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A systematic review on Parkinson's disease (PD)

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ABSTRACT

Parkinson's disease (PD) is a type of movement disorder. It happens when nerve cells in the brain don't produce enough of a brain chemical called dopamine. Sometimes it is genetic, but most cases do not seem to run in families. Exposure to chemicals in the environment might play a role. Symptoms begin gradually, often on one side of the body. Later they affect both sides. They include Trembling of hands, arms, legs, jaw and face Stiffness of the arms, legs and trunk Slowness of movement, Poor balance and coordination. As symptoms get worse, people with the disease may have trouble walking, talking, or doing simple tasks. They may also have problems such as depression, sleep problems, or trouble chewing, swallowing, or speaking. There is no lab test for PD, so it can be difficult to diagnose. Doctors use a medical history and a neurological examination to diagnose it. PD usually begins around age 60, but it can start earlier. It is more common in men than in women. There is no cure for PD. A variety of medicines sometimes help symptoms dramatically. Surgery and deep brain stimulation (DBS) can help severe cases. With DBS, electrodes are surgically implanted in the brain. They send electrical pulses to stimulate the parts of the brain that control movement.

KEY WORDS: Parkinson's disease (PD); Mutations; Motor and Non-Motor; Diagnosis; Levodopa.

INTRODUCTION

Parkinson’s (PD) is globally distributed, affecting all cultures and races, with an estimated worldwide prevalence of 6.3 million people. Parkinson's disease is a chronic (persistent or long-term) disorder of part of the brain. It is named after the doctor who first described it. Parkinson's disease was first described in 1817 by James Parkinson [1-4]. Parkinson’s disease is a progressive, degenerative neurological condition that affects a person’s control of their body movements. It mainly affects the way the brain co-ordinates the movements of the muscles in various parts of the body. It is not contagious and not fatal. It is thought to be genetic in a very small percentage of cases [5]. PD usually begins around age 60, but it can start earlier. About 5 to 10 percent of people with Parkinson's have "early onset" disease which begins before the age of 50. Early onset forms of Parkinson's are often inherited, though not always, and some have been linked to specific gene mutations. The disease affects about 50 percent more men than women; however younger people can be diagnosed with Parkinson’s too. This is referred to as Young Onset Parkinson’s [5-6]. In very rare cases, parkinsonian symptoms may appear in people before the age of 20. This condition is called juvenile Parkinsonism. It is most commonly seen in Japan but has been found in other countries (Italy or Brazil) as well. It usually begins with dystonia (sustained muscle contractions causing twisting movements) and bradykinesia (slowness of movement), and the symptoms often improve with levodopa medication. Juvenile Parkinsonism often runs in families and is sometimes linked to a mutated gene [7-9]. Evidence suggests that, in some cases, Parkinson’s disease may be inherited. An estimated 15 to 25 % of people with Parkinson's have a known relative with the disease. People with one or more close relatives who have Parkinson's have an increased risk of developing the disease themselves, but the total risk is still just 2 to 5 % unless the family has a known gene mutation for the disease [10]. A gene mutation is a change or alteration in the DNA or genetic material that makes up a gene. Researchers have discovered several genes that are linked to Parkinson's disease. The first to be identified was alpha-synuclein or SNCA. Inherited cases of Parkinson’s disease are caused by mutations in the LRRK2, PARK2 or parkin, PARK7 or DJ1, PINK1, or SNCA genes, or by mutations in genes that have not yet been identified [11-14]. Symptoms of Parkinson’s disease are caused by the progressive degeneration of nerve cells in the middle area of the brain. This causes a lack of dopamine, a chemical messenger necessary for smooth, controlled movements. The symptoms appear when about 70 per cent of the dopamine producing cells has stopped working normally. Parkinson’s disease cannot be cured, but the symptoms can be managed. With a combination of medication and multidisciplinary support, people with Parkinson’s disease can live independent and productive lives [15].

What Causes Parkinson’s?

Currently there is no known cause of understanding of why a person develops Parkinson’s. There are many theories as to the causes and it is generally thought that multiple factors are responsible. Medical experts are not yet certain what destroys the dopamine

producing nerve cells or what predisposes some people to develop Parkinson's and not others [16]. Many researchers think that the condition may be caused by a combination of genetic and environmental factors and may vary from person to person. However, Parkinson's is not an infectious disease and it is not contagious [17].

