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A Review of Parkinson's Disease: From Epidemiology to Treatment

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Abstract
Parkinson's disease (PD) is a fast-growing neurodegenerative disorder. It affects people at the ages of 55 to 65 years. PD causes substantial disability and so the patients would have a poor quality of life. There are many factors that could induce this disease such as genetic, environmental and lifestyle factors. While this disease is incurable, many scientific researchers are trying to find a cure in addition to managing the motor and non-motor symptoms. Levodopa is the key treatment for PD; though, its motor complications and induction of dyskinesia limited its long-term use. In patients with advanced stage PD, it is favorable to initiate combination therapy with dopamine agonists, catechol O methyltransferase inhibitors (COMT), or monoamine oxidase-B inhibitors (MAOs). Surgical procedures are the last option to treat patients with a late stage of the disease. In addition, managing a healthy lifestyle, balanced food and physical excesses are very crucial to improve patients' life. This review discusses epidemiology of PD, risk factors, diagnosis and treatment that can deliver ideas about patient-specific care, so diminish drugs side effects and open new paths to develop updated strategies to control the progress of this disease.**Keywords:** Parkinson's disease; neurodegeneration; genetic factors; treatment; epidemiology

الملخص:
مرض باركنسون هو اضطراب تنكسي عصبي ينمو بشكل سريع. يصيب الأشخاص الذين تتراوح أعمارهم بين ٥٥ و٦٥ عامًا. يؤدي مرض باركنسون إلى إعاقة كبيرة، مما يجعل المرضى يعانون من حياة متعبة. هناك العديد من العوامل التي يمكن أن تؤدي إلى هذا المرض مثل العوامل الوراثية والبيئية ونمط الحياة. وعلى الرغم من أن هذا المرض لا شفاء منه، فإن العديد من الباحثين العلميين يحاولون إيجاد علاج بالإضافة إلى التحكم في الأعراض الحركية وغير الحركية. يعتبر ليفودوبا العلاج الأساسي لمرض باركنسون؛ ومع ذلك، فإن حدوث مضاعفات حركية واستحداث خلل الحركة قيد استخدامه طويل الأمد. بالنسبة للمرضى الذين يعانون من مراحل متقدمة من المرض، من المستحسن بدء العلاج بالتركيبات الدوائية مع ناهضات الدوبامين أو مثبطات إنزيم كاتيكول أوكسي ميثيل ترانسفيراز (COMT) ، أو مثبطات أكسيداز أحادي الأمين B- (MAOs). الجراحة هي الخيار الأخير لعلاج المرضى في المراحل المتأخرة من المرض. بالإضافة إلى ذلك، فإن إدارة نمط حياة صحي، وتناول طعام متوازن وممارسة النشاط البدني تعد أمورًا بالغة الأهمية لتحسين حياة المرضى. يناقش هذا الاستعراض وبالأخص علم الأوبئة الخاص بمرض باركنسون والعوامل المسببة له وتشخيصه وعلاجه بهدف تقديم أفكار حول الرعاية الموجهة للمرضى لتقليل الآثار الجانبية للأدوية وفتح آفاق جديدة لتطوير استراتيجيات محدثة للسيطرة على تقدم هذا المرض

١.Introduction Globally, around six million people have been affected by Parkinson's disease (PD) in 2016 (Feigin et al., 2019). The disease's incidence and prevalence have increased rapidly in the last 20 years for unrecognized reasons (Feigin et al., 2019, Dorsey et al., 2018) which impacted the community. PD was elucidated by James Parkinson in 1817 and characterized it by basic clinical aspects of shaking at rest, slow movement (bradykinesia), stiffness and difficulty to balance, and a variety of symptoms including motor and non-motor (Jankovic, 2008, Obeso et al., 2017, Rizek et al., 2016).

