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A REVIEW ON PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a common movement condition seen in neurology, but it's difficult to diagnose and treat. Since PD patients experience a wide range of motor and non-motor symptoms, the diagnosis is clinical and can be challenging. The medical care of Parkinson's disease patients is complicated due to a shortage of drug options and the use of levodopa as the mainstay of treatment. However, in Parkinson's disease patients taking levodopa, levodopa induced dyskinesia (LID) is normal. This is a typical side effect that occurs after a long period of treatment, but it may also occur after a few days or months of treatment. Different surgical techniques, such as unilateral pallidotomy and deep brain stimulation, have shown outstandingresults in PD patients who are unable to control their symptoms with drugs alone.

KEYWORDS: Deep brain stimulation, dopaminergic medications, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative condition marked by the early death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the widespread involvement of the intracellular protein alpha synuclein (aSyn). Classic Parkinsonian motor symptoms, such as bradykinesia, tremor, rigidity, and later postural instability, are caused by dopamine deficiency in the basal ganglia. Non-motor symptoms are also linked to Parkinson's disease, and they can appear more than a decade before motor symptoms. In the later stages of Parkinson's disease, these non-motor symptoms become bothersome. Pharmacological treatment is currently the mainstay in PD management; however, these symptomatic treatments have significant drawbacks in advanced disease. Non-motor symptoms, dopamine resistant motor symptoms, and motor complications of long-term dopamine treatment are among the many debilitating characteristics that occur later in the course of the disorder. Despite significant advancements in medical and surgical care for Parkinson's disease, there is no genetic disease-modifying therapy available. Researchers are optimistic, however, that they will be able to identify new targets for disease treatment. The epidemiology, clinical characteristics, pathophysiology, diagnosis, and treatment (medical and surgical) of PD will be discussed in this study. Experimental treatments have only had minimal research results to date and will not be covered here.[1,2]

Classification

Parkinson's disease is the most common form of parkinsonism, and it's also known as "idiopathic parkinsonism," or parkinsonism with no known cause. Because of an irregular accumulation of the protein alpha-synuclein in the brain, scientists often refer to Parkinson's disease as a form of neurodegenerative disease known as synucleinopathy. The synucleinopathy classification separates Parkinson's disease from other neurodegenerative disorders, such as Alzheimer's disease, in which the brain accumulates a distinct protein called tau.[3,4,5]

Tauopathies and synucleinopathy have a lot of clinical and pathological similarities, but there are still some variations. Memory loss is the most common symptom of Alzheimer's disease, in comparison to Parkinson's disease. Parkinson's disease's hallmark symptoms (slowness, tremor, stiffness, and postural instability) are not present in Alzheimer's disease. There have been attempts to divide Parkinson's disease into subtypes based on the age of diagnosis, the progression of symptoms, and the dominance of tremor. None has yet gained widespread acceptance as a complete model.[6]

Clinical syndrome

The presence of bradykinesia and one of the following characteristics: rigidity, 4–6 Hz rest tremor, or postural instability, as well as three supportive features, are prescribed by the UK Parkinson's Disease Society Brain Bank clinical criteria for probable PD.[7] The InternationalParkinson's and Movement Disorder Society (MDS) developed their own clinical diagnostic criteria, which include (1) the occurrence of parkinsonism (bradykinesia plus either rest tremor or rigidity), (2) the absence of absolute exclusionary criteria, (3) supportive

criteria, and (4) theabsence of red flags.[8] To support the diagnosis and monitor the course of the disease, accurate diagnostic, pre-symptomatic, and progression biomarkers are being established in addition to a variety of clinical rating scales, especially the Unified Parkinson's Disease Rating Scale (UPDRS).[9]

Sign and symptom

The most noticeable signs of Parkinson's disease are those that are linked to movement ("motor"). Autonomic dysfunction, neuropsychiatric problems (mood, perception, behaviour, or thought alterations), sensory (especially altered sense of smell), and sleep difficulties are allcommon non-motor symptoms. Any of these non-motor symptoms could already be present when you're diagnosed.[10]