Genetics: Several genetic changes (mutations) have been identified as increasing a person's risk of developing Parkinson's disease, although exactly how these make some people more susceptible to the condition is unclear. Parkinson's disease can run in families as a result of faulty genes being passed to a child by their parents, however, inheriting the disease in this way is rare. Recent advances in genetic studies have identified mutations in a number of pathogenic genes (SNCA, Parkin, UCHL1, DJ-1, PINK-1, LRRK2 and ATP13A2 genes) that contribute to familial forms of PD [18-21].

Environmental factors: Some researchers also feel that environmental factors may increase a person's risk of developing Parkinson's disease. It has been suggested that pesticides and herbicides used in farming and traffic or industrial pollution may contribute to the condition. However, the evidence linking environmental factors to Parkinson's disease is inconclusive. The potential environmental risk factors include farming activity, pesticide exposures, well-water drinking, and history of head trauma [20-21].

Other causes of Parkinsonism: Parkinsonism' is the umbrella term used to describe the symptoms of tremors, muscle rigidity and slowness of movement. Parkinson's disease is the most common type of Parkinsonism, but there are also some rarer types where a specific cause can be identified [21]. These include Parkinsonism caused by:

Medication ('drug induced Parkinsonism'): where symptoms develop after taking certain medications, such as some types of antipsychotic medication, and usually improve once the medication is stopped

Other progressive brain conditions: such as progressive supranuclear palsy, multiple systems atrophy and corticobasal degeneration

Cerebral infarction: where a severe stroke causes several parts of the brain to die

What Causes Parkinson's Symptoms?

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine producing brain cells. Parkinson's disease is caused by a loss of nerve cells in part of the brain called the substantia nigra. This area of the brain sends messages down nerves in the spinal cord to help control the muscles of the body. Messages are passed between brain cells, nerves and muscles by chemicals called neurotransmitters [22-23]. Dopamine is the main neurotransmitter that is made by the brain cells in the substantia nigra. Dopamine plays a vital role in regulating the movement of the body and a reduction in dopamine is responsible for many of the symptoms of Parkinson's disease. This lack of dopamine means people can have difficulty controlling their movements and moving freely. Exactly what causes the loss of nerve cells is unclear. Most experts think that a combination of genetic and environmental factors is responsible [24-25].

PARKINSON'S SYMPTOMS

Parkinson's entails symptoms of many types – motor and non – motor. However, not every symptom affects every PwP, & the intensity of symptoms varies across individuals. In addition to these four cardinal motor symptoms there are many others which are also considered in the diagnostic process. Often the non-motor symptoms are more challenging for the person living with Parkinson's. Nonmotor symptoms such as pain, depression and problems with memory and sleep can also occur and have an impact on the day to day life of the person with Parkinson's [2, 4, 26-27]. The Four main symptoms of Parkinson's disease affect physical movement:

Tremor: The most common symptom of Parkinson's disease is the unilateral, typically resting tremor in body parts, most commonly in the upper extremities. However, this finding can spread to the other parts of the body like lips, chin, jaw and tongue during the course of the disease. It is an early symptom and is seen in about 70% of people presenting with Parkinson's. The tremor of PD is a rest tremor-the shaking occurs when the patient is not trying to use the limb, and diminishes when the limb is in use. Tremor is related to an imbalance of neurotransmitters, dopamine and acetylcholine, for this reason, tremor may be the least responsive symptom to dopamine replacement therapy. This usually begins in the hand or arm and is more likely to occur when the limb is at rest [29-33].

Slowness of movement (bradykinesia): Bradykinesia can be the most disabling symptom of the condition and refers to slowness, decreased movement amplitude, and dysrhythmia. Physical movements are much slower than normal, which can make everyday tasks difficult and can result in a distinctive slow, shuffling walk with very small steps [28, 30, 34-36].

Muscles stiffness (rigidity): Parkinson's disease can create greater tension in the tendon, leading to structural

adjustment and an increase in tendon stiffness. Muscle rigidity may not be apparent to the person with Parkinson's but is felt by the medical practitioner in limb muscles when they are passively moved. Stiffness and tension in the muscles, which can make it difficult to move around and make facial expressions and can result in painful muscle cramps (dystonia) [28, 30, 37].

Postural Instability: Postural instability is one of the most disabling features of Parkinson's disease. Postural instability is often experienced in the late stages of PD and is a marker of disease progression. Little information is available on the role of visual inputs as an adaptive strategy to compensate for postural instability in PD. Postural instability and gait disturbances often develop later in the progression of the condition. If a loss of postural reflexes and resulting falls occur early, it is not suggestive of typical Parkinson's. Postural instability is a disabling feature of Parkinson's disease (PD), contributing to recurrent falls and fall-related injuries. In early Parkinson's the posture may show a slight flexion of the neck or trunk with a slight lean to one side [38-42].

