Parkinson's Disease Sex Differences: A New Health Concern

Mike Wajoski* and Garry Link

Department of Clinical Neurosciences, University of Palermo, Palermo, Italy

*Corresponding Author**
Mike Wajoski
Division of Clinical Neurosciences
University of Palermo, Palermo
Italy
Email: wajoski121m@yahoo.com

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Abstract

An important factor in determining the epidemiological and clinical implications of Parkinson's disease is the gender discrepancy. Males are twice as likely to have Parkinson's disease as females, although females are more likely to get the illness and pass away from it. The most common Parkinson's disease symptoms are motor symptoms, which can be used to describe and diagnose the condition. Treatment options and clinical outcomes can vary greatly between men and women. Despite the fact that initial studies were unable to connect sex differences in Parkinson's Disease, important data has since been published demonstrating that women experience motor symptoms later than men, have more tremors, and have higher striatal dopaminergic activity.

Keywords: Parkinson's disease • Dopaminergic • Catechol-O-methyltransferase inhibitors

Introduction

Parkinson's Disease (PD), a neurological condition that affects 10 million individuals worldwide, is quite common. It is predicted that in Brazil, the disease will affect more than 600,000 people by 2030.3 PD affects both sexes (male and female), affecting 1% of men and 1% of women between the ages of 45 and 54, and 4% of men and 2% of women between the ages of 85 and 90. In addition to placing a heavy financial burden on governments around the world due to social security costs, medical costs, lost income, etc., PD is a disorder that is debilitating for the patient and costs the country specifically 52 billion USD.

Biological sex is currently being discussed by neuroscientists as a crucial role in the severity of PD. The National Institutes of Health (NIH) has emphasized the significance of biological sex as a vital variable for rigorous research since 2015 (NOT-OD-15-102). Few studies include sex research as an objective for the study, despite the fact that it is essential for clinical and fundamental studies to include sex in their investigations.

The disparity between the sex's plays a key role in defining the epidemiological and clinical implications of PD. PD is twice as common in males as in women, but women are more likely to develop the disease and die from it. When it comes to the most prevalent PD symptoms, motor symptoms can be used to characterize and diagnose the disease, and treatment options and clinical developments between men and women can differ significantly. Although earlier research was unable to link sex differences in PD, significant data has been published showing that women have a later onset of motor symptoms than males, a predominance of tremors, and higher striatal dopaminergic activity. Key indicators of PD manifestation include other clinical features such as cognitive, emotional, and mental deficits. Studies have revealed that dementia and cognitive decline are noticeably more prevalent in men with PD [1].

Men are more likely than women to have sensory issues with taste and smell. Women with PD are more likely to experience depressive symptoms such irritability and agitation, loss of enjoyment, self-dislike, self-punishment, and thoughts of worthlessness. Additionally, women exhibited the worst postural instability and early dyskinesias. However, compared to women with PD, men are more likely to show with writing issues, clumsiness, higher bradykinesia, and stiffness scores [2].

In addition to motor findings, there are gender differences in sleep problems as well. Women are more likely to experience symptoms of weariness, pain, neuropsychiatric disorders (anxiety and depression), restless legs syndrome, and constipation. Insomnia is a common condition in female patients. Such symptoms can interfere with sleep cycles, although males are more tolerant of sleeping disorders, which may account for why women are more likely than men to experience insomnia. Both sexes exhibit REM sleep behaviour disturbances in PD patients. Female PD patients reported much fewer fights and violent behaviour during nightmares and more disturbed sleep, suggesting that the severity of symptoms may differ by sex [3].

Although there are no medications that can stop the progression of neurodegeneration, there are many different kinds of pharmacological medicines that are used to treat the symptoms of PD. Levodopa (LD), dopamine agonists, Catechol-Methyltransferase Inhibitors (COMT), and Monoamine Oxidase Type B inhibitors (MAO-B) are some of them that the authors can specifically mention. The pharmacological prescription throughout the illness depends on a variety of criteria, including age and motor and non-motor symptoms, but it is still uncommon to take into account the patient's sex.

The most effective pharmacological option for treating motor symptoms is thought to be LD in combination with dopamine decarboxylase inhibitors (such as carbidopa); however, the treatment can be started with other medications, such as dopamine agonists (Pramipexole and Ropinirole) or anticholinergics (Benztropine), to reduce complications associated with the prolonged use of LD. Once LD medication is started, it's customary to use COMT (Entacapone and Tolcapone), MAO-B inhibitors (Selegiline and Rasagiline), and dopamine agonists or LD supplementary therapy to control motor fluctuations.