Neuropsychiatric

Parkinson's disease may cause a variety of neuropsychiatric symptoms, ranging from mild to serious. Disorders of perception, mood, actions, and thinking are all included.[11] Cognitive disturbances may occur in the early stages of the disease, often even before diagnosis, and theybecome more common as the disease progresses.[12] Executive dysfunction is the most common cognitive deficit in Parkinson's disease, and it can affect planning, cognitive flexibility, logical thought, rule acquisition, inhibiting improper behaviour, initiating appropriate actions, working memory, and attention control. Slowed cognitive processing speed, impaired memory, and impaired perception and measurement of time are some of the other cognitive issues. However, when memory is supported by prompts, there is a boost. Visual-spatial problems are also a part of the disorder, as shown by the individual's performance on measures of facial recognition and orientation perception of drawn lines.[13] When compared to the general population, people with PD have a two to six times higher risk of dementia. Parkinson's disease dementia affects up to 78 percent of individuals with the disease. Dementia prevalence rises with age and, to a lesser extent, with disease length. Dementia is linked to a lower quality of life for people with Parkinson's disease and their caregivers, as well as an increased risk of requiring nursing home treatment.[14,15]

Etiology

The relative importance of genes and environmental/lifestyle factors in the pathogenesis of Parkinson's disease has been a point of contention. The single most significant risk factor for PD is age, with a median age at onset of 60 years.[16,17] Men tend to have a higher frequencythan women (the ratio varies from 1.3 to 2.0), but the rate may be affected by variations in the prevalence of variables such as cigarette smoking, the use of postmenopausal hormones, and caffeine consumption (see section on lifestyle and protective factors). Age-related biological dysfunction, such as telomere dysfunction, genomic instability, epigenetic changes, ubiquitin-proteasome and autophagy-lysosomal system defects, and mitochondrial defects, can underpin and promote neuronal death, just as it does in other neurodegenerative diseases.[18,19]

