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Parkinson's Disease: An Integrative Analysis of Pathophysiology, Genetic Susceptibility, Diagnosis, Therapeutic Strategies, and Emerging Researches

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مرض باركنسون : تحليل تكاملي لآليات المرض الأسباب الجينية، التشخيص ، العلاج والأبحاث الناشئة

عـلى عبد الـسـلام خـليفة الـشيبـانى
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Abstract:

Parkinson's disease is a chronic , degenerative and the second most prevalent neurodegenerative disorder, with a wide spectrum of clinical features, caused by a group of interaction factors , mainly , genetic and environmental factors. PD is marked by a progressive decline in dopaminergic neurotransmission in the human midbrain, as well as, aggregation of Lewy bodies. patients with PD can demonstrate a wide array of motor symptoms, including tremor, muscle rigidity, and slowed movements (bradykinesia). Genetic studies of familial forms of PD have revealed rare causative mutations in at least three genes responsible for autosomal recessive inheritance patterns.. The accurate diagnosis of Parkinson's disorder is a vital for prognostic and therapeutic reasons and is essential for all clinical research, moreover, the available medications mainly manage the dopaminergic features of the disease, however, the medications for the management of non-motor symptoms is inadequate. Advances in genotyping technology have paved the way of a high-throughput genome-wide screening of common variants in large populations offering a novel opportunities for the investigating the genetic basis of Parkinson's disease.

Keywords: Autosomal recessive, Bradykinesia, Dopaminergic Neurotransmission, Lewy bodies, Parkinson's disease

الملخص

مرض باركنسون (PD) هو اضطراب عصبي مزمن ، وهو ثاني أكثر الاضطرابات العصبية شيوعًا، يتميز بمجموعة واسعة من السمات السريرية، و يكون ناجم بشكل أساسي بسبب مجموعة من العوامل المتداخلة ، أبرزها العوامل الوراثية والبيئية. يتميز مرض باركنسون بفقدان ناقل الدوبامين العصبي في الجزء الأوسط بالدماغ البشري، بالإضافة إلى تراكم أجسام لوي. قد يُظهر مرضى باركنسون مجموعة واسعة من الأعراض الحركية، بما في ذلك الرعاش وتصلب بالعضلات وبطء الحركة . وقد كشفت دراسات ان مرضى باركنسون العائلي بسبب طفرات نادرة تشمل ثلاثة جينات على الأقل ، تعرف بالطفرات الجسمية المتنحية. إن التشخيص الصحيح لمرض باركنسون مهم لأسباب تشخيصية وعلاجيه وهو ضروري لجميع الأبحاث السريرية. علاوة على ذلك فإن الأدوية المتاحة تعالج بشكل أساسي السمات الدوبامينية للمرض ومع ذلك، فإن الأدوية للتعامل مع الأعراض غير الحركية غير كافية. وقد مهدت سرعة التطورات في تكنولوجيا الطريق لتحديد النمط الجيني للمتغيرات الشائعة في مجموعات سكانية كبيره مما أتاح فرصًا جديدة في تحديد السبب الجيني لمرض باركنسون.

الكلمات الدالة: أجسام لوي ,الناقل العصبي دوبامين ، النمط المتنحي ، البطء الحركي ، مرض باركنسون

Introduction:

Parkinson’s Disease Overview

Parkinsonism refers to all clinical states characterised by three typical neuromotor symptoms including tremor, muscle rigidity, and slowed movements (bradykinesia). Parkinson’s Disease is the most common form of Parkinsonism. It is the second most prevalent neurodegenerative disorder of adults and is part of a group of conditions called motor system disorders. Parkinson’s Disease (PD) is associated with the loss of dopamine-

producing nerve cells in the substantia nigra as well as the accumulation of protein deposits in the cytoplasm known as Lewy Bodies. Fig (1)

Generally, onset before 20 years is considered to be juvenile-onset. Before 50 years is classified as early-onset disease. Onset after 50 years is considered to be late-onset PD.The majority of cases are sporadic and of unidentified origin, but several genes have been determined that when mutated, lead to rare, familial forms of the disease. (1.21. 23)

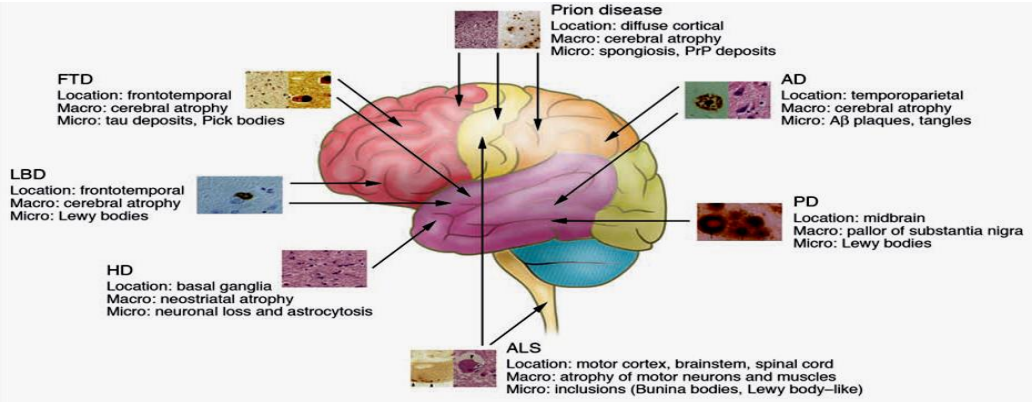

Fig. 1. Areas of the brain affected in neurodegenerative disorders, *Bertram et al 2005*

Parkinson's Disease develops because of several processes that occur in the brain.

Symptoms develop as particular cells are damaged in parts of the brain stem known as the substantia nigra (SN). These cells release dopamine which is necessary neurotransmitter. Loss of dopamine in the corpus stratia is the main defect in Parkinson's Disease and is the hallmark feature in PD.

Loss of dopamine negatively affects the nerves, influencing muscles controlling movement and coordination, resulting in the major symptoms characteristic of Parkinson's Disease Dopamine also appears to be essential for efficient information processing, and may also be responsible for problems in memory and concentration that occur in many patients (2, 21, 23)

The main objective of this review article, is to provide a extensively and integrative investigation of Parkinson's disease (PD, regarding, miscellaneous pathophysiology, genetic predisposing , diagnostic advancements, as well as emerging therapeutic strategies. this review aims to clarify the complex mechanisms contributing to the onset and progression of PD, Additionally, the article seeks to critically examine diagnostic methodologies and evaluate the efficacy and limitations of conventional and novel treatment strategies. it also highlights the knowledge and the recent research that may enhance early detection, improve patient outcomes, and eventually contribute to the enhancement of disease-modifying therapies. .