.٢EpidemiologyThe occurrence and commonness of PD rise gradually as age progresses, so it is said a disease related to age (Cong et al., 2022). Nevertheless, the misconception that PD just influences old individuals should be banished. The onset age of affected people is less than 65 years and 50 years are about (25%) and (5-10%), respectively. Individuals less than 40 years of age may also be affected. PD may occur worldwide without significant epidemiological variations, the difference may be in the fast increment in newly discovered situations in China (Tian et al., 2011) and in highly payed European countries. The world's worry about Parkinson's disease regarding deaths and disabilities has increased two times in the last 20 years (Deuschl et al., 2020).Despite that PD affects both sexes, it has been shown that women have some advantages over men experiencing lower disease incidence particularly those with age between fifty to fifty nine years (Kim et al., 2020) and higher age onset. The living with disability for a number of years is higher in men. (Jankovic, 2008). But women show some disadvantages like increased risk of movement abnormalities (dyskinesia) as well as motor and non-motor reaction variation , result in overdosing due to their lower bodyweight (Kim et al., 2020, Donzuso et al., 2023). In addition, women may experience urinary complains and depression. On the contrary, higher risk of cognitive decline observed in men (Maas et al., 2024). Women with PD exhibit different health behavior, in which access to physicians with special care is less frequent and delayed (Russillo et al., 2022). This issue may lead to under-treatment, including declined use of neurosurgical interference. In particular, women are inadequately represented in PD studies (Vaidya et al., 2021).

.٣Risk factorsThe relative genetic, environmental and lifestyle factors involved in the progress of the illness have been considered. Sixty years considered the median age of disease's onset, so age is very crucial factor for development of PD (Gonzalez-Latapi et al., 2021). The illness is very common in men than women with (1.3 - 2.0) ratio, however the occurrence may be affected by variations in factors like smoking behavior, use of hormones after menopause and caffeine containing beverages consumption (Donzuso et al., 2023). As with other neurodegenerative type of illnesses, biological impairments related to age such as defective telomere function, unstable genomics, epigenetic alteration, ubiquitin-proteasome0 and autophagy-lysosomals system, and mitochondrial abnormalities, may support and assist neuronal death (Gonzales et al., 2022).

It has been proposed that PD occurs in subtypes which categorize patients according to specific clinical groups, like tremor-dominant, and postural0-instability0- gait-disorder0 (PIGD)0subtypes0 (Hähnel et al., 2024, Savica et al., 2019). Numerous investigations found that the PIGD phenotype possess severe symptoms and progress faster than the tremor-dominant Parkinson's disease. The clinical subtypes dictate the phenotype and the normal progress of the disease as proposed. Additionally, they indicate causes and specific pathogenic mechanisms. However, this conception showed that motor subtypes are unstable and rather switch with progress of the illness and with therapy (Mestre et al., 2018, De Pablo-Fernández et al., 2019).

٣،١Environmental risk factorsClinical investigations explore the potential link between causes and outcomes, focusing on aetiological factors and diseases, through both cross-sectional and prospective methodologies (hospital-community-based and population-based, respectively). Factors that might play a role include exposure to pesticides and heavy metals, rural lifestyles, agricultural jobs, traumatic brain injuries, melanoma history, dairy product intake, type 2 diabetes mellitus (which can be mitigated by antidiabetic medications), among others (Gonzalez-Latapi et al., 2021). Recently, a meta-analysis included quantitative and qualitative investigation of different environmental exposures, show inconsistency in some of these relationships (like rural living, 0well-water consumption, farming and pesticide exposure) (Breckenridge et al., 2016). Whereas another meta-analyses suggested a consistent relation with subjection to pesticides (Yan et al., 2018), others showed no supported relation with traumatic injury of the head (Huang et al., 2018). Due to various conflicts and internal limitations, it is not unexpected that these epidemiological studies sometimes reveal conflicting results. Smoking and the consumption of caffeine considered protective factors related to risk reduction of PD (Breckenridge et al., 2016). Other associations have been reported among many include high serum urate, the use of ibuprofen and exercise (Pohl and Dikic, 2019). The inversed relationship between smoking and PD is very interesting. This opposite relation is unexplained, however it have been proposed that Parkinson's disease related vigilant personality (avoidance trait) causes patients to quit smoking as a neuroprotective biological mechanism associated in Parkinson's disease (Ritz et al., 2014). The other postulate relates nicotine to protection of dopaminergic neurons because it has been demonstrated to trigger dopamine release in the striatum and protect the function of dopamine in experimental systems. Cigarette smoke may possibly contain other neuroprotective constituents that have not been identified .Caffeine consumers show relative reduction in risk of Parkinson's disease ranging between 0.5 and 0.8, a dose-dependent consequence that has been revealed in many investigations just like smoking (Pohl and Dikic, 2019) It has been postulated that Caffeine exhibit a

