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Parkinson Disease, Recent Updates: Literature Review

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Abstract

Background: Parkinson's Disease (PD) is considered a chronic progressive neurodegenerative disorder and it can affect both motor and nonmotor functions. Around one million Americans have the disease and 1-3% of the individuals who are older than 60 years of age of the general population are affected worldwide. The progression of PD, from the first damage of the nervous system cells to the appearance of clinical symptoms, takes a considerable long period. Therefore, it is very important to identify the affected individuals before the appearance of the clinical manifestations to start protective strategies as early as possible. **Objective:** To evaluate Parkinson's disease, pathophysiology, symptomology, and management in the published and provide an adequate review tackling these topics. **Method:** PubMed database was used for article selection, and the following keys were used in the mesh ((“Parkinson Disease"[Mesh]) AND (“management”[Mesh]) OR (“evaluation"[Mesh])). **Conclusion:** The treatment of PD is symptoms-based and the medications are targeted toward the dopaminergic pathway. The most effective treatment for PD is levodopa. It treats most of the symptoms successfully. However, levodopa is associated with severe adverse effects. Therefore, other medications such as Monoamine Oxidase B (MAO-B) inhibitors and dopamine agonists can be started to delay the need for levodopa. A non-medical approach such as physical therapy and exercise is recommended along with medical therapy.

Keywords: Parkinson disease, diagnosis, mamagement approach.

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Introduction

PD is the second most common neurodegenerative disease that is progressive and results in death (Ball et al., 2019; Scorza et al., 2017). It affects 1-3% of the individuals who are older than 60 years of age of the general population worldwide (Hirsch et al., 2016; Shalash et al., 2018). Around one million Americans have the disease according to the Parkinson Disease Foundation. The incidence in the US is around 20 cases per 100,000 people per year. Nevertheless, it is important to note that these numbers do not include or estimate undiagnosed cases (De Lau and Breteler, 2006; Driver et al., 2009).

PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (El-Agnaf et al., 2006). It consists of 2 types, the first one is familial which can be autosomal recessive or dominant and the second type is idiopathic which is developed by geno-environmental interactions (Lill, 2016; Gao and Hong, 2011). The idiopathic or the sporadic type is the most common type accounting for approximately 90% of PD cases (Verstraeten et al., 2015).

The progression of PD, from the first damage of the nervous system cells to the appearance of clinical symptoms, takes a considerable long period because the clinical manifestations usually develop when most of the dopaminergic neurons have already been damaged (El-Agnaf et al., 2006; Emamzadeh and Surguchov, 2018). More than 70% of neuronal death usually occurs before the clinical manifestations appear (Jakubowski and Labrie, 2017). Therefore, it is very important to identify the affected individuals before the appearance of the clinical manifestations to start protective strategies as early as possible (Berendse et al., 2001). We aim in this article to review the published literature that discussed PD, pathophysiology, diagnosis, and management.

Method:

PubMed database was used for article selection, and the following keys were used in the mesh ((“Parkinson Disease"[Mesh]) AND (“management”[Mesh]) OR (“evaluation"[Mesh])).

In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics: Parkinson's Disease, pathophysiology, evaluation, and management.

Exclusion criteria were all other articles, which did not have one of these topics as their primary endpoint.

Discussion:

In 1817, Dr. James Parkinson described Parkinson's disease for the first time and called it “shaking palsy” (Parkinson, 1817). The disease is considered a chronic progressive neurodegenerative disorder that can affect both motor and nonmotor functions. It causes several burdensome symptoms that can impact the quality of life of the patients, their families, and their caregivers through its course of progression on muscle functionality. The main pathology behind this motor dysfunction is the gradual impairment of striatal dopaminergic neurons. Regarding Parkinsonism, it is a term that is used to describe the complex motor symptoms of PD, which are tremor at rest, cogwheel rigidity, and bradykinesia. Parkinsonism is caused by Parkinson's disease as the most common cause as well as other different secondary causes such as antipsychotic drugs like phenothiazines and toxins like pesticides (DeMaagd and Philip, 2015; Twelves et al., 2003).

