of PD.

Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease that affects approximately 2.0% of adults over the age of 65 (Lieberman 2006), and 1 in 300 in the general population (Schapira and others 2006). PD is most commonly linked with a degeneration of the dopamine synthesizing neurons in the substantia nigra that project to the striatum, a degeneration that causes an overall loss in motor function, as presented by tremors and rigidity in movement (Dauer and Przedborski 2003, Lieberman 2006, McGeer and McGeer 2004, Mendez and others 2008, Poewe 2008, Richardson and others 1997, Schapira and others 2006, Shahed and Jankovic 2007). Recent data points to the possibility that chronic inflammation and sustained immune responses in the brain in cause dopaminergic cell death in PD (McGeer and McGeer 2004). However, PD affects more than the dopaminergic systems, including areas of the brain that are

not directly related to motor control, such as the amygdala and peripheral autonomic nervous system (Lieberman 2006, Poewe 2008). Defects in these areas lead to the nonmotor symptoms that affect many PD patients, such as pain, cognitive and sensory dysfunction (Poewe 2008), as well as the depression and other mood disorders seen in 20-40% of PD patients (Lieberman 2006). Thus, the aim of this review is to examine both the motor and nonmotor symptoms of PD and to review the current understanding of the associated biochemical pathways.

Motor Symptoms

PD is often associated with overt motor symptoms that include the asymmetric onset of bradykinesia, tremors, and rigidity due to the degeneration of dopaminergic nigrostriatal neurons of the basal ganglia (Dauer and Przedborski 2003, Lieberman 2006, McGeer and McGeer 2004, Mendez and others 2008, Poewe 2008, Richardson and others 1997, Schapira and others 2006, Shahed and Jankovic 2007). Bradykinesia, or a slowness of movement, is a trademark of basal ganglia disorders and is a clearly identifiable symptom of PD (Shahed and Jankovic 2007). With this symptom, PD patients experience a decrease in dexterity and fine motor control. Of all the motor symptoms, the "rest tremor" is the best known and is the classic motor dysfunction associated with PD. This type of tremor occurs when the muscle is at rest but decreases with voluntary movement (Dauer and Przedborski 2003). Tremors can be observed in the hands, lip, chin, jaw and legs, but this symptom almost never involves the neck-head regions or the voice (Shahed and Jankovic 2007). Although the tremors usually remain asymmetric, as PD progresses it may manifest increasingly as bilateral tremors (Shahed and Jankovic 2007). The pathophysiology of the rest tremors is not fully understood, but it has been generally accepted to

be caused by atypical synchronous oscillating neuronal activity within the basal ganglia (Shahed and Jankovic 2007). Tremors often accompany rigidity, or the resistance seen in the passive movement of a limb (Shahed and Jankovic 2007). Rigidity may also play a role in the recurrent pain afflicting PD patients. When rigidity increases with reinforcing movements and is seen ipsilateral to the rest tremor, an early diagnosis of PD is strongly supported (Shahed and Jankovic 2007). At later stages, postural instability develops as one of the major devastating symptoms of PD and a main cause of falls in PD patients (Shahed and Jankovic 2007). Postural instability contributes to gait abnormalities seen in patients with PD, who often shuffle with slow, narrow steps in a characteristically stooped posture (Shahed and Jankovic 2007).

Neuronal Mechanisms Governing Motor Symptoms

Smooth, well-coordinated muscle movement is determined by the direct and indirect output pathways of the basal ganglia to the globus pallidus and the substantia nigra (Richardson and others 1997). While the direct pathways disinhibit the thalamocortical neurons, the indirect pathways inhibit them (Richardson and others 1997). These neurons are influenced by excitatory inputs from the cortex and thalamus and by regulatory control through dopamine release from the nigrostriatal neurons (Richardson and others 1997). In PD, when nigrostriatial neurons die, dopamine denervation occurs. This degeneration in turn causes an imbalance in the activity of the two basal ganglion pathways, an imbalance that is thought to correlate with the motor symptoms seen in PD (Richardson and others 1997, Schapira and others 2006).