neuroprotective effect by antagonizing adenosine A2a receptor. Some drinks (e.g. tea) may contain antioxidants leading to a protective role, independent of caffeine. Purine metabolism yields uric acid as an antioxidant activity. A meta-analysis included thirteen studies has showed lower uric acid serum levels in Parkinson's disease group than control group, also the same paradigm was shown in patients in progressed stage of illness in contrast to early stage of the illness (Wen et al., 2017). Nevertheless, the Copenhagen General Population Study (CGPS) and few other investigations have shown no association with the causes, where the existence of unknown co-founders has been suggested (Kobylecki et al., 2018). Studies showed the use of Ibuprofen has lowered the risk of Parkinson's disease, while other non-steroidal anti-inflammatory drugs showed no association (Pohl and Dikic, 2019). Extensive studies concerning the use of Statins and levels of lipids have been conducted. But, it is hard to obtain definite conclusions concerning the specific interactions between each category of statins in terms of solubility and levels of each type of lipid as well as, methodological differences (Ng and Tan, 2017).

٣,٢GeneticsIn 1997, the first Parkinson's disease linked gene known as α-synuclein (SNCA) was discovered based on studies conducted on twins and on a number of families displaying a Mendelian inheritances patterns (dominant and recessive) (Maas et al., 2024). After one year, identification of mutation in Parkin0 (PRKN) gene, related to autosomal0recessive type of Parkinson's disease (33). The International0 Parkinson's and Movements Disorders0 Society0 used the genes' names0 in the0 classification of 'PARK' genes rather than numbers (Rizek et al., 2016).As a result of the developments of genetics' techniques and populations' investigations that included genome-wide association studies (GWAS), more than thirty four types of Parkinson's disease resulted from a single gene have been reported and (> 100) loci were determined as PD risk factors (Blauwendraat et al., 2020) .

.٤Causes:Parkinson's disease (PD) is a multifaceted neurodegenerative disorder through complex etiological underpinnings (Klein and Westenberger, 2012). The causes of Parkinson's disease can be broadly categorized into genetic, environmental, and cellular factors, each contributing in varying degrees to the disease's beginning and development (Gorell and Rybicki, 2003).

٤,١Genetic Influences :Hereditary mutations play an important role in the etiology of Parkinson's disease. Variants in several genes have been implicated in PD, including *SNCA* (Kouli et al., 2018). Which encodes alpha-synuclein protein that is vital to PD pathology. Mutations in *LRRK2* and *PINK1* gens are linked with inherited forms of PD (Miller and O'Callaghan, 2015). Consequently, these genetic mutations can interrupt normal cellular functions and thus contribute to neurodegeneration. Research has recognized rare and familial forms of PD that linked to specific gene mutations that increase exposure to the disease (Mortezazadeh et al., 2021).