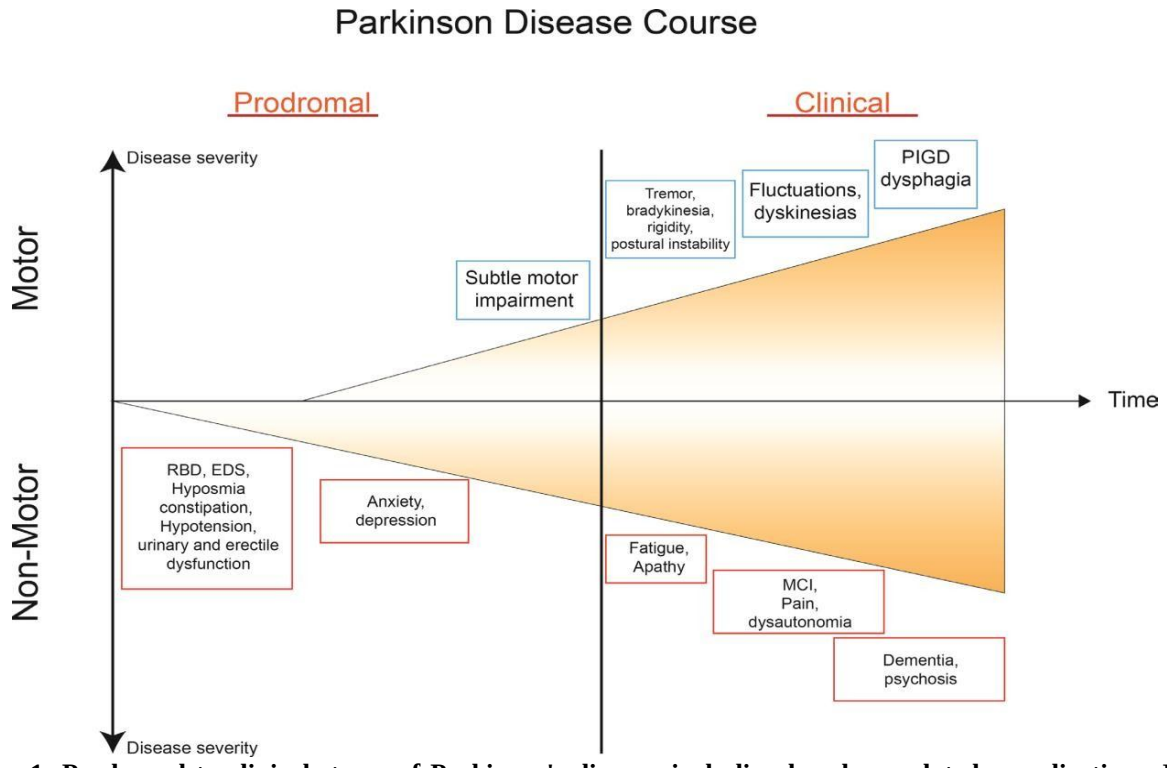

Figure 1: Prodromal to clinical stages of Parkinson's disease, including levodopa-related complications. RBD, rapid eye movement sleep behaviour disorder; PD, Parkinson's disease; PIGD, postural-instability-gait-disorder; PIGD, postural-instability-gait-disorder; PIGD, postural-instability-gait-disorder.

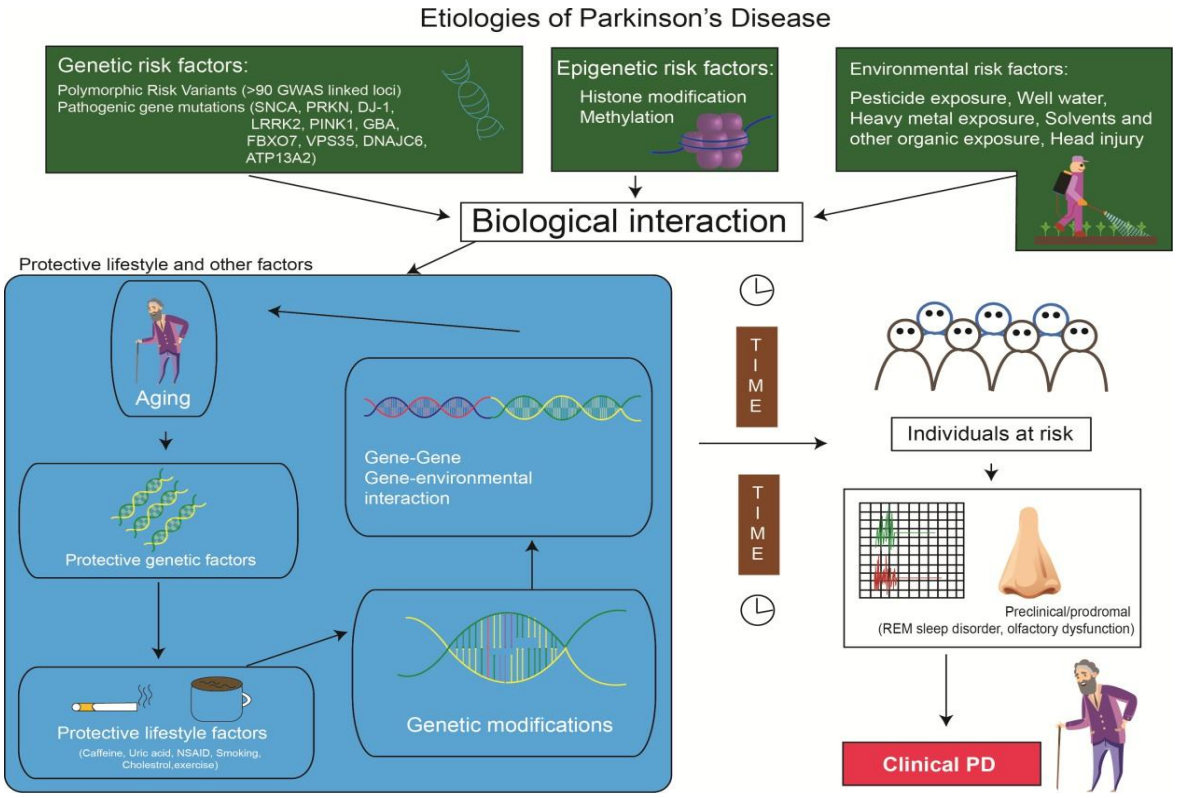

Figure 2: Genetic, epigenetic, and environmental factors combine to cause Parkinson's disease. REM stands for rapid eye movement, and PD stands for Parkinson's disease.