The symptoms of Parkinson diseases

The symptoms of PD are due to the reduction the brain cells required to produce a chemical called dopamine in a specific part of the brain namely, the ***substantia nigra***. Fig(2)

This chemical is required for several pathway functions in the brain, particularly those involved in controlled movement, cognitive function, behavioural control and control of other brain functions.

The most recognisable symptoms associated with PD are tremor (involuntary rhythmic muscle contractions), muscle rigidity, and slowed movements (bradykinesia). (20. 21)

Fig. 2 The specific part of brain known as (the substantia nigra.)

1. Tremors

Parkinson's Disease (PD) symptoms often begin with tremor, which may occur in the following ways:

Tremors may be only occasional, starting in one finger and spreading , eventually to involve the whole arm. The tremor is often rhythmic , 4 - 5 cycles per second), and frequently causes an action of the thumb and fingers known as pill rolling.

Tremors may manifest when the limb is either at rest or maintained in a rigid, unsupported position. They usually disappear briefly throughout movement and do not arise during sleep.
Tremors can also finally occur in the head, lips, tongue, and feet, and also symptoms can occur in one or both sides of the body. However, approximately 25% of patients diagnosed with Parkinson's Disease do not exhibit tremor symptoms.(15)

2. Motion and Motor Impairment

Akinesia is a result of severely diminished dopaminergic cell activity in the pathways associated with movement. It is common in severe cases of PD which is seen as slowness of motion, particularly when initiating any movement.
Bradykinesia , is the progressive slowing of voluntary movements, represents one of the cardinal motor symptoms of Parkinson's disease.
Patients may eventually develop a curved posture and a slow, shuffling walk. Patients' posture can be unstable and there is an increased risk for falls, the gait, also can be inconsistent and unsteady making it complicated to pass through narrow spaces such as doorways.
Intestinal motility (the ability to swallow, digest, and eliminate) may slow down, causing eating problems and **constipation**. Muscles may become rigid and often begins in the legs and neck. Muscle rigidity in the face can create a mask-like, staring appearance. Motor abnormalities that limit action in the hand may develop in late stages. Handwriting for instance often becomes small. (30.32)

3. Motor Features of Parkinson's Disease
PD is also associated with a wide range of non-motor symptoms also which may affect individuals.
A full list of the most widespread for all motor and non-motor symptoms included bellow as :
Neuropsychiatric dysfunction and mood disorders
Apathy and anhedonia
Frontal executive dysfunction
Dementia and psychosis
Sleep disorders
Sleep fragmentation.
Excessive daytime somnolence
Autonomic dysfunction
Orthostatic hypotension
Urogenital dysfunction
Constipation
Sensory symptoms. (24.32)

Aetiology of Parkinson
The exact cause of sporadic Parkinson's Disease is unidentified. Scientists assume that PD is probably due to a combination of genetic and environmental factors. (1)

1. **Genetic Susceptibility of** PD
Specific genetic factors appear to play a vital role in early-onset Parkinson's Disease, an uncommon form of the disease. Recent research suggests that multiple genetic factors may also be involved in some cases of late-onset Parkinson's Disease. (1. 24)

Causative genes of inherited Parkinson's Disease

Most PD cases are sporadic and idiopathic and only 10–15% of cases are familial due to Mendelian inheritance.
Currently mutations in five genes definitively cause familial PD. Mutations in at least three genes cause autosomal recessive, Levodopa-responsive parkinsonism with early-onset and no atypical signs. A fourth gene (ATP13A2), initially associated with atypical multisystemic phenotype, might also play a role in rare cases with early-onset PD.
In addition, several chromosomal loci are also linked to familial PD. Table. (1)
Mutations and over expression of α-synuclein cause intracellular inclusions and early rapid onset PD. Lewy bodies, eosinophilic cytoplasmic proteinaceous inclusions composed of fibrillar filaments are the pathologic hallmarks of the dominantly inherited PD as well as the idiopathic PD. (1.17. 20.42)

Gene	Mode of Inheritance	Phenotype	Proposed function in PD
α-Synuclein	Autosomal dominant	Early onset	Binding to synaptic vesicle (SV)
Parkin	Autosomal recessive	Early onset (<40 yrs)	E3ligase
UCH-L1	UNCLEAR	Classic	Ubiquitin hydrolase
PINK1	Autosomal recessive	Early onset	Mitochondrial Kinase
DJ-1	Autosomal recessive	Early onset	Molecular chaperone
LRRK2	Autosomal dominant	Classic	hyperactive kinase

Table:**1**. Genes associated with Mendelian PD. α-Synuclein (**SNCA**) Central role to PD pathology due to Lewy body formation and disrupts synaptic vesicle, **Parkin** function as E3 ubiquitin ligase; mitophagy regulation, mitochondrial quality control, **UCH-L1** mutations impair ubiquitin hydrolase, **PINK1** acts as Kinase activating Parkin; mitophagy initiation, and mitochondrial homeostasis, **DJ-1** mitigates oxidative damage, **LRRK2** involved in vesicular trafficking, autophagy, and neuroinflammation. (49.50..51)

SNCA / Synuclein/ (PARK1.

Synuclein is a soluble protein consist of 140 amino acid with unknown function. High levels are observed in the neurons, particularly the presynaptic terminals. The protein appears to form the structural element of Lewy body. (40, 47)

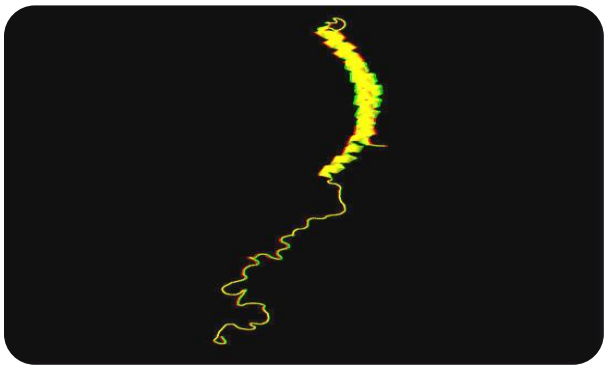

Fig. 3. structure and dynamics of micelle-bound α-synuclein consists of two curved α-helices, termed helix-N (Val^{3}-Val^{37}) and helix-C (Lys^{45}-Thr^{92}), the misfolding of the protein α-synuclein **(αS)**, associates with presynaptic vesicles, has been implicated in Parkinson's disease. *Marco A. Saraiva* 2021.

