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A Systematic Review on Contemporary Methods for Analysis and Diagnosis of Parkinson's Disease

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Abstract: Parkinson's disease is a prevalent movement disorder in neurological practice, but its diagnosis and management present significant challenges. Diagnosing Parkinson's disease is primarily clinical and can be difficult due to the wide range of motor and non-motor symptoms experienced by patients. Managing Parkinson's disease medically is also complex, as the selection of drugs is limited, with levodopa being the primary treatment. However, levodopa-induced dyskinesia (LID), a common side effect, often develops in patients after prolonged treatment and can sometimes appear even after just a few days or months. For patients who cannot be effectively managed with medications alone, various surgical approaches, including unilateral pallidotomy and deep brain stimulation, have shown excellent results. These surgical interventions offer hope for improved quality of life in patients with advanced Parkinson's disease.

Keywords: Classification, Evaluation, Pain, Parkinson's disease, Risk factors.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder marked by the early and prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and widespread presence of alpha-synuclein (aSyn), an intracellular protein. The resulting dopamine deficiency in the basal ganglia leads to the classical motor symptoms of Parkinson's: bradykinesia, tremor, rigidity, and later, postural instability. PD is also associated with non-motor symptoms, which can precede motor symptoms by more than a decade and become particularly troublesome in the later stages of the disease.

Currently, pharmacological therapy is the cornerstone of PD management. However, these treatments primarily address symptoms and have significant limitations, especially in advanced disease stages. Over time, patients may develop disabling features such as non-motor symptoms, dopamine-resistant motor symptoms, and complications from long-term dopamine therapy. While there have been significant advances in both medical and surgical treatments for PD, a definitive disease-modifying therapy is still lacking. Nevertheless, researchers are hopeful about identifying potential targets for disease modification.

This review will discuss the epidemiology, clinical features, pathophysiology, diagnosis, and management (both medical and surgical) of PD. Experimental therapies, which have so far yielded limited results, will not be covered in this discussion.

2. Epidemiology

The incidence and prevalence of PD increase with advancing age, affecting approximately 1% of people over the age of 65. Early-onset Parkinson's disease (EOPD), defined as the onset of parkinsonian features before the age of 40, accounts for 3-5% of all PD cases. EOPD is further classified into 'juvenile' PD (occurring before the age of 21) and 'young-onset' PD (YOPD, occurring between 21 and 40 years of age) . PD is twice as common in men as in women in most populations. This male preponderance may be due to the protective effects of female sex hormones, gender-associated genetic mechanisms, or gender-specific differences in exposure to environmental risk factors.

There is no homogeneous and large-scale epidemiological data on Parkinson's disease (PD) from India. However, regional studies offer some insight into its prevalence. Razdan et al. reported a crude prevalence rate of 14.1 per 100,000 among a population of 63,645 in rural Kashmir, in northern India, with a prevalence rate of 247 per 100,000 in those over 60 years old. In southern India, Bangalore reported a low prevalence rate of 27 per 100,000, while rural Bengal in the east had a prevalence rate of 16.1 per 100,000. In contrast, Bharucha et al. found a high crude prevalence rate of 328.3 per 100,000 among 14,010 Parsis living in colonies in Mumbai, western India.

Genetic forms of PD account for only 5–10% of all cases. A family history of the disease, early onset, and specific clinical features (such as dystonia as a presenting symptom) suggest a genetic form. More than 10% of individuals with young-onset Parkinson's disease (YOPD) have a genetic basis for the disease, with this proportion rising to over 40% for those whose disease onset is before the age of 30. The major genes identified and proven to be causal in PD include Parkin (PARK2), Leucine-rich repeat kinase 2 (LRRK2/PARK8), Alpha-synuclein (SNCA-PARK1/PARK4), PTEN-induced putative kinase 1 (PINK1/PARK6), DJ-1 (PARK7), Ubiquitin C-terminal hydrolase L1 (UCH-L1), and ATPase type 13A2 (ATP13A2). These genetic discoveries have significantly advanced our understanding of the pathophysiology of PD and have opened new avenues for research into potential disease-modifying therapies.

3. Genetics of PD in India

Mutations in the Parkin gene are the most frequently reported among Indian case series, varying from 1.96% to 39.1%. While

mutations are absent in the SNCA gene, they are less frequent in DJ1, PINK1, and LRRK2. Parkin gene mutations are implicated in autosomal recessive (AR) early-onset Parkinson's disease (PD) and vary significantly among subjects from different regions in India. Chaudhary et al. (2006) found that Parkin mutations accounted for 14.3% of familial PD cases, 6.9% of young-onset cases (onset age ≤40 years), and 5.9% of late-onset sporadic cases (onset age ≥41 years). Padmaja MV et al. (2012) reported Parkin mutations in 68% of early-onset PD cases in a study from southern India. Differentiating Parkin-positive young-onset PD patients from Parkin-negative patients based solely on clinical features is not feasible.