The exact cause of PD is still unknown but it is believed that complex interactions between genetic and environmental factors can lead to PD (Massano and Bhatia, 2012). Idiopathic PD has several risk factors such as age, positive family history of PD, exposure to toxins, and oophorectomy. The most common risk factor is age and it is expected for the prevalence of the disease to increase in the next few years as life expectancy increases and the aging population increases worldwide (De Lau and Breteler, 2006; Bronstein et al., 2009).

Pathogenesis:

It has been found that the disease’s manifestations appear because of the deficits of dopamine in the striatum because of the depletion of dopaminergic neurons (Rizek et al., 2016). Normally, unwanted proteins are cleared in healthy neurons by the lysosomes or the proteasomes. However, this function can be impaired in a stress condition leaving damaged proteins circulating freely causing the pathological effect of specific diseases such as a-synuclein aggregates in PD (Emamzadeh and Surguchov, 2018).

α-synuclein aggregates are harmful to the dopaminergic neurons in the substantia nigra in PD as they trigger the transmission of toxic proteins among healthy brain cells leading to the formation of Lewy bodies and resulting in cell death. It has been suggested that the increase of this substance in the nervous system starts from the GI tract. Then, it transmits from the enteric nervous system to the brain through the vagus nerve (Steiner et al., 2018; Liddle, 2018; Luk et al., 2012).

The pathophysiology of PD is staged into 6 stages depending on the location of the affected brain regions. To identify the damaged neurons, Lewy body staining was used. The first stage involves the lower medulla oblongata affecting mainly the dorsal motor nucleus of the vagal nerve and the anterior olfactory parts. The second stage shows worse damage to the first stage’s lesions as well as Lewy neuritis in the locus ceruleus. Substantia nigra’s damages show in the third stage. In the fourth stage, the cortex starts to get involved and the most affected area is the temporal mesocortex. Stage 5 is when the lesions reach the adjoining temporal neocortical area. When clear damage becomes apparent on the cortex, this is considered stage 6. Moreover, the development of the neuropathological stages correlates with cognitive status and the development of the disease’s manifestations (Braak et al., 2003).

Diagnosis:

Regarding diagnosis, there is no specific test to diagnose PD. The disease is diagnosed clinically depending on the assessment of the symptoms and ruling out the differential diagnoses such as essential tremor and multiple-system atrophy (DeMaagd and Philip, 2015; Grosset et al., 2010). The usual first clinical features of PD are resting tremor (4-Hz to 6-Hz), cogwheel rigidity, and bradykinesia. These are the cardinal motor finding and they are called the classical triad of PD. Half of the patient may show an additional feature which is postural instability mostly after 5 years of diagnosis (Berardelli et al., 2013).

Even though PD is considered a geriatric disease that mostly affects people who are older than 60 years old, it is also possible to affect people who are younger than 60 years of age due to some genetic variations (Kavuri and Sivanesan, 2019; Kariat et al., 2019; Moayeri et al., 2019; Elnozhe et al., 2019). However, the bradykinesia and the rigidity are less severe but this might lead to late or missed diagnosis (Reichmann, 2010). Bradykinesia can be defined as a slow and low-amplitude movement. It occurs in 90% of PD patients. Rigidity also occurs in 90% of PD patients and it is defined as resistant limbs' flexion and extension to passive movement. It is mostly cogwheel rigidity, which is intermittent resistance to passive movement. The third feature is resting tremor and it is common in most of the patients especially at the beginning. It is predominantly seen in the hands but it can also be seen in the lips, chins, tongue, and legs. It usually disappears during sleep or with action. In the late stages of PD, postural disability can appear which predisposes PD patients to falls and injuries. It is mostly caused due to postural reflexes loss (DeMaagd and Philip, 2015).

Traditionally, the main focus in the symptomatology of PD was focused on motor symptoms ignoring the non-motor symptoms of PD which can be as useful as motor symptoms in diagnosing, managing, and assessing disease prognosis. Recently, non-motor symptoms have been shown an increased interest because some of them can appear before the classical motor symptoms by years

(Massano and Bhatia, 2012). Examples of these symptoms include constipation, rapid eye movement (REM) behavior disorder, hyposmia, and depression. Easy fatigability and vague shoulder pain can also present before the onset of the classical motor symptoms. Moreover, other non-motor symptoms can present in the late stages of the disease such as hallucinations and dementia. Most of the patients develop dementia after 20 years of the disease course. Other examples of neuropsychiatric manifestations include apathy, anxiety, orthostatic hypotension, urinary dysfunction, sleep disturbance, drooling, and paresthesias (Lim et al., 2009; Gallagher et al., 2010; Hawkes et al., 2010; Healy et al., 2008).

