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A Review : Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disease. Although many non-motorized symptoms appear, common clinical features include movement disorders including bradykinesia, restless tremors, and stiffness, and postural instability that occurs later. The cause of PD is unknown, but a number of genetic predisposition has been identified, as well as a number of genes that cause rare family types of PD. Environmental influences such as smoking, caffeine consumption, and pesticide exposure have been proposed to reverse the risk of PD development, although the role of this is still unclear. Movement disorder arises as a result of the loss of dopaminergic neurons of substantia nigra pars compacta, with pathological signals being intracellular aggregates of α-synuclein, in the form of Lewy and Lewy neurites. Several mechanisms have been implicated in PD, including mitochondrial dysfunction, defective protein removal mechanisms, and neuroinflammation, but how these mechanisms interact is often not fully understood.

KEYWORDS : α-synuclein, Lewy body, neuroα-synuclein, Lewy body, neurodegeneration, Parkinson's disease, pathogenesis.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by premature death of dopaminergic neurons in substantia nigra pars compacta (SNpc) and a broad spectrum of alpha synuclein (aSyn), a protein within the cell. Dopamine deficiency in the basal ganglia leads to old Parkinsonian motor deficits namely, bradykinesia, tremors, stiffness and postural instability.[1] PD is also associated with non-motorized symptoms, which may precede car symptoms for more than a decade. These non-motorized symptoms are becoming more severe symptoms in the later stages of PD. Currently, the pillar of PD management is drug therapy; however, these symptomatic therapies have significant limitations in advanced diseases.[2] Parkinson's disease (PD) is a common neurodegenerative disease common in 100/1100,000 in Western Europe rising to ∼4% of people over 80.1 In the elderly population, treatment for PD is likely to be even more important and a challenging aspect of medical practice for neurologists and general practitioners. Our understanding of the pathogenesis of this disease has been improved over the past decade by identifying several genetic mutations that may shed light on pathogenesis pathways in rare cases of PD.[2]

Pathology, etiology and pathogenesis

Incidence and prevalence of PD are increasing with age, occurring in 1% of people over the age of 65. Early-start Parkinson's disease (EOPD) is defined as the onset of parkinsonian symptoms before age 40. It accounts for 3-5% of all PD cases. They are divided into 'adolescents' (occurring before the age of 21) and 'young-start' PD (YOPD, occurring in the age group of 21-40 years). PD is twice as common in men as in women in many areas[3]. The protective effect of female sex hormones is evident. The presence of genetically linked genes and / or specific gender differences in exposure to harmful environmental factors may explain this growth in men.[3]

A pathological symptom of PD is cell loss within the substantia nigra which mainly affects the ventral portion of the pars compacta. At the time of death, this brain region had lost 50-70% of neurons compared to the same region in unaffected individuals. The first recorded pathological changes in PD3 have been observed in the medulla oblongata / pontine tegmentum and olfactory bulb. In the early stages — Braak 1 and 2 — patients develop early symptoms. As the disease progresses — Braak stages 3 and 4 — substantia nigra, areas of the midbrain and basal forebrain are involved. Finally, pathological changes occur in the neocortex.

This pathological phase is based on the spread of contaminated bodies. Lewy bodies are a pathological sign of PD. They are α-synuclein-immunoreactive inclusions made up of a number of neurofilament proteins and proteins responsible for proteolysis. These include ubiquitin, a heat-shocking protein that plays a key role in directing other proteins to break down. Genetic mutations in the α-synuclein gene are responsible for certain family types of PD where lewy bodies are also seen. Mutations in the protein parkin produce parkinsonian syndrome outside the lewy bodies in pediatric cases suggesting that parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquination) to other proteins such as α-synuclein interacting protein synphilin-1 leading to the formation of lewy bodies.4 Lewy bodies are found in PD and Dementia with lewy bodies (DLB)), but it is not a pathological symptom of any other neurodegenerative disease.[4]

Genetics of PD

Although PD is usually a rare disease, there is a growing number of single genetic mutations identified. At the time of writing, 11 genes were mapped by linking the identified genes: α-synuclein (SNCA), ubiquitin C-terminal hydrolase 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes.[6] These single genes other than significant LRRK 2 are responsible for only a small number of patients with PD, although more importantly their identification and the proteins they insert provide important insights into pathways that may be responsible for PD and other neurodegenerative diseases. Genetic modification of the SNCA leads to premature onset of PD in members affected by autosomal dominant pattern. Interestingly, the repetition or repetition of SNCA genes in the affected organs leads to an increase in PD symptoms in recent years in the fourth or fifth decades suggesting that it is possible that SNCA hypertension may be a factor in rare disease.[5]

There has been extensive research on mitochondrial gene and function in PD. Abnormalities in Complex 1 of the oxidative phosphorylation enzyme pathway are the most consistent findings, as found in PD brains, blood platelets and skeletal muscle, although reports of other complications have been reported.[7]

Pars compacta cells appear to be at risk of oxidative damage. Mitochondrial DNA studies have so far failed to identify genetic mutations that confirm the deficiency of oxidative phosphorylation in PD. However, it appears that mitochondrial dysfunction may play a role in pathways leading to cell dysfunction and death. The genetic code PINK1 is complex mitochondrial and has been shown to be responsible for the autosomal recessive nature of PD, although it is not a major risk factor for rare disease.[8]