DJ-1 mutations, which are seen in AR Parkinsonism, are responsible for the early onset of PD symptoms with a benign course, characterized by a good response to levodopa and often associated with dystonia. The prevalence of DJ-1 mutations in Indian PD patients is modest (~5%). Two studies examined the prevalence of DJ-1 mutations in Indian PD patients: one reported a prevalence of 3.9% of DJ-1 variants, while the other did not identify any pathogenic mutations.

LRRK2 (autosomal dominant [AD] Parkinsonism) is the most common cause of familial and sporadic PD globally, with mutation frequencies of 5-7% in patients with a family history of PD. However, LRRK2 mutations are less frequently seen in India. The most common and well-studied LRRK2 mutation is the substitution of glycine by serine at position 2019 (c.6055G>A). A study by Vijayan B et al. did not find any contribution of the G2019S mutation to the pathogenesis of PD. Similarly, a study by Punia et al. in northern India reported LRRK2 mutations in less than 0.1% of PD cases.

A point mutation in the SNCA gene causes early-onset PD (AD), and its overexpression leads to PD symptoms appearing in the fourth or fifth decades of life. However, SNCA mutations rarely contribute to PD in India. A limited study with 100 PD cases from north Karnataka suggested that SNCA mutations might be population-specific and may not play a causal role in all studied populations.

The PINK1 gene, which codes for a mitochondrial complex, has been implicated in causing an autosomal recessive (AR) form of Parkinsonism. However, the contribution of PINK1 variants to the causation of Parkinson's disease (PD) in India is limited. Tamali Halder et al. observed that 1.8% (2 out of 106) of PD patients in northern India harbored PINK1 variants. In 2016, Sudhaman et al. discovered a novel frameshift mutation in the podocalyxin-like (PODXL) gene as a likely cause of early-onset Parkinsonism (AR) in one Indian family, where tests for mutations in the Parkin, PINK1, and DJ1 genes were negative.

New mutations are being identified regularly, expanding the spectrum of genetic causation of PD. However, the contribution of genetic testing to the management of PD remains limited, as positive genetic test results do not currently influence treatment decisions.

4. Neuropathology

The pathophysiology of Parkinson's disease (PD) involves the loss or degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of Lewy bodies, which are abnormal intracellular aggregates containing proteins like alpha-synuclein (aSyn) and ubiquitin. Approximately 60-70% of neurons in the SNpc are lost before symptoms appear. Research has shown that the pathogenic process in PD affects regions of both the peripheral and central nervous systems, in addition to the dopaminergic neurons of the SNpc.

Lewy body pathology begins in cholinergic and monoaminergic brainstem neurons and in the neurons of the olfactory system, eventually involving the limbic and neocortical brain regions as the disease progresses. The loss of dopaminergic neurons, initially restricted to the SNpc, becomes more widespread by the time the disease reaches its end stage.

5. Motor circuit changes in PD

The selective loss of dopaminergic neurons in the striatum causes impairment of motor control in individuals with Parkinson's disease (PD). The motor circuit in PD involves corticostriatal projections from the primary motor cortex, supplementary motor area, cingulate motor cortex, and premotor cortex, which terminate on the dendrites of the striatal medium spiny neurons. The direct pathway is a monosynaptic connection between the medium spiny neurons that express dopamine D1 receptors and GABAergic (gamma-aminobutyric acid-ergic) neurons in the globus pallidus internus (Gpi) and the substantia nigra pars reticulata (SNpr). The indirect pathway originates from medium spiny neurons that express D2 receptors, which project to the globus pallidus externus (Gpe) and reach the Gpi via the subthalamic nucleus (STN) as a glutamatergic relay.

Through these two pathways, the striatal dopaminergic tone regulates the GABAergic output activity of the basal ganglia. In PD, there is a reduction in D1-mediated direct pathway activity and an increase in D2-mediated indirect pathway activity, resulting in a net increase in the firing rate of basal ganglia output neurons (GABA), which over-inhibit downstream thalamocortical and brainstem areas. Changes in cerebellar activity and the interaction between the basal ganglia and cerebellum contribute to the pathophysiology of tremor in PD. Abnormalities in balance and gait arise from dysfunction of the basal ganglia output via projections into the midbrain locomotor region, specifically the pedunculopontine and cuneiform nuclei.