Parkin (PARK 2)

Parkin is known as the causative gene in autosomal recessive juvenile parkinsonism (ARJP). It's role is in ubiquitination of target proteins for degradation. Loss of function mutations of parkin is thought to cause the accumulation of one or more parkin substrates. Four substrates have so far been identified. (38.42)

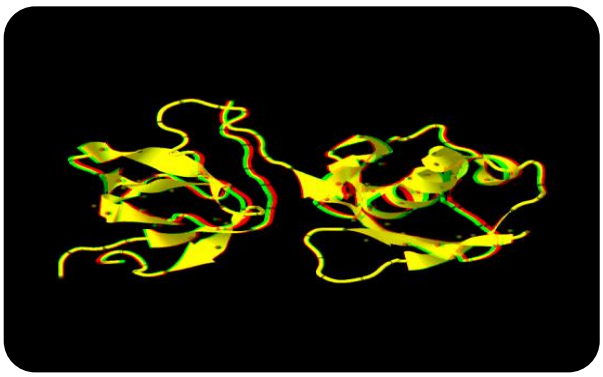

Fig 4. Solution NMR (Nuclear Magnetic Resonance) structure of the parkin Ubl domain in complex with the endophilin-A1(endocytic **BAR** proteins) SH3 domain. Parkin is a RING-type E3 ubiquitin ligase with an N-terminal

ubiquitin-like domain. Mutations in the **parkin** gene are responsible for a common inherited form of Parkinson's disease (PD). (50)

PINK1 (PARK6): Mutations in the PINK1 gene are the second most frequent known cause of autosomal recessive early onset parkinsonism. PINK1 mutations account for percentages ranging from 1% to 8% of the sporadic cases with early- onset PD.The clinical phenotype in PINK1-related disease appears broadly similar to that of parkin- and DJ-1-related disease.(23, 49, 51).

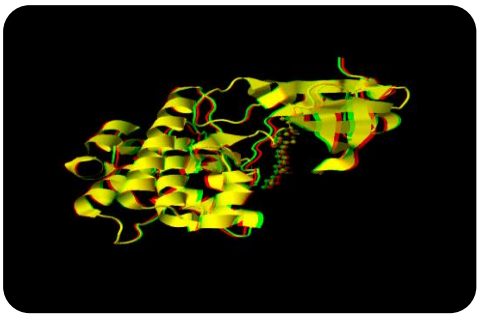

Fig 5. Aurora A kinase activated mutant (T287D) in complex with A 5-aminopyrimidinyl qinazoline inhibitor.
The **PINK1 gene** encodes the **PTEN-induced putative kinase 1 (PINK1)**, a mitochondrial **serine/threonine**-protein kinase crucial for maintaining mitochondrial function and protecting cells from stress-induced damage. AURKA's hyperactivity could suppress PINK1-mediated protective pathways. *Wiggins et al.*, 2019.

DJ-1 (PARK7): DJ-1 is another gene causing autosomal recessive early onset Parkinsonism. Found mainly in the brain where it is largely cytoplasmic except for a pool of DJ-1, which localises to mitochondria. DJ-1 is also, involved in antioxidative defence mechanisms and its mutants are susceptible to environmental toxins.
DJ-1 is oxidatively damaged in the brains of patients with idiopathic PD, thus suggesting a mechanism of protein aggregation in these diseases that is mediated by high levels of oxidative stress. (49.51)

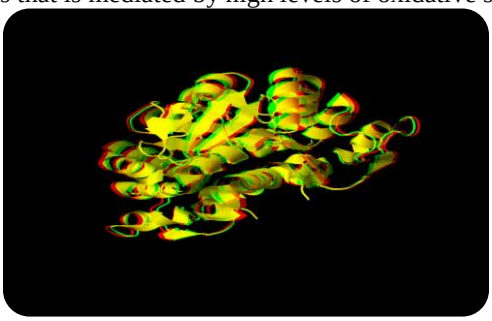

Fig. 6. Crystal structure of E18Q DJ-1 with oxidized C106.

E18Q. A missense mutation where glutamic acid (E) at position 18 is replaced by glutamine (Q). This mutation alters DJ-1's structure and function. ooxidised C106 (C106-SO_2H): The oxidized form of C106, which is essential for DJ-1's neuroprotective function. *Wilson, M. A., et al.* 2021

LRRK2 (PARK8): Is a large gene consist of 51 exons which encodes a large and complex protein, termed LRRK2 (or **dardarin**). LRRK2 mutations might account for up to ~10% of the autosomal dominant PD families.LRRK2 is unique among the known PD-causing genes in that mutation is low penetrance, LRRK2 mutations have been described in both familial and sporadic. (20.49)

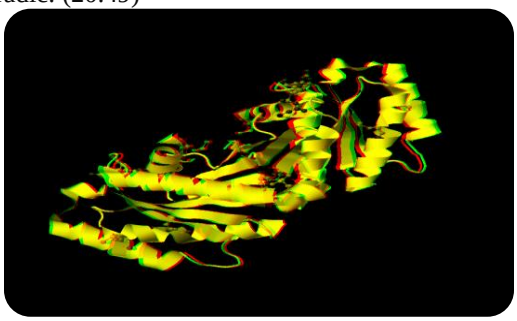

Fig. 7. Structure of the **ROC** domain from the Parkinson's Disease-associated leucine-rich repeat kinase 2(**LRRK2**) reveals a dimeric GTPase. The ROC (Ras of Complex proteins) domain is a critical **GTPase** domain found in the leucine-rich repeat kinase 2 (**LRRK2**), which is associated with Parkinson's disease (PD). The ROC domain

forms a dimeric structure and plays a key role in regulating LRRK2's kinase activity through GTP binding and hydrolysis. Mutations in the **ROC** domain are linked to familial PD. *Purlyte et al*. 2022.