٤,٢Environmental Factors :Another very curial, aspect are environmental impacts. Some toxins, both of pesticides and also heavy metals, have been found to raise the risk of PD in the etiology of PD. Furthermore, lifestyle aspects such as smoking and specific types of job hazards can be associated with genetics to further heighten the risk of acquiring the PD disease. Epidemiological revisions propose that prolonged exposure to environmental factors can cause neuronal toxicity and enhance risk of Parkinson's disease, thereby laying a lasting role for environmental factors. (Fitzgerald et al., 2019).

٤,٣Cellular and Molecular Mechanisms :PD is characterised at the cellular level by severe loss of dopaminergic neurons in the substantia nigra of the brain which governing motor regulator. Oxidative stress, mitochondrial dysfunction and inflammation process are the most logical offenders in the neurodegenerative process at the cellular level (Pajares et al.,2020). Mitochondrial dysfunction impairs ATP production which in turn results in metabolic and cell stress, leading to hypoxia and apoptosis. Oxidative stress could lead to drives neurotoxicity due to reduction of reactive oxygen species and antioxidant defenses mechanism.Neuro inflammation, triggered by traveling immune system cells and stored glial cells, can contribute to neuro degeneration (Buneeva et al., 2020).

٤,٤Protein Aggregation: PD is characterized by the accumulation of aggregated protein - mainly alpha-synuclein. Insoluble aggregates of misfolded alpha-synuclein, called Lewy bodies, accumulate in neurons and lead the cells to dysfunction and death. This aggregation of proteins disrupt normal cellular activities and further compromises neuronal functions (Munhoz et al., 2024).

.٥Diagnosis:The vagueness of signs and symptoms of PD and their overlap with other neurological diseases makes diagnosing it rather complicated. To manage and treat properly, accurate finding is always important. Changes in clinical assessment methods, neuroimaging technology, biomarker research, and advances are

refining diagnostic precision. This is a Summary of current research findings relating to diagnosis of Parkinson disease (Munhoz et al., 2024).

٥,١Clinical DiagnosisThe clinical diagnosis of PD is based on a number of criteria. The most frequently used criteria is UK PD Society Brain Bank (UKPDSBB) criteria, which require at least two out of three cardinal motor features to be present: rigidity, bradykinesia (slowed movement), and resting tremor. Importantly also, other diseases that can mimic PD were to be excluded. As such, diagnoses require careful patient history and clinical examination, symptom progression, as well as response to dopaminergic treatment (Jankovic 2020) .

٥,٢Neuroimaging TechniquesNeuroimaging was an essential component in assisting with PD diagnosis. Different imaging modalities allow for the visualization of abnormalities in brain structure and function that develop before observable symptoms of PD appear (Politis, 2014).MRI: MRI is often used to exclude other conditions that can present with parkinsonism, such as stroke or tumors. Even though MRI is not very sensitive in detecting early PD, it can show atrophy of brain structures including the substantia nigra affected in PD. High-resolution MRI allows identification of structural changes related to the disease as explained in a scientific study, but it is used more when proving that PD does not occur than diagnosing PD itself (Tuite, 2017).Positron Emission Tomography (PET) — Imaging via PET permits an understanding of the functional changes in the brain. Example: PET – Dopaminergic activity and dopamine transporter density (Pine et al 2001). Other studies using PET have demonstrated that decreased PET tracer binding to dopamine transporters reflects PD. Nevertheless, PET is rarely performed in a clinical setting because it is expensive and less available.

٥,٤Single Photon Emission Computed Tomography (SPECT) — SPECT imaging is more frequently employed than PET in the diagnosis of PD. We use radiolabeled ligands that bind to dopamine receptors or transporters to allow SPECT to assess the function of neurons that produce this important neurotransmitter. This technique is helpful in the differentiation between the Parkinsons disease and other parkinsonian like syndromes (Yao et al., 2020). According to Zhang et al. (2023), SPECT imaging can reveal reduced striatal dopamine uptake, which is a hallmark of Parkinson's disease (Kim et al., 2023).