Clinical Dignosis of PD

The hallmarks of PD are bradykinesia, stiffness and restlessness. These may not all be present. Postural instability may be a factor, although early postural back instability especially with a history of falls strongly suggests progressive supranuclear palsy (PSP). Clinical findings are generally asymmetrical to PD. The clinical diagnosis may seem straightforward, though it is worth noting that post-mortem research has shown an alternative way to diagnose patients with PD diagnosed by general anesthesiologists. Notably, there is a very small diagnostic error in patients found in mobility specialist clinics which reinforces the issue of early referral of patients to mobility specialists.[9]

The reduced sense of smell, however, is worth asking about as this may be one of the early symptoms of PD. As the disease progresses, hypophonia, saliva dripping (from reduced swallowing) and impaired function of postural reflexes. Non-motor vehicle complications are often more severe as the disease progresses. It is helpful to ask about the symptoms of depression that occur in about 40% of patients with PD. Diagnosis of significant tremors should be considered when the patient exhibits an equal tremor, which is worse with standing and pressure. [10] Head or voice tremors may also be present. In this case, there may be a predominant autosomal heredity, alcoholism and there should be no evidence of stiffness or bradykinesia in the test. Dystonia that begins in adults may also present with unequal rest tremor and may describe some patients previously labeled ‘benign tremulous PD’ with scans that have no evidence of dopaminergic dysfunction.[11]

One photon emission of computerized tomography (SPECT) imaging using dopamine transporter (DAT) can be helpful in distinguishing PD from several conditions, including significant tremors and dystonic tremors, neuroleptic-induced parkinsonism and psychogenic parkinsonism all. which shows the standard scan of DAT. Intake of the basal ganglia is reduced in PD, parkinsonian syndromes and DLB.[11]

Management of PD

The time to start drug treatment for PD, especially in the early stages of the disease, when there may be a slight lack of function can be difficult. The decision to be made with the full involvement of the patient is determined by the degree of physical disability that is limited to the problems that may be associated with drug treatment. A growing issue is the issue of whether early treatment provides neuro-protective protection. This remains unresolved, despite a large number of in vitro, in vivo and many recent human studies are using PET or SPECT imaging as surrogate agents for nigrostriatal dopaminergic function.[12]

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First line levodopa treatment

Intestinal gel Levodopa-carbidopa (LCIG) is an approved treatment for inpatient patients with advanced PD. LCIG is continuously delivered through a percutaneous endoscopic gastrojejunostomy tube (PEG-J), via a portable input pump. Reduce L-dopa-plasma fluctuations and thus reduce motor problems. Recently, researchers tested an 'accordion pill' for an extended LD / CD form with gastroretenant properties. Other levodopa formulations currently active in the study include ND-0612, ODM-101, CVT-301 and cyclops. ND-0612 is an LD / CD-based liquid formulation that allows for subcutaneous administration with a small patch-pump device; also, ODM-101ne new oral formulation of levodopa / carbidopa / entacapone containing high amounts of carbidopa (65 or 105 mg). CVT-301 and cyclops levodopa inhalation powders. With a quick start to the action, they promise people who will be looking for PD treatment.[12]

Dopamine agonists

Dopamine receptors are mainly related to the D2 receptor family. The first members of this drug family were ergoline derivatives. Ergoline drugs have raised cardiovascular and lung safety and currently used all non-ergoline drugs, e.g., pramipexole, ropinirole, apomorphine, piribedil, rotigotine. Dopamine agonists attract less stimulation of the pulsatile striatal dopamine receptor than levodopa and can significantly reduce the risk of motor problems when used as a first monotherapy.[12]

First-line MAO-B inhibitors

MAO-B inhibitors have been widely used following the DATATOP30 study for their proven effectiveness in symptom development and the perceived 'neuroprotective effect'. However, a subsequent study of the United Kingdom Parkinson's Disease Research Trial Group31 following more than 700 patients with premature PD showed a significant increase in mortality in patients treated with selegiline and levodopa compared with levodopa alone or bromocriptine alone. These findings were not repeated in other studies that suggested the exact opposite, a possible reduction in mortality. The most recent meta-analysis of randomized controlled trials involving a total of 3525 patients came to the conclusion that MAO-B inhibitors reduce disability, levodopa need and motor incidence, without significant side effects or increased mortality. Most of these studies were short-lived and did not compare selegiline with initial treatment with a dopamine agonist. However, MAO-B inhibitors have a potential role as first-line monotherapy in PD patients. Studies using rasagiline, a novel MAO-B inhibitor, have shown efficacy in early and advanced diseases. TEMPO bath tests have yielded results that are consistent with the effect of mutation, although like the dopamine agonist studies mentioned above, more work needs to be done to confirm the neuroprotective effect.[12]