2. Mitochondrial dysfunction:

Mitochondrial involvement in sporadic PD has been considered as studies have shown that within the substantia nigra the mitochondria show complex I deficiency. This has also been seen in several animal models.
Environmental toxins such as MPTP have been suggested to interfere with the mitochondria in nerve cells. (2, 33)

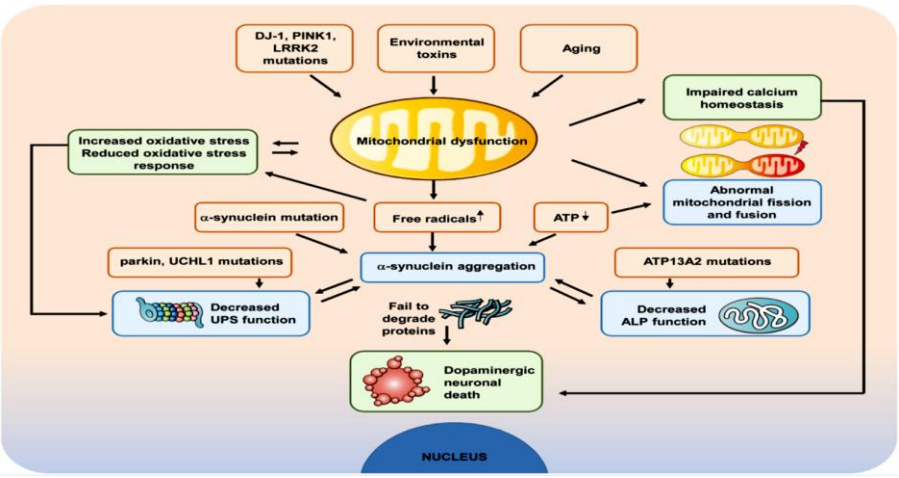

FIG.8. Mitochondria dysfunction and dopaminergic cell death in PD pathogenesis. several factors, including genetics, aging and environmental toxins, or combinations, have been associated with the etiology of PD. Abnormal metabolic function, abnormal morphology, and impaired fission-fusion balance have been seen in mitochondria in some forms of PD. Increased **OS** (oxidative stress) may result to impaired function of the (ubiquitin–proteasomal system (**UPS**), thus further affecting cell survival. All these may directly or indirectly impact the mitochondrial function of protein degradation systems, including **UPS** and **ALP** (the autophagy lysosomal pathway) thus, leadin the death of dopamine neurons. *Kim et al* 2005

2. Environmental Factors:
although environmental factors alone are unlikely to be a direct cause of Parkinson's disease, they may contribute to its onset in individuals with a genetic predisposition. Emerging evidence suggests that exposure to certain pesticides and herbicides could play a role in some cases. This is supported by the observed higher prevalence of parkinsonism in rural populations, mostly amongst agricultural workforce and those who consume private well water.. (1, 38)

3. Risk Factors:

Age. The average age of onset of Parkinson's Disease is 55 years old . Approximately 10% of Parkinson's cases are in people younger than 40 years old. Older adults are at higher risk for both Parkinsonism and Parkinson's Disease.
Gender. Parkinson's Disease is more common in men than in women.
Family History. People with siblings or parents who developed Parkinson's at a younger age are at higher risk for Parkinson's Disease, but relatives of those who were elderly when they had the disease appear to have an usual risk.
As to Race and Ethnicity, African and Asian-Americans show to have a lower risk than Caucasians. (1)

Diagnosis of Parkinson's Disease.

Parkinson's disease (PD) is a multifaceted movement disorder that shares clinical features with several other neurological conditions. Given the overlapping symptomatology, accurate diagnosis relies on a thorough differential diagnosis. Clinicians must therefore be knowledgeable in distinguishing PD from similar disorders to ensure appropriate management.
The early diagnosis of Parkinson's disease presents considerable challenges and there is currently no diagnostic test that can confirm PD but thorough understanding of the broad clinical features is important in detection and diagnosis. An early diagnosis of Parkinson's disease is highly desirable, as it facilitates well-timed intervention and may assist slow the progression of the disease. (35)
Diagnosis is based on neurological examination, which includes evaluation of typical symptoms and their severity.

Neuroimaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), Electroencephalograms (EEGs), or positron-emission tomography (PET) may be very useful for differentiating PD from other disorders with similar symptoms but they are not effective in determining Parkinson's. Fig.8 (6. 3. 37)

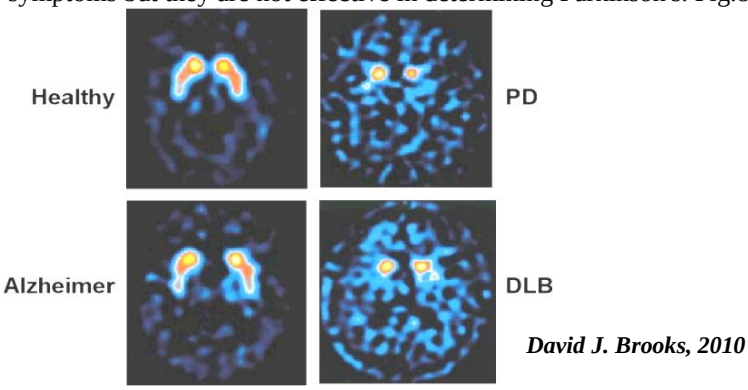

Fig. 9. images of healthy subject and PD, Alzheimer, and DLB (Dementia with Lewy bodies) patients.

The Neurologic Examination:

A neurologic examination is conducted to assess patients with a movement disorder. The clinician takes a medical history and performs a physical examination to evaluate the nervous system. The neurologist will observes various aspects of the patient's movement, coordination and balance, paying particular attention to determining whether tremor, rigidity and slowness of movement are present.

This examination has several components with each one focusing on a specific part of the nervous system, which include: mental status, cranial nerves, motor system, coordination and the cerebellum, the deep tendon reflexes, and sensory system. The neurological examination can lead to inaccurate diagnoses, so careful assessment is required in addition to patience, and collaboration from the patient to avoid an inaccurate diagnoses.(21. 34)

Management and Treatment of Parkinson's Disease:

In fact, medical advances have been rapid in recent years, there is still no treatment for Parkinson's Disease (PD). Research is continually exploring new areas and refining current therapies as well as examining the causes of PD. However there are a number of options to enhance the quality of life for PD sufferers. Ultimately, treatment is a personalised process that involves finding the right balance for each patient and may require a period of trial and error to achieve an effective result. (36)

Pharmaceutical Approaches to PD Treatment:

Currently medications are the major intervention of choice to assist manage the symptoms of PD , changes not be as the PD symptoms are predominately as a result of the loss of dopamine producing cells in the brain this is target for most pharmaceuticals. Choice of drugs depends on several criteria such as patient age, the severity of the symptoms and drug tolerance, as patients may respond differently, so that, these considerations should be taken into account when determining treatment (23. 36)

Levodopa.

Levodopa is the most valuable choice for symptomatic control and is considered the gold standard for treating Parkinson's Disease. However, long-term treatment leads to involuntary movements and response to fluctuations which add to the difficulties of later disease management.

Levodopa is converted to dopamine in the brain which increases levels necessary to alleviate symptoms.

Carbidopa delays the biochemical transformation of Levodopa to dopamine until it crosses the blood-brain barrier. It improves the activity of Levodopa which can reduce some of the side effects, particularly nausea. Therefore most patients are given Levodopa combined with Carbidopa. Dosages of Levodopa can vary greatly from person to person as the disease progresses and according to individual metabolism. Certain foodstuffs, particularly protein, appear to affect the absorption of Levodopa. Therefore it has been recommended to be administered only after a light meal. (23.30)

Dopamine Agonists.