Neuronal loss observed in brains of PD patients may be due to the presence of Lewy bodies, or masses of fine fibers, as illustrated in Figure 1. Lewy bodies serve as defining histological characteristics of PD and have been found in various areas of the central and peripheral nervous systems in PD patients (Wakabayashi and others 2007). The extensive distribution of these Lewy bodies may also be linked to the wide range of motor and non-motor symptoms seen in PD patients (Wakabayashi and others 2007).

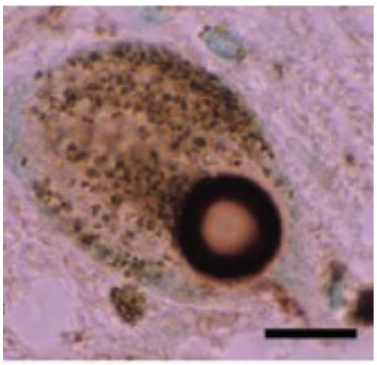

Figure 1. A typical Lewy Body found in the substantia nigra. Bar, 10 □m.

(Wakabayashi and others 2007)

In PD, Lewy bodies are mainly comprised of a presynaptic nerve terminal protein known as □-synuclein (Wakabayashi and others 2007). In a healthy brain, □-synuclein is found in presynaptic terminals and is absent in the neuronal cytoplasm. In the normal aging process, the protein □-synuclein accumulates non-pathologically in the substantia nigra, but not in other dopamine neuronal nuclei (Mendez and others 2008). However, in PD, □-synuclein develops inside nerve cells as pale and diffuse cytoplamsic inclusions, thus displacing other components of the cell (Mendez and others 2008, Schapira and others 2006). The molecular components of □-synuclein are cytotoxic, and as long as these toxins are made, Lewy bodies expand. This causes an excessive build-up of protein aggregates in the host cell and leads to cell death.

Early Nonmotor Symptoms

Nonmotor symptoms afflicting patients with PD often precede the more obvious motor symptoms associated with the disease. Olfactory dysfunction, for example, eventually effects up to 90% of patients with PD (Poewe 2008, Chaudhuri and others 2006). Recent data have been found to show a relationship between the decreased sensitivity to odors and an increased risk of developing PD (Chaudhuri and others 2006). One recent hypothesis suggests that the Lewy body pathology develops only after the olfactory system and lower brainstem areas have become affected (Poewe 2008). Another common early symptom seen in PD patients is constipation (Chaudhuri and others 2006). This may be one of the earliest symptoms of Lewy body degeneration as seen in PD. Lewy bodies, which have been found to affect the peripheral autonomic nervous system, also affect the colonic sympathetic denervation that has been associated with a prolonged intestinal passage time, a condition leading to constipation (Poewe 2008). Indeed, constipation has been reported as one of the main complaints preceding the classic motor symptoms in about half of PD patients (Poewe 2008). In one longitudinal study following the bowel habits of 7000 men over the course of 24 years, those with initial constipation were three times more likely of developing PD over a mean time period of 10 years (Chaudhuri and others 2006). Therefore, the identification of early non-motor symptoms, such as the decrease in function of the olfactory system and the onset of constipation, could lead to an earlier diagnosis of PD.

Neuropsychiatric Dysfunctions

PD patients are affected not only by somatic nonmotor symptoms but also by neuropsychiatric nonmotor symptoms ranging from apathy and depression to anxiety. Studies have indicated that depression, characterized by sadness, remorse, and lack of confidence (Chaudhuri and others 2006), often occurs alongside anxiety in PD patients (Lieberman 2006). Depression or panic attacks have been seen to antedate the onset of motor symptoms in up to 30% of patients with PD (Poewe 2008). Separate from the depression that is usually seen in PD patients, apathy has also been recognized as a unique symptom of PD (Chaudhuri and others 2006). Apathy is defined as the presence of reduced motivation that is not related to a decrease in conscious state or emotional distress (Lieberman 2006). It could be caused by the neuronal degeneration in the reward centers of the brain, such as the dopaminergic projections between the ventral tegmentum and nucleus accumbens (Chaudhuri and others 2006). Anxiety and apathy are both commonly seen early on in PD (Poewe 2008) and can be preclinical risk factors (Chaudhuri and others 2006).