Catecohol-O-methyl transferase (COMT) inhibitors

Current levodopa preparations contain carbidopa or Benserazide to prevent peripheral metabolism of dopamine and, therefore, these drugs improve the bioavailability of the previous drug. This shifts the peripheral metabolism of levodopa into a second pathway that includes COMT. The inhibition of the COMT pathway will improve bioavailability and the levodopa life span, thus, helping patients with motor impairment. Triple therapy with levodopa / carbidopa / COMT inhibitor increases ON time, reduces SO-OFF time, and significantly improves quality of life. The use of tolcapone is limited due to its side effects. Entocapone, another safe alternative, is currently available but does not work well. In phase II trials, nebicapone was found to be more effective than entacapone and safer than tolcapone. Opicapone, in the oral dose system once a day, has also been proven to reduce the OFF time and increase the on time without severe dyskinesias, in patients with advanced PD.[13]

Surgical treatment

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal globus pallidus is a well-known treatment in patients with motor problems. With epilepsy treatment, thalamic DBS is a. active option. Surgical treatment is preferred when autoimmune and dyskinesias are disabled despite the response of motor symptoms to levodopa. The average time before DBS was performed was about 10-13 years after Parkinson's disease was diagnosed. Findings from the EARLYSTIM study, various randomized controlled trials have shown that DBS early onset of disease (7.5 years of disease, and autoimmune disease for <3 years) can improve patient quality of life and a few second-stage measures in addition to better medical treatment.[14]

Conclusion

PD is a common neurodegenerative disease. The combination of genetic and environmental factors may be important in producing abnormal protein interactions between selected groups of neurones, leading to cell dysfunction and death. Diagnosis is always clinical, and there should be a high level of suspicion to rule out other causes of parkinsonism. A large number of agents and surgical interventions are now available to treat pre- and post-PD problems. Increasing attention is being given to the diagnosis and treatment of non-motorized problems in PD. Future developments in PD are likely to focus on the concept of neuroprotection drugs.

Reference

1. Goldman SM, Tanner C. Etiology of Parkinson's's disease. In: Jankovic J, Tolosa E, editors. Parkinson's's disease and movement disorders, 3rd ed. Baltimore, MD: Lippincott-Williams and Wilkins; 1998. p. 133-58.
2. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset Parkinson'sism, Lancet Neurol 2006; 5:355-63.
3. Baldereschi M, Di Carlo A, Rocca, WA, Vanni P, Maggi S, Perissinotto E, et al. Parkinson's disease and Parkinsonism in a longitudinal study: Two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology 2000;55. 1358-63.
4. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, et al. Incidence of Parkinson's disease: Variation by age, gender, and race/ethnicity. Am J Epidemiol 2003;157:1015-22.

5. Razdan S, Kaul RL, Motta A, Kaul S, Bhatt RK. Prevalence and pattern of major neurological disorders in rural Kashmir (India) in 1986. Neuroepidemiology 1994;13:113-9.
6. Abbas MM, Govindappa ST, Sudhaman S, Thelma BK, Juyal RC, Behari M, et al. Early onset Parkinson's disease due to DJ1 mutations: An Indian study. Parkinsonism Relat Disord 2016;32:20-24.
7. Vijayan B, Gopala S, Kishore A. LRRK2 G2019S mutation does not contribute to Parkinson's disease in South India. Neurol India 2011;59:157-60.
8. SanyalJ, Sarkar B, Ojha S, Banerjee TK, Ray BC, Rao VR. Absence of commonly reported leucine-rich repeat kinase 2 mutations in Eastern Indian Parkinson's disease patients. Genet Test Mol Biomarkers 2010;14:691-4.
9. Punia S, Behari M, Govindappa ST, Swaminnath PV, Jayaram S, Goyal V, et al. Absence/rarity of commonly reported LRRK2 mutations in Indian Parkinson's's disease patients. Neurosci Lett 2006;409:83-88.
10. Sadhukhan T, Vishal M, Das G, Sharma A, Mukhopadhyay A, Das SK, et al. Evaluation of the role of LRRK2 gene in Parkinson's disease in an East Indian cohort. Dis Markers.2012;32:355-62.
11. Paisan-Ruiz C. LRRK2 gene variation and its contribution to Parkinson's disease. Hum Mutat 2009;30:1153-60.
12. Nagar S, Juyal RC, Chaudhary S, Behari M, Gupta M, Rao SN, et al. Mutations in the alpha-synuclein gene in Parkinson's disease among Indians. Acta Neurol Scand 2001;103:120-22.
13. Dirkx MF, den Ouden H, Aarts E, Timmer M, Bloem BR, Toni I, et al. The cerebral network of Parkinson's tremor: An effective connectivity fMRI Study. J Neurosci 2016;36:5362-72.
14. Windels F, Thevathasan W, Silburn P, Sah P. Where and what is the PPN and what is its role in locomotion? Brain 2015;138:1133-4.
15. MulakA, BonazB. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol 2015;21:10609-20.
16. SampsonTR, DebeliusJW, ThronT, Janssen S, Shastri GG, Khan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016;167:1469-80.
17. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 2015;30:350-8.
18. Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord 2015;30:1351-60.
19. Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Bürmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord 2016;32:66-72.
20. Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, et al. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's's disease. PLoS ONE 2015;10:e0142164.