Dopamine Agonists has been revealed to be less effective than Levodopa in the treatment of mild-to-moderate symptoms of Parkinson's Disease when used independently . It can therefore be used collectively with Levodopa which stimulates dopamine receptors and produces a direct effect at the sites where dopamine is active in the brain.

Dopamine Agonists may be utilised alone as the initial therapy for people with newly diagnosed Parkinson's Disease in order to postpone treatment with Levodopa which is associated with a variety of side effects due to long term usage. This is particularly important in those diagnosed at a young age.
Moreover, Dopamine Agonists can be used combined with Levodopa. The effectiveness of this combined therapy can be used to reduce the dosage of Levodopa required initially, therefore can be used on long-term. (5.44)

Apomorphine

Apomorphine is a dopamine agonist administered via injection or infusion, is typically prescribed as an alternative treatment for individuals with advanced Parkinson's disease. .
Apomorphine is used with patients who are finding that their usual medications less effective by not providing an adequate balance between mobility and psychiatric side effects, such as hallucinations, anxiety or delusions. (5.18)
While the medication is not universally effective, it is increasingly utilized in individuals experiencing 'off' periods lasting 30 minutes or longer, particularly when symptom control remains suboptimal despite adjustments to standard pharmacological regimens. (5.37)

Amantadine

Amantadine is less effective than levodopa in managing the motor symptoms of Parkinson's disease, although it demonstrates greater efficacy in the later stages of the disease, particularly in alleviating levodopa-induced dyskinesias. However, the Current research findings concerning the overall efficiency of Amantadine in individuals with Parkinson's disease remains limited. (23,36)

Anticholinergics

Anticholinergic are considered to be beneficial in the management of Parkinson's disease, chiefly in patients younger than 70 years, in whom tremor is the predominant symptom. These agents may be administered as monotherapy or incorporated into combination treatment regimens, including administration with levodopa. While anticholinergics have shown efficacy in alleviating motor symptoms, such as resting tremor and dystonia, their use is associated with a range of neuropsychiatric adverse effects. (39)

COMT Inhibitors (Catechol-O-methyltransferase).

Catechol-O-methyltransferase (COMT) inhibitors are utilised only to treat patients with motor symptoms. COMT inhibitors do not directly treat Parkinson's Disease symptoms when used alone, but can be administrated combination with Levodopa or Carbidopa to facilitate a larger amount of Levodopa to reach the brain and enhances dopamine levels, thereby preventing drug destruction. Moreover, COMT inhibitors enable the dose of Levodopa to be reduced, thus potentially mitigate the severity of dyskinesias. (41)

MAO-B Inhibitors (Monoamine oxidase)

Monoamine oxidase inhibitors (MAO-B) are utilised in the early stages of Parkinson's Disease to manage mild symptoms and delay the need for Levodopa or other more intense medications. It can be used combined with Levodopa or as monotherapy with a lower incidence of adverse effects. MAO-B inhibitors may reduce fluctuations that may emerge after prolonged dopaminergic treatment. Their therapeutic effect is mediated by inhibition of dopamine metabolism in the brain, thereby prolonging dopaminergic activity. (23.35)
Although, pharmacological treatment remains the primary choice to manage the symptoms of PD, it may be associated with side effects in some patients, particularly, for patients at more advanced stages of the disease which includes:
Levodopa: the The predominant side effects of Levodopa are nausea, vomiting, decreased appetite, constipation, blurred vision, low blood pressure, fatigue, insomnia, psychiatric manifestations such as hallucinations, sudden sleepiness, and dyskinesia. (30, 35)

Dopamine agonists: possible side effects are nausea, vomiting, orthostatic hypotension by stimulating peripheral dopamine receptors, nightmares, hallucinations, and constipation is frequently observed among patients receiving these medication. (5)
Apomorphine: Common side effects associated with Apomorphine include, nausea, vomiting, dizziness headache, sore throat, runny nose, yawning, chest pain, increased sweating, flushing, and pallor. (37)
Amantadine: It has few side-effects such as nausea, dizziness and insomnia.
Anticholinergics: Possible side effects include dry mouth, constipation, urinary difficulties, mental confusion and sleep. (9, 41)

COMT inhibitors: These medications may cause side effects such as dyskinesias, nausea, vomiting, and potential liver impairment.(35)
MAO-B inhibitors: Generally, It frequently has few side effects such as hallucinations and hypotension is a potential side-effect. (36)

Management and recommendation for PD related symptoms.

The management of symptoms in PD is primarily indicative , since no pharmacologic therapies of the disorder are presently obtainable. It also requires an extensive strategies that integrates individualisation and interdisciplinary approach to deal with both motor and non-motor symptoms to enhance quality of life and overall function. (22.31)

Preliminary Monotherapy

it is an essential to account for the differences of efficiency and side-effect profiles of available drug classes when selection of an initial monotherapy for Parkinson's disease is taken, moreover, individual patient factors such as age, coexisting, and psychosocial conditions.

Levodopa is highly effective with the earlier onset of motor difficulties such as fluctuations and dyskinesias, at high doses or with a pulsatile dosing routine. In contrast, MAO-B inhibitors and dopamine agonists are linked to a lower risk of these complications in the early stages of treatment. As a result, these alternatives may be more suitable as first-line therapy in younger patients. (14.19)

Combination therapy

Combined pharmacological therapy should be considered when initial monotherapy at a reasonable dose fails to adequately manage dopamine-responsive symptoms, or when increasing the monotherapy dose is limited by intolerable side effects. In such cases, combining different medications such as levodopa with dopamine agonists and/or MAO-B inhibitors may be an useful approach, chiefly in the treatment of Parkinson's disease (PD) without motor fluctuations. (10.19)

Management of Motor Symptoms:

Motor fluctuations, these complications can be managed by administering a adjusting dosage of Levodopa or adding other agents such as, dopamine agonists, MAO-B inhibitors, or COMT inhibitors. The choice of these treatment options should be guided by individual patient factors, including therapeutic effectiveness, potential side effects, and personal preferences. (10.12. 13. 31)

Dyskinesia, for such Symptoms , Amantadine should be used to reduce dyskinesias in PD patients who experiencing motor difficulties induced by levodopa, however, its use should take into account the potential for anticholinergics and hallucinogenic side effects. Safinamide is another option that may be effective for treating moderate to severe dyskinesias. (12. 19.43)