Environmental risk factor

Clinical interaction studies using a cross-sectional (hospital and community-based) or prospective (population-based) approach have historically been used to investigate the possible cause and effect relationship between etiologic factors and disease. Pesticide and heavy metal exposure, rural life, agricultural occupation, traumatic head injury, history of melanoma, intake of dairy products, type 2 diabetes mellitus (reduced by the use of antidiabetic drugs), and several other factors have been linked to the disease. (See Figure 2) Despite the fact that these connections are backed by biological plausibility, a number of the findings have not been reliably replicated. According to a recent meta-analysis that included both quantitative and qualitative studies of different environmental exposures, several of these correlations lack robust consistency (such as rural living, well-water consumption, farming and pesticide exposure).[20] While other meta-analyses confirmed a link between pesticide exposure and cancer,[21] Others discovered a lack of evidence for a connection to traumatic brain injury.[22]

Lifestyle and other protective factors

The two most consistent protective factors linked to a lower risk of Parkinson's disease are cigarette smoking and caffeine intake.[20,21] Higher serum urate, ibuprofen use, and exercise, among other things, have also been linked.[16]

Pathophysiologic mechanisms

Neuronal failure in the substantia nigra par compacta, locus coeruleus, and other neuronal populations is well documented in human post mortem studies.[23] Early pathological changes, according to the Braak hypothesis, arise in the medulla oblongata and olfactory bulb (Braak stages 1 and 2) before progressing rostrally to the substantia nigra and midbrain (Braak stages 3 and 4), by which time clinical symptoms and indications are likely to be present. the cortical regions are gradually affected in late stages It is beyond the reach of this study to go through all of the potential pathophysiologic pathways in detail. However, several primary molecular events and hallmarks have been consistently identified in human postmortem tissues, in vitro human cell lines, human brain organoids, and animal models, regardless of the underlying aetiologies (environmental, genetic, or other risk factors) (1A). Misfolding and aggregation of -synuclein, mitochondrial dysfunction, protein clearance deficiency (involving key ubiquitin-proteasome and autophagy-lysosomal systems), neuroinflammation, and oxidative stress are among them (figure 3). These major molecular and cellular hallmarks are frequently related to a variety of other events, including vesicular transport disturbance, loss of microtubular integrity, neuronal excitotoxicity, trophic factor disruption, iron metabolic pathway dysregulation, endoplasmic reticulum dysfunction, polyn (ADP-ribose) polymerase and other enzymatic activation, to name a few. Axonal mitochondria are especially fragile, and their dysfunction can lead to impaired axonal transport. Some researchers have speculated that distal axons in the striatum could be the first site of neurodegeneration in Parkinson's disease.[24]