Other Symptoms: Anosmia, Anxiety, Constipation, Depression, Fatigue, Festination of speech, Postural hypotension and Micrographia [27, 43].

Progression of Parkinson's: Parkinson's is a neurological disorder that progresses slowly with time. Symptoms normally begin on one side of the body and usually spread to the other side as Parkinson's progresses. It is difficult to estimate the rate of progression as every individual with Parkinson's may experience different symptoms. Symptoms present in the earlier stages of the condition may worsen and new symptoms may appear during the course of Parkinson's. Medications help in managing the symptoms but unfortunately, aren't implicated for slowing the progression of Parkinson's [44].

Early Parkinson's: During the initial stages of Parkinson's, the symptoms may be mild and interfere with fine motor activities like buttoning a shirt, tying shoe laces, a change in handwriting and slowed movement. Tremor if present may appear on one side of the body, starting either with the finger/hand or toe/foot [45].

Advanced Parkinson's: As Parkinson's progresses, the symptoms that appeared earlier tend to become more pronounced and problems with balance and change in posture become evident. After years of Parkinson's, a PwP tends to walk with a stooped posture with short steps.

Symptoms of Parkinson's develop slowly and gradually progress over time. Each person is affected differently and the rate of progression varies greatly between individuals. Parkinson's doesn't directly cause people to die and it is possible to live with Parkinson's for a long time, although symptoms do get worse over time [44].

PARKINSON'S DIAGNOSIS

It is not easy to diagnose Parkinson's. There are no laboratory tests (such as a blood test or brain scan), so it is important that the diagnosis is made by a specialist, such as a neurologist. The specialist will examine the person for any physical signs of Parkinson's and take a detailed history of the symptoms they're experiencing [16]. Parkinson's is often difficult to diagnose and the early signs are missed. Early detection would help in initiating treatment and leading a healthier life. Below is a list of symptoms that happen during the initial stage of Parkinson's. Having just one symptom as listed below doesn't call for immediate concern. However if you have two or more of the following symptoms, Such as Small crowded handwriting, Loss of smell/Anosmia, Facial Masking, Stooped posture, Slowed and stiff movements, Tremor, Frozen Shoulder, Change in voice and Sleep disturbances. It would be advisable to take an appointment with a neurologist [17].

Currently there is no definitive biological test or radiological procedure which diagnoses Parkinson's and autopsy-based studies have shown that even among neurologists, diagnostic accuracy results in up to 25% of cases proven incorrect at time of death [16].

In spite of medical advances in the management of Parkinson's, the provisional medical diagnosis continues to be based on the clinical picture of four cardinal symptoms and a positive response to levodopa. The diagnostic check list of symptoms is composed of Tremor, Bradykinesia, Muscle rigidity, Postural instability [46].

Diagnostic Investigations: Brain scans may help in detecting the loss of dopamine in the brain and reduce misdiagnosis. Neuro imaging that may be done might include:

MRI Scan (Magnetic Resonance Imaging): This uses magnetic currents to create images of the brain. This gives a better view of the deep structures of the brain. MRI scans are usually normal in Parkinson's but are useful at times in identifying conditions that can mimic Parkinson's and helps in distinguishing Parkinson's from other forms of Parkinsonism (like Progressive Supranuclear Palsy (PSP) or Multiple System Atrophy (MSA) [47-48].

CT scan (Computerized Tomography): This includes a series of X rays that are passed through different directions that provide an anatomical view of the brain.

This helps in excluding blood diseases and tumors of the brain which can mimic Parkinson's. Computerized tomography (CT) does not reveal any Parkinson's related changes but will rule out structural abnormalities which may result in Parkinson's-like symptoms [49-51].

DaT Scan (Dopamine transporter Scan): An FDA approved imaging technique since 2011, a DaT scan helps in capturing images of the dopamine system in the brain. In this, a radioactive dye is injected into the body which then binds to dopamine releasing neurons. Signals are then recorded by specialized cameras. A low signal (i.e. an abnormal DAT scan) indicates that there are fewer dopamine producing neurons, supporting the diagnosis of Parkinson's. DaT scans can also be used for differentiating Parkinson's from essential tremor. However, it should be noted that a DaT scan cannot be used to diagnose Parkinson's by itself; It also needs to be supported by a clinical examination. DaT scans can be abnormal in other Parkinson mimics as well including PSP and MSA hence have to be interpreted in the light of the clinical findings [52-56].

