PARKINSON'S DISEASE

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SUMMARY – Parkinson's disease is one of the most common neurodegenerative diseases caused by degeneration of dopaminergic neurons in substantia nigra. The neuropathologic hallmark of Parkinson's disease is the presence of Lewy bodies composed mostly of alpha-synuclein and ubiquitin. It is believed that the occurrence of Parkinson's disease is due to a combination of genetic and environmental factors, but the exact mechanism of Parkinson's disease development is not fully elucidated. The most characteristic motor symptoms for Parkinson's disease include bradykinesia, rigidity, resting tremor and postural instability, while many patients also have non-motor signs and symptoms. The key therapeutic agent in the treatment of Parkinson's disease is L-dopa, and the others are dopaminergic agents, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine and anticholinergic agents.

Key words: *Parkinson disease – etiology; Parkinson disease – diagnosis; Parkinson disease – therapy*

Introduction

Parkinson's disease (PD) is named after James Parkinson, an English physician who described it in his work entitled An assay on the shaking palsy from 1817. The disease is a progressive neurodegenerative disorder caused by the loss of dopaminergic nigrostriatal neurons. The most prominent clinical features include resting tremor, rigidity, bradykinesia and postural instability. Idiopathic PD is primarily caused by degeneration of dopaminergic nigrostriatal neurons. First clinical symptoms of PD occur after at least 60%-80% of nigrostriatal dopaminergic neurons have lost their function[1].

Pathophysiology

The major neuropathologic finding in PD is the loss of pigmented dopaminergic neurons in the pars compacta of substantia nigra and the presence of Lewy bodies. Lewy bodies are concentric, eosinophilic, cytoplasmic inclusions with peripheral halos and dense cores composed mainly of alpha-synuclein. Lewy bodies stain for alpha-synuclein and also for ubiquitin. The presence of Lewy bodies within pigmented neurons of the substantia nigra is characteristic of idiopathic PD. Lewy bodies are also found in other parts of the brain such as locus ceruleus, nucleus basalis, intermediolateral column of the spinal cord, cortex, and other areas. Braak *et al.* demonstrated the Lewy body pathology in PD to begin in the olfactory bulb and lower brainstem (Braak stage 1), ascending to upper brainstem (Braak stage 2), midbrain and nigrostriatal dopaminergic neurons (Braak stage 3), archicortex (Braak stage 4), and primary and associative parts of the cortex (Braak stages 5 and 6)[2]. Early stages (1-2) are associated with symptoms such as loss of the sense of smell and rapid eye movement (REM) sleep behavior disorder (RBD)[3]. Braak stage 3 correlates with development of motor symptoms when patients may exhibit bradykinesia, rigidity and tremor.

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In Braak stages 4, 5 and 6, patients may exhibit cognitive dysfunction and dementia.

This sequence of Lewy body pathology favors olfactory testing as a possible screening method for preclinical PD. Impaired olfactory function was found in 40 of 49 (82%) PD patients. The sensitivity of olfactory dysfunction for PD was 0.82, specificity 0.82 and predictive value 0.77[4].

Epidemiology

PD is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60. The incidence has been estimated to 4.5-21 cases *per* 100,000 population *per* year. Estimates of PD prevalence range from 18 to 328 *per* 100,000 population, with most studies yielding a prevalence of approximately 120 *per* 100,000. The incidence and prevalence of PD increase with age. PD is about 1.5 times more common in men than in women. The average age at onset is 60 years, while the onset in persons younger than 40 is uncommon[5].

Etiology

Idiopathic PD is believed to be due to a combination of genetic and environmental factors. Environmental risk factors associated with the development of PD include use of pesticides, living in a rural setting, consumption of well water, exposure to herbicides, and proximity to industrial plants or quarries, while cigarette smoking and caffeine consumption have some protective role[6,7].

Several individuals have been identified that developed parkinsonism after self-injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[8].

The oxidation hypothesis suggests that dopamine oxidative metabolism produces free radicals that could play a role in the development or progression of PD. The oxidative metabolism of dopamine leads to the formation of hydrogen peroxide. Hydrogen peroxide normally is cleared rapidly by glutathione. If hydrogen peroxide is not cleared adequately, it may lead to the formation of highly reactive hydroxyl radicals that can react with cell membrane lipids to cause lipid peroxidation and cell damage. In PD, the levels of reduced glutathione are decreased, suggesting the loss of protection against formation of free radicals. Iron is increased in the substantia nigra and may serve as a source of donor electrons, thereby promoting the formation of free radicals. Increased iron accumulation in substantia nigra could be the cause of hyperechogenicity seen in most PD patients on transcranial sonography[9]. Thus, PD is associated with an increased dopamine turnover, decreased protective mechanisms (glutathione), increased iron (a pro-oxidation molecule), and evidence of increased lipid peroxidation.