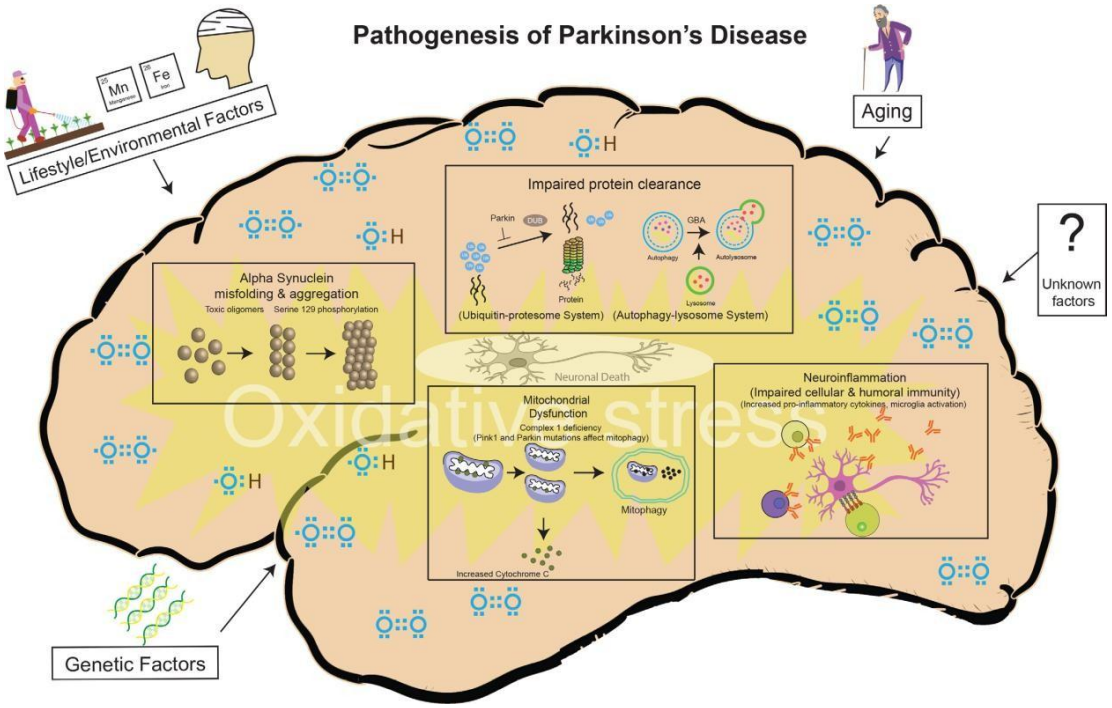

Figure 3: Pathogenesis of Parkinson's disease: a number of cellular pathways, along with lifestyle/environmental and genetic factors, lead to PD-related neurodegeneration. Parkinson'sdisease is referred to as PD.

Treatment

Parkinson's disease is a complex neurodegenerative disease with a wide range of motor and non-motor symptoms that necessitates a tailored treatment strategy. Clinical studies that are intended to include evidence-based results must provide a well-defined population of patients and controls, as well as the most objective, accurate, and validated instruments for evaluating the therapeutic intervention's effects. While a number of clinical rating scales and other instruments have been used to determine response to different treatments, the UPDRS is the most commonly used as the primary outcome indicator in clinical trials. Table 1 and figure 4 provide a description of medical and surgical therapeutic choices for patients with Parkinson's disease at different stages of the disease. In addition to traditional treatments, we discuss evidence-based, as well as new and experimental PD therapeutics.[25]