Metaiodobenzylguanidine (MIBG) scan: MIBG uptake may provide a unique opportunity to detect very early PD in situ within a pre-clinical window. A metaiodabenzylguanidine scan may be ordered to assist the differential diagnosis between Parkinson's and related Lewy Body Disease and a group of conditions known as Parkinson's Plus [57-59].

TREATMENT

Parkinson disease is the second most common neurodegenerative disease in the world, there is currently no cure for Parkinson's disease, but treatments are available to help relieve the symptoms and maintain your quality of life. Current treatments only alleviate some of the symptoms for a few years, but they become ineffective in the long run and do not stop the disease. Therefore it is of outmost importance to develop therapeutic strategies that can prevent, stop, or cure Parkinson disease. The symptoms can be controlled using a combination of drugs, therapies and occasionally surgery. As Parkinson's progresses, an increased amount of care and support may be required, although many people maintain a good quality of life with limited care or treatment [60-62].

Supportive therapies: There are several therapies that can make living with Parkinson's disease easier and can help you deal with your symptoms on a day to day basis. Whether art therapy can be an effective rehabilitative treatment for people with brain or mental diseases (e.g., dementia, Alzheimer's disease, Parkinson's disease) is a long-standing and highly debated issue There are efforts underway to try and increase the availability of these supportive therapies for Parkinson's patients [63-65].

Physiotherapy: A physiotherapist can work with you to relieve muscle stiffness and joint pain through movement (manipulation) and exercise. The physiotherapist aims to make moving easier and improve your walking and flexibility. They also try to improve your fitness levels and your ability to manage things for yourself [66-69].

Occupational therapy: An occupational therapist can identify areas of difficulty in your everyday life, for example dressing yourself or getting to the local shops. They can help you to work out practical solutions and ensure your home is safe and properly set up for you. This will help you maintain your independence for as long as possible [70].

Speech Therapy: This therapy focuses on improving the clarity and volume of speech and provides tips for better communication [71-73].

Medication: Medication can be used to improve the main symptoms of Parkinson's disease, such as tremors (uncontrollable shaking) and movement problems. However, not all the medications available are useful for everyone, and the short and long term effects of each are different. It is primarily related to a lack of dopamine as a result of degeneration of dopamine producing neurons within the mid-brain. Dopamine is a neurotransmitter which conveys messages between neurons to ensure effective planning, initiation and maintenance of movement [74-76].

Most pharmaceutical treatment options focus on restoring the balance of dopamine and other neurotransmitters by several means: Three main types of medication are commonly used. These are levodopa, dopamine agonists and monoamine oxidase-B inhibitors.

Levodopa: Most people with Parkinson's disease will eventually need to have a medication called levodopa. Levodopa is absorbed by the nerve cells in your brain and turned into the chemical dopamine, which is used to transmit messages between the parts of the brain and nerves that control movement. Increasing the levels of dopamine using levodopa usually improves movement problems. Levodopa is usually taken as a tablet, Capsule (Sinemet®) or liquid and is often combined with other medication, such as benserazide or carbidopa. These additional medications stop the levodopa being broken down in the bloodstream before it has a chance to get to the brain [77-81]. They also reduce the side effects of levodopa, which include feeling sick (nausea), vomiting, tiredness and dizziness. At first, levodopa can cause a dramatic improvement in the symptoms. However, its

effects can be less long lasting over the following years because, as more nerve cells in the brain are lost, there are fewer of them to absorb the medicine. This means that the dose may need to be increased from time to time. Long term use of levodopa is also linked to problems such as uncontrollable, jerky muscle movements (dyskinesias) and 'on off' affects-where the person suddenly switches between being able to move (on) and being immobile (off) [82-83].

Duodopa: If you have severe on off swings, a type of levodopa called duodopa may be used. This medication comes as a gel that is continuously pumped into your gut through a tube inserted through your abdominal wall (tummy). There is a small external pump attached to the end of the tube, which you wear on your belt [84-86].