Tremor, In cases of Parkinson's disease (PD) where tremor does not respond sufficiently to optimal doses of Levodopa, increasing the total daily dosage or administering higher single doses may produce clinical benefit in select patients. However, any long-term escalation of Levodopa should be carefully weighed against the heightened risk of motor complications associated with chronic use. Dopamine agonists are commonly utilised either as monotherapy or in combination with Levodopa to alleviate symptoms such as akinesia and rigidity; these agents often also yield improvements in tremor severity. The use of anticholinergics medications is commonly limited to exceptional cases in which tremor remains resistant to other treatments, due to their side effect profile. Additionally, beta-blockers may be considered specifically for the management of postural tremor in PD. (10. 13.19.43)

Advanced therapies, such as deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CSAI) are considered in patients experiencing persistent motor fluctuations or tremor unresponsive to an usual medication.(10.12)

Management of non- motor Symptoms:

Pain and fatigue, the mainstay of effective pain management in Parkinson's disease (PD) is the optimisation of dopaminergic therapy, as many pain symptoms are directly linked to motor fluctuations and rigidity.

Management of Receptors related pain (nociceptive pain) should be guided with the World Health Organisation's three –steps,Neuropathic pain should be treated with anticonvulsants and/or antidepressants, furthermore, **gabapentin** and **duloxetine** are preferred, mostly when depression represented as a coexisting condition.(19.43)

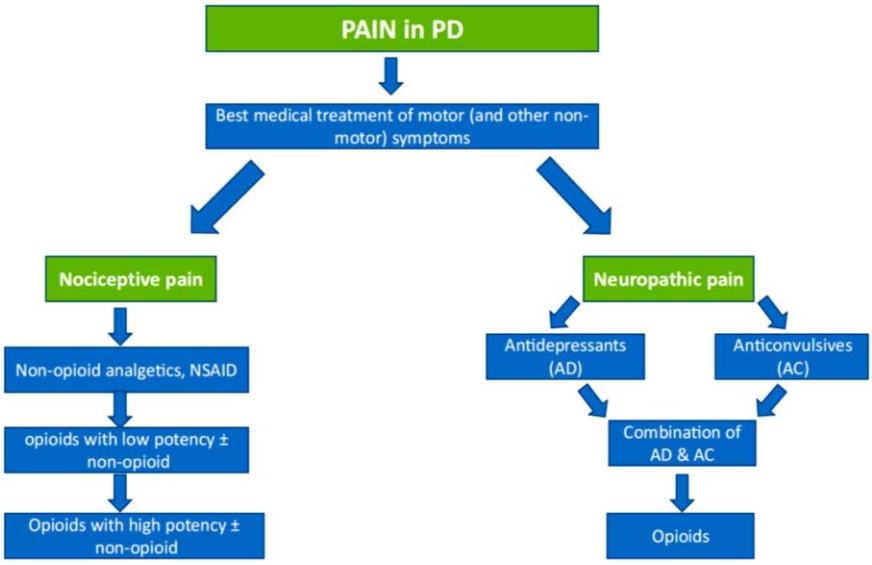

Fig.10Treatment algorithm for pain in PD patients; nociceptive pain according to WHO three-step-pain treatment scheme

Furthermore, optimising dopaminergic therapy is an essential for fatigue management in patients with Parkinson's disease (PD), If personalised treatment with dopamine agonists is appropriate, ***rotigotine*** may be a feasible option. **Modafinil** or **Safinamide** may be considered as a potential therapy for fatigue in PD patients. (7.10. 19)

Psychosis, Management for Psychosis cases should commence with the implementation of general non-pharmacological approaches. including strategies such as environmental modifications to lessen sensory overstimulation, reorientation techniques, and maintaining for the restoration of a normal circadian cycle.
Particular attention should be paid to reducing drugs with **anticholinergic**, **antiglutamatergic**, or **sedative** properties. Adjusting dose to antiparkinsonian medications should also be taken into an account , particularly, agents such as **amantadine**, **monoamine** oxidase B (**MAO-B**) inhibitors, **dopamine agonists**, and catechol-O-methyltransferase (**COMT**) inhibitors, as monotherapy or in combination. In case of cognitive impairment to an acetylcholinesterase inhibitor can be administrated as a potential therapy (10,12. 19)

Sleep disturbances: **REM** (Rapid Eye Movement) sleep behaviour disorder may respond to melatonin or low-dose clonazepam, it is also important to consider proper modifications to the patient's dopaminergic medication regimen if clinical evidences shows that that fluctuations in dopaminergic activity whether motor or non-motor are contributing to the sleep disturbance. Additionally, cognitive behavioural therapy is also offered as beneficial approach. (4.6.19.43)

Orthostatic Hypotension, The initial approach should focus on addressing any underlying factors, such as infections, dehydration, or other physiological stressors. A comprehensive review of the patient's current medications is essential, particularly in cases where antihypertensive agents are prescribed, besides dose reduction should be considered where appropriate.
Non-pharmacological strategies should be initiated early and include ensuring adequate fluid and salt intake, provided there are no contraindications such as cardiac, hepatic, or renal insufficiency. These measures form the foundation of symptom management and may significantly mitigate the occurrence and severity of orthostatic hypotension episodes. It also using Abdominal compression bandages during the daytime demonstrate greater efficiency compared to compression stockings.
As to pharmacological interventions for the management of orthostatic hypotension in PD patients, therapy with **midodrine** is recommended. Treatment with **fludrocortisone** may also be considered, and **droxidopa** represents an additional therapeutic choice. (12.19.43)

Therapy strategies

While a range of medications is commonly prescribed to manage the symptoms of Parkinson's, additional therapeutic approaches are available and are often necessary to enhance the overall well-being of persons diagnosed with Parkinson's disease. This may include general lifestyle changes and access to certain therapeutic options throughout the various stages of disease.

1. Physical Therapy

The primary object of physical therapy is to boost independence and the overall quality of patients life with Parkinson's Disease by improving movement and function, as well as, alleviating the pain.

Physiotherapists as qualified health professionals who utilize a range of physical treatments, including exercise, to manage joint stiffness, restore muscle strength and mobility.(14.22)

2. Occupational Therapy

The role of the occupational therapist is to support individuals with Parkinson's Disease and to allow them to maintain their normal level of self-care, employment and leisure activities for as long as possible.

Occupational therapists are clinical professionals trained to support and assist individuals with mobility impairment to achieve optimal function and independence, additionally, assessing an individual's ability to accomplish the activities of daily living and and providing recommendations to enhance safety at workplaces and home with manageability, which may involves recommendation about appropriate adaptations, aids or a certain equipment, particularly with movement disorder cases , it may also to engage carefully with selected tasks and activities. (9)

3. Speech Therapy

For some people with Parkinson's Disease, the muscles involved in speech and swallowing including those of the voice box,, throat, roof of the mouth, tongue, and lips may become weakened. Therefore patient may be referred to a speech therapist to maintain as many communication skills as possible.