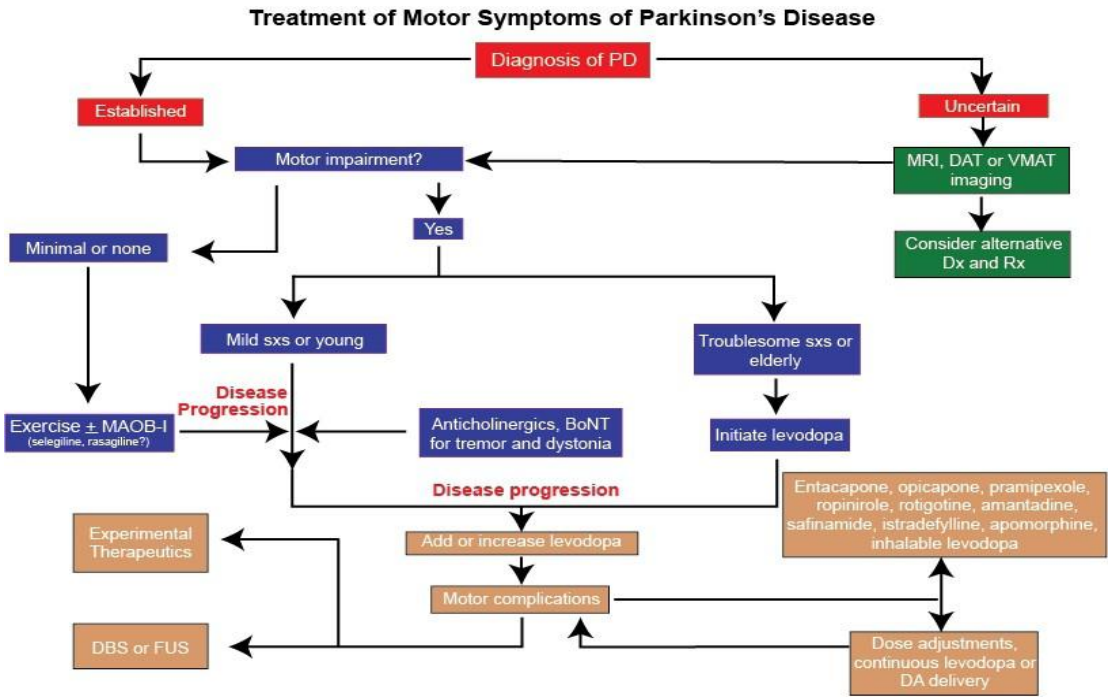

Figure 4: Algorithm for treating Parkinson's disease motor symptoms. DBS stands for deep brain stimulation, MAOB stands for I monoamine-oxidase type B inhibitor, and PD stands forParkinson's disease.

Symptomatic treatment of motor symptoms

Levodopa is a drug that is used to treat Parkinson's disease Within two years of symptom initiation, the majority of patients with PD require levodopa therapy. Carbidopa or benserazide, aromatic acid decarboxylase inhibitors that prevent levodopa's peripheral metabolism and significantly minimise the risk of nausea, are almost always used with levodopa, the most common medication in the treatment of Parkinson's disease. It has been shown that increasing the carbidopa: levodopa ratio from the current norm of 1:4 increases on time without dyskinesia and decreases off time.[26] Levodopa's antiparkinsonian effectiveness is so consistent that a positive clinical response is used to confirm the diagnosis of Parkinson's disease. Nausea and vomiting, orthostatic hypotension, sedation, confusion, sleep disruption, hallucinations, and dyskinesias are all side effects of levodopa. There are many different forms of dyskinesia, but the most common are peak-dose chorea or stereotypy and wearing-off dystonia.[27] Within two years of starting levodopa treatment, about half of the patients' experience wear off, and a third experience dyskinesias. Through taking levodopa on an empty stomach (if tolerated without nausea), avoiding or minimising protein consumption, or crushing the levodopa tablet and combining it with a carbonated beverage, the time between ingestion and detectable therapeutic benefit may be shortened. Many patients and clinicians are hesitant to begin levodopa therapy despite the presence of troubling symptoms due to concerns about the occurrence of levodopa-related motor complications. This is particularly true in patients with young-onset PD, who are more likely to experience motor fluctuations and dyskinesia early on in their treatment with levodopa.[28,29] In patients with a limited period of reaction to levodopa, fractionation of the total daily dose is also used to smooth out variability and prevent symptoms from wearing off (figure 4). Blocking dopamine metabolism with MAOIs or catechol-O-methyl transferase inhibitors (COMTIs), or adding dopamine agonists or extended- release amantadine preparations, may increase the period of gain from each dose of levodopa (see below).[30] Agonists of dopamine receptor agonists activate dopamine receptors (G protein-coupled, two main families, D2-like (D1 and D5) and D1-like (D2, D3, and D4)) and postpone levodopa-related problems like motor fluctuations and dyskinesias when used early in the course of PD therapy. However, there is no evidence to support the theory that early dopamine agonist administration delays disease development or even increases long-term quality of life. Pramipexole, ropinirole, rotigotine, and apomorphine are examples of non-ergot dopamine agonists commonly used in clinical practise. When symptoms are not adequately monitored by levodopa or when motor fluctuations are present, dopamine agonists may be usedas a monotherapy or as an alternative therapy.[31] In an open-label randomised trial involving 1620 newly diagnosed Parkinson's disease patients, those given levodopa alone had higher mobility scores than those given dopamine agonists or the MAOBI.[32] An earlier 5-year study found that people taking ropinirole had less dyskinesias than people taking levodopa.[33]

CONCLUSION

Parkinson's disease is one of the most common neurodegenerative disorders affecting the elderly, and it is linked to higher morbidity and mortality rates. For the best-case management, it is important to be aware of the disease manifestations, medications, and the disease's long- term progression. The neuropathology of Parkinson's disease and its development in the nervous system have made tremendous strides. None of these therapies, however, are curative. Because of the severity of treatment-resistant motor problems and non-motor symptoms, PD remains a chronic condition that ultimately causes serious impairment. The main unmet needs to be resolved by current and future research projects include modifying factors that contribute to disease progression and further delaying impairment.

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