6. Gut and PD

Parasympathetic nerves and the enteric nervous system are among the earliest structures affected by alpha-synuclein (aSyn) pathology in Parkinson's disease (PD). Dysfunction of the brain-gut-microbiota axis in PD may be associated with non-motor symptoms that precede the classical motor symptoms, supporting the hypothesis that the pathological process spreads from the gut to the brain. The gut microbiome plays an important role in regulating movement disorders, and alterations in the microbiota might be a risk factor for PD. Sampson et al. reported that in mice overexpressing aSyn, alterations in the gut microbiota were required for motor

deficits, microglial activation, and aSyn pathology to develop. Antibiotic treatment ameliorated these conditions, while microbial re-colonization promoted the pathophysiology in adult animals, suggesting that postnatal signaling between the gut and the brain modulates the onset and course of the disease. Oral administration of specific microbial metabolites, such as short-chain fatty acids (SCFAs), to germ-free mice promoted the development of neuroinflammation and motor symptoms. Research has shown that alterations in the gut microbiome are related to several clinical features of PD. A recent Finnish study found that changes in the microbiota composition, particularly the abundance of Enterobacteriaceae, are positively associated with the severity of postural instability and gait difficulty in PD patients. Keshavarzian et al. and Unger et al. observed that feces from PD patients contained fewer SCFAs, including butyrate, which are produced by bacteria with potential anti-inflammatory properties. Increased intestinal permeability and dysfunction in intestinal symbiosis have also been proposed as mechanisms responsible for the development and progression of PD.

Recently, Hill-Burns et al. observed significantly altered abundances of several taxa in 197 PD patients and demonstrated the independent effects of PD medications on these microbiomes, providing further insights into the pathophysiology and treatment of PD.

7. Clinical Diagnosis and Natural History

Parkinson's disease (PD) is clinically defined by the presence of bradykinesia combined with at least one additional manifestation: muscular rigidity, rest tremor, or postural instability (the latter being a feature of the more advanced form of the disease). Motor symptoms typically start unilaterally, and asymmetry persists throughout the course of the disease. Non-motor symptoms are seen in a large proportion of patients and can precede the onset of cardinal motor symptoms by years. These non-motor symptoms include sleep disorders (e.g., frequent waking, rapid eye movement sleep behavior disorder (RBD), and daytime somnolence), hyposmia, autonomic dysfunction (e.g., orthostatic hypotension, urogenital dysfunction, and constipation), cognitive impairment, mood disorders, and pain.

The Sydney Multicentre Study of Parkinson's disease reported that among patients who had survived for 20 years after the onset of the disease, dementia was observed in 83%, hallucinosis in 74%, symptomatic hypotension in 48%, constipation in 40%, and urinary incontinence in 20%. Additionally, freezing of gait, postural instability and falling, and choking were reported in 81%, 87%, and 48% of the patients, respectively.

Although there is no consensus on the classification of PD subtypes, clinical observations suggest two major subtypes: tremor-dominant PD (characterized by a relative absence of other motor symptoms) and non-tremor-dominant PD (which includes phenotypes described as the akinetic-rigid syndrome and the postural instability gait disorder (PIGD)). Tremor-dominant PD is often associated with a slower rate of progression and less functional disability compared to non-tremor-dominant PD.

Nearly 90% of patients with Parkinson's disease (PD) experience non-motor symptoms throughout the course of their illness, which typically do not respond well to dopamine therapy. Mood disorders and constipation nearly double an individual's risk of developing PD later in life. Idiopathic rapid eye movement sleep behavior disorder (RBD) carries a high risk for the development of PD and other α-synucleinopathies. The average latency between the onset of RBD and the appearance of Parkinsonian motor symptoms is approximately 12–14 years.

Autonomic symptoms, such as those mentioned earlier, increase with age, disease severity, and higher doses of dopaminergic medications. Urinary symptoms in PD include urgency, frequency, nocturia, and urge incontinence, with storage problems being more common than voiding difficulties. These symptoms are more frequent and occur earlier in multisystem atrophy (MSA) compared to PD.

Painful sensory symptoms are present in two-thirds of PD patients and are believed to result from abnormal nociceptive processing. There is a six-fold increased risk for subcortical type dementia in patients with PD, occurring later in the disease course. Up to 60% of PD patients develop dementia within 12 years of diagnosis.

Hyposmia, reduced sense of smell, occurs in approximately 90% of early-stage PD patients and precedes typical motor symptoms by several years. Its occurrence may predict a higher risk of developing PD, and olfactory testing can aid in differentiating PD from other parkinsonian syndromes.

8. Conclusion

Parkinson's disease (PD) is among the most prevalent neurodegenerative conditions affecting aging populations, leading to increased morbidity and mortality. Awareness of its manifestations, treatments, and progressive long-term course is crucial for optimal management. Significant strides have been made in understanding PD's neuropathology and its spread throughout the nervous system. However, current treatments are not curative, and PD remains a progressive disorder. Over time, it results in severe disability due to worsening motor problems resistant to treatment and the emergence of non-motor symptoms.

Addressing the factors that drive disease progression and finding ways to delay disability are critical unmet needs in current and future PD research efforts.

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