Speech and language therapists are healthcare professionals who specialise in all aspects of communication, from facial expression and body language to speech and specialised communication aids.

If a patient demonstrate difficulties with communication or swallowing, a speech and language therapist can provide guidance on appropriate exercises, and specialised equipment to support these crucial functions and enhance quality of life. (28)

4. Complementary Therapies

Complementary therapies occasionally referred to as 'alternative medicine' are non-conventional health treatments, that are used alongside standard medical treatment as a complement, rather than an alternative.

Although there is currently insufficient evidence and limited research to regard the benefit from complementary therapies in Parkinson's Disease, some individuals find these therapies are useful particularly in terms of benefits from massage and relaxation for muscular stiffness, yoga for balance struggle, acupuncture for pain and discomfort and herbal remedies for concentration and mood inconvenience. (28)

5. Surgical Options

Deep brain stimulation (DBS**):** Deep brain stimulation is not appropriate for all individuals and is not considered as therapy for Parkinson's symptoms. However for some case it may assist to alleviate motor symptoms such as rigidity and tremor. (4)

Lesioning Techniques: Involve creating selective damage (a lesion) to specific cells within certain areas of the brain. The selected area is accurately identified using computer-assisted imaging, an electrode is then inserted to the optimum point through which a current is applied to create a lesion. These interventions have revealed to be beneficial for several PD symptoms.

The above-mentioned procedure are the most common surgical approaches, there are also other techniques, for instance, Infusion of chemical agents directly into the basal ganglia, to deliver growth factors which either prevent the degeneration of nerve cells or enhance growth of the dopamine-producing cells in the brain.

Researchers estimate that its effeminacy, safety issues and the long-term outcomes may require an additional 10 to 20 years of study.(4. 38)

Research of Parkinson's disease.

The actual causes of Parkinson's Disease (PD) remain largely unknown.. Through research, ideas and hypotheses have been developed , rejected, then re-evaluated as new evidence and new technology have emerged .

PD is such a interesting area of global research with comprehensive studies that conducted on a range of areas including diagnostic techniques, the stem cell therapy and the role of mitochondria in the pathogenesis of Parkinson's Disease for instance.

Research of stem cell therapy

Stem cell therapy has offered a hope for many individuals with PD though extensive research is still required. This study investigates a transplant of own bone-marrow derived mesenchymal stem cells into the sublateral ventricular zone using stereotaxic surgery, participants (aged between 22-62) were then followed up. An improvement in their UPDRS (the Unified Parkinson's Disease Rating Scale) score was observed, though the study was not sufficiently powered to confidently demonstrate safety and efficacy of the method. Nevertheless, it suggests a direction for further larger studies to be implemented. (15. 37)

The role of mitochondria in the pathogenesis of Parkinson's Disease

It has been identified that a damage which may accrue to mitochondrial proteins and nucleic acid, a cell will remove the damaged organelles. Mitochondria are known to be closely correlated with the pathogenesis of neurological conditions such as PD. Mutations in the **Parkin** gene can produce a protein that specifically binds to uncoupled mitochondria, essentially tagging them for self destruction. (42)

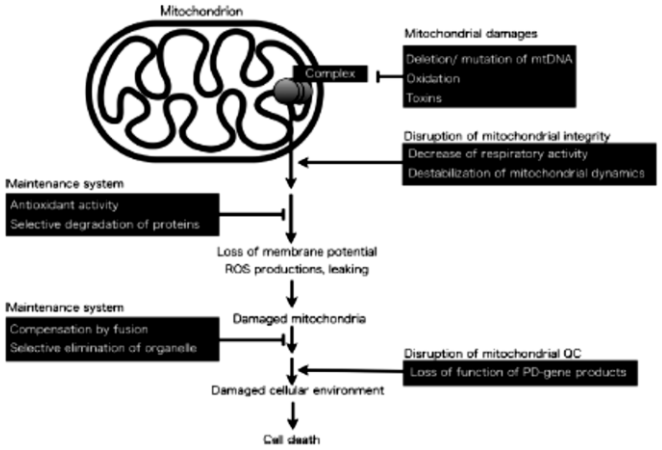

Fig. 11.The stress result from mtDNA mutations and oxidative stress, can impair mitochondrial functions which lead to self destruction.

Diagnostic techniques.

By demonstrating abnormalities in the midbrain of individuals suspected of having PD by transcranial sonography or diffusion-weighted MRI as well as dopamine terminal dysfunction with PET or SPECT can provide strong evidence for PD and justify certain treatments. These approaches are also useful for differentiation of non-standard presentations. (6, 27) (FIG. 10)

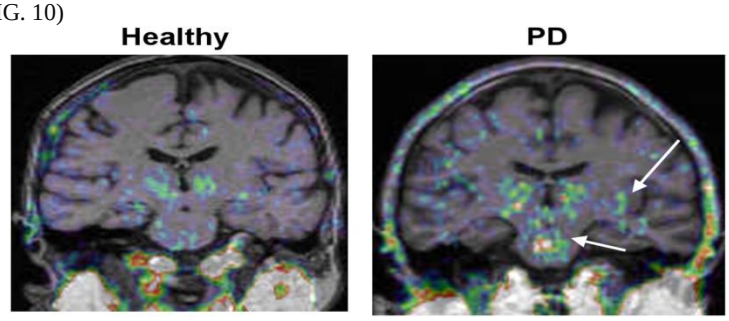

Fig. 12. PET scans of healthy person and PD patient. *David J. Brooks 2010*

Genetic research in Parkinson's disease as risk factor.