Dopamine agonists: Dopamine agonists act as a substitute for dopamine in the brain and have a similar but milder effect compared to levodopa. They are used to treat early Parkinson's disease as they are less likely to cause involuntary movements (dyskinesias) than levodopa. Dopamine agonists are often taken as a tablet, but a type called apomorphine can be injected under the skin (subcutaneously). Sometimes, dopamine agonists are taken at the same time as levodopa as this allows lower doses of levodopa to be used. Possible side effects of dopamine agonists include nausea, vomiting, tiredness and dizziness [87-88]. Dopamine agonists can also cause hallucinations and episodes of confusion, so they need to be used with caution, particularly in elderly patients who are more susceptible. For some people, dopamine agonists, especially at high doses, have been linked to the development of compulsive behaviours, including addictive gambling and an excessively increased libido. Talk to your healthcare specialist if you think you may be experiencing these problems. As the person themselves may not realise the problem, it is key that carers and family members also note any abnormal behaviour and discuss it with an appropriate professional at the earliest opportunity. If you are prescribed a course of dopamine agonists, the initial dose will usually be very small to prevent nausea. The dosage is gradually increased over a few weeks. If nausea becomes a problem, your GP may prescribe antisickness medication. You may need blood tests and a chest Xray before some types of dopamine agonist are prescribed [89-91].

Monoamine oxidase-B inhibitors: Monoamine oxidase-B (MAOB) inhibitors, including selegiline and rasagiline, are another alternative to levodopa for treating early Parkinson's disease. They block the effects of a brain chemical that destroys dopamine (monoamine oxidase-B). Both selegiline and rasagiline can improve the symptoms of Parkinson's disease, although their effects are small compared with levodopa. They can be used alongside levodopa or dopamine agonists. MAOB inhibitors can cause a wide range of side effects, including nausea, headache and abdominal pain [92-94].

Catechol-O-methyltransferase inhibitors: Novel enzyme inhibitors enhancing Levodopa efficacy and half-life are also still being developed, including a novel catechol-O methyltransferase inhibitor with once-daily pharmacokinetics, and there are studies testing the effects of increasing the dose of amino acid decarboxylase inhibitors given concomitantly with Levodopa. Intrajejunal infusion of a gel formulation of Levodopa/carbidopa is in clinical use in Europe, and its efficacy to smooth out motor fluctuations has recently been shown in a randomized, controlled trial. Catechol-O-methyltransferase (COMT) inhibitors are prescribed for people in later stages of Parkinson's disease. They prevent levodopa from being broken down by the enzyme COMT. Side effects of COMT inhibitors include nausea, vomiting, diarrhoea and abdominal pain. If the COMT inhibitor tolcapone is used, you will need tests to check your liver health every two weeks [95-96].

Amantadine: Amantadine acts like a dopamine replacement medicine but works on different sites in your brain. It has few side-effects, but is only used in the early stages of the disease and has a limited effect so isn't a first choice drug [97].

Anticholinergic medicines: Anticholinergic medicines block the action of the brain chemical acetylcholine. They help to correct the balance between dopamine and acetylcholine. These medicines only help with tremor and are less effective than the medicines that replace dopamine, so doctors don't use them very often [98].

Surgery: Most people with Parkinson's disease are treated with medication, although a type of surgery called deep brain stimulation is used in some cases [99]. The three most common forms of surgery for Parkinson's disease are:

Thalamotomy: The surgeon makes a lesion (cut) on part of the brain to alleviate some forms of tremor.

Pallidotomy: The surgeon makes a lesion on a different part of the brain to alleviate dyskinesia (wriggling movements).

Deep brain stimulation: The surgeon places an electronic deep-brain stimulator in the brain to control specific symptoms. This is connected to one or two fine wires placed under the skin and inserted precisely into specific areas in your brain. A tiny electric current is

produced from the pulse generator, which runs through the wire and stimulates the part of your brain affected by Parkinson's disease. The electrical impulse creates a lesion, which blocks abnormal nerve signals and reduces the targeted symptom. This device is sometimes called a brain pacemaker. Although surgery does not cure Parkinson's disease, it can ease the symptoms for some [100].

CONCLUSION

Parkinson's is a neurological disorder that is mainly characterized by problems with body movements, although other symptoms can also occur. Currently there is no known cause of understanding of why a person develops Parkinson's. There are many theories as to the causes and it is generally thought that multiple factors are responsible. No, there is currently no cure for Parkinson's disease. However, there are medicines that can help to treat the symptoms of the disease. Research is ongoing to find new treatments for Parkinson's disease. Gene therapy, which involves delivering normal genes directly to your brain to help prevent the death of brain cells, is one example. Other research is looking at whether nerve cells that are lost in people with Parkinson's disease can be replaced with new healthy cells from stem cells grown in the laboratory.

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