Neuronal Mechanisms Governing Depression as seen in PD

Depression in PD patients may be caused less by a reaction to the disease itself than by the more biological factor of damage to limbic noradrenergic and dopaminergic mechanisms and to serotoninergic neurotransmission (Chauduri and others 2006). This may occur because neurons in the ventral mesencephalon, located near the substantia nigra, project into limbic and cortical structures that control cognition, emotions, and reward-seeking behavior (Lieberman 2006). There is a greater degeneration of dopaminergic neurons in this area in PD patients who

have depression than in those who do not (Lieberman 2006). Furthermore, depression associated with PD is associated with a decrease of serotonin in the dorsal raphe nucleus and of norepinephrine in the locus coeruleus (Lieberman 2006). The locus coeruleus projects to the anterior cingulated gyrus, the hippocampus, the ventral striatum, and the amygdala (Lieberman 2006). Thus, PD may be linked to depression biologically because the amygdala, a region of the brain closely associated with motivation and emotional behavior, is atrophied and contains Lewy bodies in PD patients with depression (Lieberman 2006). In fact, depression does not necessarily increase as the severity of PD increases. Therefore, this relatively weak correlation suggests that depression is not a psychological reaction to PD but part of PD itself (Lieberman 2006).

Cognitive Impairment

Dementia, another nonmotor symptom, is seen in up to 40% of PD patients—a rate about six times greater than that of healthy individuals (Chaudhuri and others 2006, Poewe 2008). Dementia is clinically characterized by impairment to visuospatial abilities, memory, and the executive attention in the control of thoughts and emotions (Chaudhuri and others 2006, Poewe 2008). Personality disorders, hallucinosis, and psychosis are also seen in PD patients afflicted with dementia (Poewe 2008). Dementia advances gradually but is associated with a rapid progression of disability, which often puts many PD patients at risk of nursing home placement. Some hypotheses propose that depression antecedes dementia (Lieberman 2006).

Neuronal Mechanisms Governing Dementia as seen in PD

The underlying mechanisms of dementia in PD are not yet fully understood. There have been hypotheses that Lewy body degeneration is a main driving factor for the development of dementia in PD (Poewe 2008). There have been studies linking the presence of Alzheimer-type changes in the brain, such as senile plaques, with the □-synuclein of Lewy bodies (Caballol and others 2007). In PD patients with dementia, there has been observed a decrease in hippocampal volume that is comparable in extent to the decrease seen in individuals afflicted with Alzheimer's disease (Chaudhuri and others 2006). Connections have also been made between the severity of motor symptoms and of intellectual impairment (Huber and others 1988). Using the Mini-Mental State examination to assess intellectual status, Huber and others found a significant negative correlation between intellectual impairment and the severity of both rigidity and bradykinesia. This seemed to suggest that these motor symptoms were related to the increased intellectual impairment seen in patients with PD.

Discussion

PD, a disease that is usually categorized as a motor system disorder, also has many nonmotor symptoms. Neurodegeneration in PD affects the central nervous system as well as the peripheral nervous system, leading to a wide range of classic motor symptoms, such as bradykinesia, tremors, and rigidity (Lieberman 2006, McGeer and McGeer 2004, Mendez and others 2008, Poewe 2008, Richardson and others 1997, Schapira and others 2006, Shahed and Jankovic 2007), in addition to nonmotor symptoms. Many non-motor symptoms, such as sensory dysfunction and depression, often precede the more obvious motor symptoms.

Therefore, it is important to pay attention and correctly identify early non-motor symptoms, as they could lead to an earlier diagnosis of PD.

Although many drugs are currently prescribed to relieve the classic motor system malfunctions seen in PD patients, these drugs often worsen nonmotor symptoms and decrease the quality of life (Poewe 2008, Richardson and others 1997, Schapira and others 2006). While newer treatments are beginning to treat both motor and nonmotor symptoms, there are currently no medications that stop the degeneration of dopaminergic neurons (Dauer and Przedborski 2003). Thus, future studies that aim to gain a better understanding of the relationship between the biochemical pathways of PD and the motor and nonmotor symptoms are warranted. Furthermore, the ability to pinpoint those neurons most susceptible to neurodegeneration could lead to more effective treatment options for relieving both motor and nonmotor symptoms in PD.

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