٥,٣BiomarkersIntroduction Biomarkers are emerging to advance the specificity and early diagnosis of PD. Presently the research is trying to recognize definitive organic markers in blood, cerebrospinal liquid (CSF), or even by means of imaging strategies (Lotankar et al., 2017).

.٥,٣,١Alpha-SynucleinClump of alpha-synuclein protein inside wonderfully named Lewy bodies are one of the main pathological features of Parkinson's disease. Researchers have previously suggested that CSF levels of alpha-synuclein or specific alpha-synuclein aggregates could help confirm PD diagnosis. Other highlights of the study include stating that developments in biomarker research such as detection for misfolded alpha-synuclein may allow more accurate diagnosis. (Lotankar et al., 2017).

٥,٣,٢Neuroimaging BiomarkersDevelopment of advanced imaging methods for detecting Parkinson's disease biomarkers is very useful method in PK diagnosis. The application of certain PET tracers specifically binding to neuroinflammatory markers or tau proteins may add complementary diagnostic information.

٥,٣,٣Genetic Biomarkers :Genetic testing is appropriate and utilized when there is a robust family history of PD or early-onset1 PD. Finding a change in a genetic risk factor such as LRRK2 or PINK11 can provide confirmation of the diagnosis, especially when the disease runs in families. On the other hand, for sporadic Parkinson's disease cases genetic testing is not standard of care yet. (Cook et al., 2021).

٥,٣,٤Differential DiagnosisParkinson's disease can only be accurately diagnosed through exclusion — in other words, it must be distinguished from other similar ailments. Distinguishing different disorders is important, as some disorders (such as essential tremor, progressive supranuclear palsy [PSP], or multiple system atrophy [MSA]) can have overlapping symptoms. Parkinson's disease is differentiated from these other disorders based on clinical features, response to treatment, and imaging findings. Savitt et al. To accurately compare and contrast Parkinson's disease to parkinsonian syndromes, Wong et al. (2022) point out the importance of a thorough clinical evaluation whether through patient history, phenomenon reports or diagnostic imaging findings. (Bu et al., 2019).

.٦Treatment

There is currently no cure for Parkinson's disease but, it can be mange the symptoms and not prevent the disease. To achieve the best benefits, it requires individualized therapeutic approach and depends on the disease severity, duration and time of onset (Titova and Chaudhuri, 2017). PD treatment may require a combination between symptomatic pharmacological and non-pharmacological treatment.

٦,١Pharmacological treatment

٦,١,١Levodopa

Levodopa, the main effective drug in treatment of PD. Although levodopa may control motor problems that caused by low dopamine levels, it cannot control motor problems produced by low acetylcholine level in another pathway (Olanow et al., 2004, Talebi et al., 2024).Furthermore, after several years of LD treatment, many patients develop motor complications , including wearing-off in between doses and dyskinesias, which impact on their activities of daily living routine and impaired quality of life (Espay et al., 2018). For that, current Levodopa formulation is always combined with carbidopa, which is an aromatic acid decarboxylase inhibitors to prevent its peripheral metabolism and consequently diminish the risk of nausea and increase drug bioavailability (Müller, 2020). Continuous administration of Levodopa with other medications is recommended in order to reduce the complications initiated by high doses of a single Levodopa (Livingston and Monroe-Duprey, 2024).The duration of levodopa activity may be boosted by blocking dopamine metabolism by adding Monoamine oxidase inhibitors (MAOIs), catechol-O-methyl transferase inhibitors (COMTIs), or dopamine agonists drugs (Hasna et al., 2024, Regensburger et al., 2023).

٦,١,٢Dopamine agonistsDopamine agonists medication straight stimulate dopamine receptors (D1 to D5) at postsynaptic site and they used as treatment method for motor symptoms. The lack of dopamine availability in the nigrostratial pathway is cause of many PD symptoms (Luo et al., 2020).