A multinational study has determined that there is a strong risk associated with mutations in the Glucocerebrosidase gene and Parkinson's Disease. This gene is also strongly linked, when deficient to Gaucher's Disease. A total of 16 research centers participated to compare the genetic variations in ~6000 patients and ~5000 controls. An Odds Ratio of **5.43** was obtained for any **GBA** (encodes a lysosomal enzyme (β-glucocerebrosidase) mutation in patients, versus controls. The study also demonstrated that individuals with any GBA mutation presented earlier with disease, had more affected family members and the symptoms seen were more varied. (39)

Furthermore, a new mouse model has been developed which will greatly help in the development and testing of new Parkinson's Disease therapies as well as helping to generate understanding of the underlying pathogenesis of the disorder. This particular mouse model expresses a mutated copy of the LRRK2 gene (Leucine rich repeat kinase 2) which is a seen frequently in cases of **PD**. Without this option it has been difficult to develop treatments and explore the disease process as without such an accurate representation of Parkinson's Disease. *Beal et al 2009.*

Simón-Sánchez et al, have performed a study on **1700** cases and **4000** controls and the findings subsequently replicated in a further 3400 cases and **4600** controls. Signals obtained were to genome-wide significance, confirming the SNCA and MAPT locus, as well as elucidating PARK16 as another significant risk factor in Parkinson's Disease. The LRRK2 locus was also implicated as a disease modifier. By Studying both Caucasian and Japanese populations, at this study, It was also determined a population-specific genetic heterogeneity in PD. (17,20,49,.50)

Genome-Wide Association Studies and Other Large-Scale Studies

Since 2007 there has been the facility to utilise a powerful research tool known as the Genome Wide Association Study or GWAS. The technique examines very large numbers of biomarkers across the whole genome in enormous numbers of samples for genetic variation that is associated with the disease/trait under investigation, based on the Common Disease Common Variant hypothesis (CDCV) (29.40)

GWAS considered to be significantly powerful to detect genes associated with common disease, more than linkage and candidate gene studies and is considered to be a priority . The three key developments that have enabled the advancement of genome-wide association studies (GWAS) are:

Completion of Phase 1 of the international **HapMap** project, which provide an extensive catalogue of genome-wide variation and linkage disequilibrium in four different populations, also, advances in technology, the production of intense genotyping array chips which contain many 100's of thousands of SNP's distributed across the genome. Besides , certain companies have been at the forefront of chip manufacture, namely Affymetrix and Illumina. (11.34)

Finally, there has been prior forethought across the worldwide research community to commence collection and facilitate access to large numbers of cases and controls needed for such studies. This was before the idea of this type of large study was considered, and the generation of large sample groups is a current process.

However, despite the fact that, GWAS is powerful to detect common variants, rare variants are relatively difficult to identify. (40)

To accomplish this, High-Throughput sequencing technology is required. This suggests that current technology allows 100-200Gb/run is possible, however this is not sufficient for examining the numbers of samples to the depth required to actually identify the rare disease causing variants, the cost considerations should be taken into an account.(25)

Next Generation Sequencing (NGS) is still too expensive for many required study. There is already a significant challenges with data storage generated from current GWAS, the data volume from genom resequencing is expected to exponentially increase, as well as, he analysis of such large-scale data . Bioinformatics tools are continually developing, however, it still poses uncertainty, as to keeping pace with a such rapid technology. (46)

Bioinformatics Tool for Parkinson's disease.

The Mutation Database For Parkinson's Disease (**MDPD**) provides an straightforward access resource for examining the genes that have been associated with PD , and the database features an intuitive search interface

There are a number of cross-references with other importan sites and databases such as OMIM, Entrez, and provides comprehensive information on identified genetic variants, including their potential for causing disorders.

PD Gene Database

One of the most useful tools for examining the outcome of Genome-Wide Association Studies is the PD Gene database. This facility has been generated by the Massachusetts General Hospital, Harvard Medical School, the Michael J. Fox Foundation and the Alzheimer Research Forum to provide a catalogue of all GWAS completed so far and an open access forum of results.

The site is comprehensive and simple to navigate, likely to be likely to be comprehensively utilised in academic studies, , presentations and further research. The database is frequently updated and supported by the research community.

Simón-Sánchez et al, have performed a study on **1700** cases and **4000** controls and the findings subsequently replicated in a further **3400** cases and **4600** controls. Signals obtained were to genome-wide significance, confirming the SNCA and MAPT locus, as well as elucidating PARK16 as another significant risk factor in Parkinson's Disease. The LRRK2 locus was also implicated as a disease modifier. By Studying both Caucasian and Japanese populations, at this study, It was also determined a population-specific genetic heterogeneity in PD. (40)

Therapeutic research in Parkinson's disease.

The hypothesis has been tested that PD risk and PD symptomatic decline can be measured using increasing concentrations of **urate**. This is actually a by-product of purine metabolism but also has antioxidant properties. The idea behind the study is that there has been known for a long time a correlation between raised **urate** levels and minimizing disease progression in PD. This has also highlighted the need for a clinical study to investigate this phenomenon and explore ways to slow the progression of Parkinson's disease. (36)

Whilst there is no treatment for Parkinson's Disease at the moment, it is hoped that the current research may assist to achieve the ultimate objective .Many of the treatments currently is being used to alleviate symptoms and allow individuals to lead an almost 'normal' life, the same methods do not suitable for all individuals and it can be a matter of trial and error. Nerve cell transplants have been attempted and some individuals have been seen to benefit, hence, the more research is required.

Gene therapy is yet to be fully explored. This is where new genes are added to nerve cells already in the brain which allows them to work differently or better. Currently this option is being concluded in animals and trialled in humans with promising results. A phase 1/2 trial is currently ongoing to assess CERE-120 gene therapy delivery to dying nerve cell, (50)

Conclusion:

Parkinson's Disease (PD) is a multifactorial neurodegenerative disease , result from a complex combination of genetic predispositions, environmental exposures, and, in some cases, geographical influences. This heterogeneity in etiology contributes to onset of disease and expressivity among individuals. Clinically, PD is primarily marked by motor symptoms such as bradykinesia, muscle rigidity , and tremors, alongside non-motor symptoms including speech impairments, cognitive decline, and mood instability.

Early diagnosis of Parkinson's Disease is of paramount importance, and Can profoundly influence the progression of the disease Early-stage detection enables the accomplishment of therapeutic strategies intended to symptom management, delaying disease progression, and enhancing efficient independency for a prolonged period.

Recent advancements in the medical and neuroscientific fieldsr through novel medication , neuroprotective strategies, or technological innovations such as deep brain stimulation are essentially improving the quality of life for individuals with PD.

In addition to conventional pharmacotherapy, non-pharmacological interventions play a essential role in comprehensive care. For instance, physical therapy, occupational therapy, and speech-language pathology, have been shown to alleviate motor and non-motor symptoms and improve functional outcomes. Complementary and alternative approaches such as acupuncture, nutritional support, and dietary modifications are also having recognized areas for their valuable benefits in mitigating symptom and overall well-being.

Given that Parkinson's Disease is a chronic and progressively deteriorating **condition.** there is an escalating emphasis amongst clinicians and researchers on evaluating the patients outcomes, principally, health-related aspects of quality of life. Combined quality of life assessments alongside clinical and laboratory findings offers a more deep understanding of disease impact and therapeutic efficacy, ultimately providing more personalised and successful management strategies.

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