Mutations in the alpha-synuclein gene can cause PD. It is now clear that these mutations are an exceedingly rare cause of PD. Alpha-synuclein is a major component of Lewy bodies in all PD cases. Lewy bodies contain alpha-synuclein, and most also contain ubiquitin, which conjugates with proteins targeted for proteolysis. Abnormal aggregation of alpha-synuclein into filamentous structures may precede ubiquitization. One hypothesis states that the mutation alters the configuration of alpha-synuclein from alpha helix to beta-structure that could aggregate into sheets. Therefore, PD may be associated with abnormal folding of alpha-synuclein, leading to excessive aggregation causing neuronal death. Also, PD could be caused by abnormalities of the proteosome system responsible for clearing abnormal proteins.

Clinical Features

PD may have a long premotor stage. Features that commonly precede the onset of motor signs include decreased sense of smell and REM behavior disorder (RBD). RBD is a sleep disorder in which there is the loss of normal atony during REM sleep and it is common throughout the course of PD.

The onset of motor signs in PD is typically asymmetric. About 20% of patients first experience clumsiness in one hand. Over time, patients notice tremor and symptoms related to progressive bradykinesia, rigidity, and postural instability. Resting tremor usually begins in one upper extremity and initially may be intermittent. The amplitude increases with stress and resolves during sleep. Over time, axial posture becomes progressively flexed and strides become shorter. Decreased swallowing may lead to excess saliva in the mouth and drooling. Symptoms of autonomic dysfunction are common and include constipation, sweating abnormalities, sexual dysfunction, and seborrheic dermatitis[10].

Dementia generally occurs late in PD and affects 15%-30% of patients. Cognitive dysfunction within a

year of onset of motor features suggests the diagnosis of Lewy body disease.

Diagnosis

PD is diagnosed by clinical criteria; there is no definitive test for the diagnosis. Historically, pathologic confirmation of the hallmark of Lewy body on autopsy has been considered the criterion standard for the diagnosis[11]. Diagnostic criteria have been developed by the UK Parkinson's Disease Society Brain Bank[12] and National Institute of Neurological Disorders and Stroke (NINDS)[13]. Differentiating PD from other forms of parkinsonism can be challenging early in the course of the disease, when signs and symptoms overlap with other syndromes.

Therapy

Pharmacological treatment of PD includes L-dopa usually combined with 3.4-dihydroxyphenylalanine (DOPA) decarboxylase inhibitors (such as carbidopa and benserazide that reduce decarboxylation of levodopa before it reaches the brain), selective monoamine oxidase-B (MAO-B) inhibitors (selegiline and rasagiline), catechol-O-methyltransferase (COMT) inhibitors (entacapone and tolcapone), dopamine receptor agonists (pramipexole and ropirinile), amantadine and anticholinergics. Patients with PD respond to these agents with improvement in disease signs and symptoms.

Levodopa, a dopamine precursor, is considered to be the most effective antiparkinsonian agent. In randomized trials comparing levodopa and a dopamine agonist, activities of daily living and motor features of PD improved with levodopa by about 40% to 50% (as compared with approximately 30% with dopamine agonists).

Dopamine agonists are slightly less effective than levodopa, they are alternative first-line agents for PD, especially in younger patients. In general, anticholinergic agents are not used for PD because of associated adverse effects. However, they are sometimes added if tremor is particularly bothersome and unresponsive to other drugs, although evidence is lacking to support particular efficacy of these agents in treating tremor. MAO-B inhibitors and amantadine have fewer adverse effects and require little titration to reach therapeutic doses[14-17].

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Sažetak

PARKINSONOVA BOLEST

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Parkinsonova bolest je jedna od najčešćih neurodegenerativnih bolesti koju uzrokuje degeneracija dopaminergičnih neurona u supstanciji nigri. Neuropatološko obilježje Parkinsonove bolesti je nalaz Lewyjevih tjelešaca koja su najvećim dijelom građena od alfa sinukleina i ubikvitina. Pojavu Parkinsonove bolesti uzrokuje međudjelovanje genetskih čimbenika i čimbenika iz okoliša, ali točan mehanizam nastanka bolesti nije u potpunosti poznat. Najznačajniji motorni simptomi bolesti su bradikinezija, rigiditet, tremor u mirovanju i posturalna nestabilnost. Najznačajniji lijek u liječenju Parkinsonove bolesti je L-dopa, a primjenjuju se i dopaminergični agonisti, inhibitori monoaminooksidaze B (MAO-B), inhibitori katehol-O-metil transferaze (COMT), amantadin i antikolinergični lijekovi.

Ključne riječi: *Parkinsonova bolest – etiologija; Parkinsonova bolest – dijagnostika; Parkinsonova bolest – terapija*