Dopamine agonists can be administrated as mono-therapy for motor symptoms or as combination with levodopa when the symptoms are not well controlled and when motor fluctuations are existent (Ruan et al., 2021, Latif et al., 2021). This group includes bromocriptine, pergolide , pramipexole , and ropinirole. Pramiprexole is useful in mange non-motor symptoms like depression (Latif et al., 2021).

The most recorded adverse effects of dopamine agonists include anxiety, orthostatic hypotension hallucinations and oedema. Additionally, this group of drugs have been connected to some behavioural problems including pathological gambling, eating, depression and compulsive shopping (Isaacson et al., 2023, Mohammad et al., 2021).

٦,١,٣Monoamine oxidase inhibitorsMonoamine oxidase inhibitors (MAOIs), include rasagilin, selegiline and safinamide work to reduce the breakdown of dopamine and levodopa in synapsis and prolong their therapeutic effects (Özdemir et al., 2021). They could be used in patients with mild symptoms at the beginning of the disease or to reduce tremor or dyskinesias at the late stage (Tan et al., 2022).

٦,١,٤Catechol-O-methyl transferase inhibitorsThis group includes entacapone, tolcapone and opicapone. They prevent degradation of levodopa peripherally and centrally, and so, rise central levodopa and dopamine levels and increase their duration of action. That could avoid the end of-dose wearing-off side effect of levodopa (Song et al., 2021, Müller, 2015).Their adverse effect involves nausea, diarrhoea, postural hypotension, also orange discoloration of urine is common. The usage of tolcapone is limited due to its hepatotoxicity effect (Müller, 2015).

٦,١,٥AnticholinergicsAnticholinergics are antagonists of acetylcholine muscarinic receptors that located in postsynaptic position. They are primarily used to decrease tremor as well as have no effect on bradykinesia (Jankovic and Tan, 2020). Though, they have low effectiveness and a high frequency of adverse effects like cognitive impairment, confusion, blurred vision, gastrointestinal effect and urinary retention. This group include trihexyphenidyl and benztropine (Salamon et al., 2022).

٦,١,٦Neurotrophic factorsAll Nerve cells need neurotrophic factors (NTFs) to develop and survive. They are small natural proteins that help preserve the morphology and function of nerve cells. NTFs are transported by the nerve terminals and moved to the soma of the projecting neurons to protection, this is termed “neurotrophic hypothesis” (Rotondo et al., 2023). Current study showed that the outcomes of clinical studies reported beneficial effects of NTFs like improvements in motor signs besides quality of life (Mahato and Saarma, 2024).

٦,٢Surgical treatment Many patients with advanced disease have a problems includes fluctuating response, dyskinesia and levodopa resistant. Therefore surgical approaches for example, stereotactic destruction of physiologically overactive brain is a good strategy (Jankovic, 2008). A study include carrying out a stereotactic posteroventral pallidotomies on many patients, showed nearly a complete assistance to reduce rigidity, tremor and hypokinesia in many patients (Foltynie et al., 2024, Al Aghory et al., 2024) .

٦,٣Non-drug treatment Patients with PD move slowly when the disease progresses and their muscles steadily become weaker with time. For that, exercises and sports are helpful to slow that process (Lee and Yankee, 2021). Change life style is important that include drinking a plenty of water, eating regular small meals and avoiding alcohol intake. To control hypotension, salt supplementation helps plasma volume expansion with eater intake to elevate the blood pressure (Lee and Yankee, 2021, Ahn et al., 2017).

.٧Conclusion Parkinson's disease has been known for more than 200 years. It becomes wide spread all over the globe, which called scientists to find a combination of treatment with other healthy style agents to able patients to live a better life.Now days, significant strides have been achieved in comprehending the etiopathogenesis of PD and in managing the symptoms associated with PD. Nonetheless, as it stands, there are no viable neuroprotective or disease-modifying treatments that can impede the progression of the disorder. The physical, psychological, social, and financial strains imposed by PD are overwhelming and remain the most formidable therapeutic challenge, particularly during the later stages of the illness.

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