Management:

Unfortunately, there are no available disease-modifying treatments for PD currently. The treatment is symptoms-based and the medications are targeted toward the dopaminergic pathway such as levodopa, Monoamine Oxidase B inhibitors, and dopamine agonists (Balestrino and Schapira, 2019).

Levodopa:

The most effective treatment and the gold standard medication for PD is levodopa (Fox et al., 2011). It is mostly given as tablets. However, it can be administered as a gel given directly in the duodenum through a gastrostomy catheter by a pump. This method is used in advanced PD with severe poorly-managed complications and it has proven safety and efficacy in reducing the severity of motor fluctuations in advanced cases. The mechanism of action of levodopa starts after crossing the blood-brain barrier when it gets converted to dopamine in the remaining dopaminergic neurons of the substantia nigra pars compacta.

The disadvantages of levodopa are it can cause dopaminergic adverse effects such as hypotension, nausea, sleepiness, hallucinations, and confusion. Moreover, the patient on levodopa can develop compulsive and impulsive behavioral problems or impulse control disorders, for example, punding, compulsive shopping, gambling, and hypersexuality (Beaulieu-Boire and Lang, 2015; Olanow et al., 2006).

MAO-B inhibitors:

MAO-B enzyme has the responsibility for breaking down dopamine. Therefore, MAO-B inhibitors work in reducing this function to preserve endogenous dopamine levels and subsequently, increasing dopaminergic activity within the striatum. clinically, they have shown good outcomes in relieving motor symptoms, therefore, they can be used as first-line PD treatment and postponing the need for levodopa regimen initiation to avoid levodopa's adverse effects and complications as long as possible (Goldenberg, 2008).

Regardless, most of the patients will need levodopa therapy eventually. however, combination therapy of MAO-B inhibitors and levodopa can be used to obtain better results and reduce the need for high doses of levodopa. The most common side effect of MAO-B inhibitors is gastric discomfort but they are well tolerated in general. examples of MAO-B inhibitors' side effects include dry mouth, dizziness, headache, arthralgia, and sleep disturbance (Bianchi et al., 2019).

Dopamine agonists:

Another medical solution to delay the use of levodopa is the use of dopamine agonists (Jankovic and Aguilar, 2008). Dopamine agonists can be used as initial dopaminergic therapy to avoid early levodopa initiation until the quality of life and the patient's muscle functionality become affected. This will delay levodopa-induced complications as long as possible (Jankovic, 2000).

There is an improvement of parkinsonism symptoms with the use of dopamine agonists as monotherapy. However, this improvement is not considered as significant but it is enough to delay the initiation of levodopa therapy for a couple of years (Jankovic, 2005). The mechanism of dopamine agonists is to directly activate dopamine receptors bypassing dopamine presynaptic synthesis.

In the past, ergot dopamine agonists such as pergolide and bromocriptine were used but they appeared to increase the risk of valvular heart disease. therefore, they have been discontinued. The new generation of dopamine agonists such as ropinirole and pramipexole are non-ergolines. so, they are usually associated with a lower risk of adverse effects than ergot dopamine agonists. examples of these adverse effects are peptic ulcer, pulmonary fibrosis, vasoconstrictive effects, and valvular heart disease (Jankovic and Aguilar, 2008; Brooks, 2000).

The majority of the antiparkinsonian drugs are effective in controlling the symptoms for 3 to 6 years. Then, the disease continues in progressing and starts resisting the medications. Therefore, the management of PD should be multidisciplinary which means adding physical therapy and other non-medical therapies to the management process. When a structured program of physical therapy is conducted, patients show significant improvements especially in their gait, stability, balance, and general activities.

Conclusion:

The treatment of PD is symptoms-based and the medications are targeted toward the dopaminergic pathway. The most effective treatment for PD is levodopa. It treats most of the symptoms successfully. However, levodopa is associated with severe adverse effects. Therefore, other medications such as Monoamine Oxidase B (MAO-B) inhibitors and dopamine agonists can be started to delay the need for levodopa. A non-medical approach such as physical therapy and exercise is recommended along with medical therapy.

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