There is evidence that sex disparities exist in the pharmacokinetics and pharmacodynamics of PD medication dosing. Although well tolerated, tolcapone is a COMT inhibitor used as an adjuvant with LD. Females are more vulnerable to gastrointestinal and orthostatic side effects. The dopaminergic agonist pramipexole has a higher bioavailability in females, which is likely due to a decreased rate of oral clearance. Additionally, it was shown that the female sex had higher LD bioavailability than the male sex, as seen by higher AUC and Cmax, two indicators of the drug's plasma concentration.

Given that the female sex is associated with lower body weight, the results suggest that body weight may be a factor in sex differences. However, the difference persists even after controlling for this variable, suggesting that there are additional mechanisms at play in addition to body weight that contribute to the higher levodopa availability in females. This difference may be partly explained by reduced LD clearance and COMT activity in females, as well as a decrease in COMT expression brought on by 17β-estradiol. To shed more light on the claim that sex can change how a person reacts to medications, more research is required [4,5].

This is significant because levodopa-induced dyskinesia, one of the major side effects of the medication, is more likely to occur in female patients. Additionally, it was discovered during the DEEP investigation that women have an 80.1% higher risk of having Wearing-Off (WO), which is the shortening of the period that LD regulates symptoms. Patients frequently experience a resurgence of motor and non bmotor symptoms during the "off" periods, which is noteworthy given that women are more likely to develop WO. Even if they are common in the PD community as a whole, impulse control issues may be linked to the consumption of large dosages of LD and dopaminergic agonist [3].

Additionally, there are variations in the neurodegenerative process. Male patients had a higher rate of cholinergic dopaminergic denervation in the caudate and neocortical nucleus than female patients do. In comparison to men, women had higher levels of striatal dopamine and the striatal dopamine transporter, which suggests greater protection against the development of PD associated with men.

In Dopaminergic (DA) neurons, women have been found to express glutamate and vesicular glutamate transporter 2 (VGLLUT2) at higher levels than men, suggesting that women are better protected from the loss of DA neurons and have higher permeabilities than men. Signal transduction and neuronal maturation regulatory genes are positively regulated in females, whereas the PD pathogenesis genes -synuclein and PINK1 are under expressed in males. Due to the sensitivity of DA neurons in the substantia nigra to stress conditions and the positive regulation of genes like -synuclein and PINK1, a protein necessary for mitophagy in DA neurons, these findings highlight significant genetic traits. These findings could impact PD treatment plans and motor or non-motor symptoms [4,5].

Given the numerous disparities between the sexes, a neuroprotective impact may be implied, indicating that endogenous hormones may play a role. Menopause and other periods of hormonal instability may contribute to the development of Parkinson's disease, but some studies have not identified a connection between these factors and PD. Neither have they been linked to menarche age or menopause age. The use of hormone therapy has been proposed as a potential PD treatment. Because of its neuroprotective properties, oestrogen may shield neurons from poisons. Increased oestrogen levels can cause the endometrium to develop and enlarge the uterine wall, a condition known as endometrial hyperplasia.

Progestin, a synthetic version of progesterone, is used to stop this growth, thus it must be taken in addition to the treatment. However, several studies have found that using hormonal therapy with oestrogen and progestin may raise the incidence of PD. However, Gatto et al. and colleagues demonstrated that PD risk was decreased when endogenous or exogenous oestrogen treatment was used for the largest cumulative period of time. Following a diagnosis of PD in postmenopausal women, conjugated equine oestrogen hormone therapy appears to improve the disease's motor symptoms [6].

Age-related testosterone reduction in men may contribute to the development of Parkinson's disease. The use of androgen (testosterone) hormone therapy does not appear to have the same neuroprotective effects as seen in oestrogen, according to research, despite the decline in testosterone. More research is required to determine whether testosterone supplementation increases the likelihood of PD progression or reduces its symptoms [7].

These are merely the more widely used sex hormones that are available to both sexes. The intricacies of sex hormones in relation to the beginning and development of Parkinson's Disease (PD) require further study.

Last but not least, the dearth of studies on people that document the differences between sexes in clinical traits, symptoms, treatments, neurodegeneration, and hormones opens up new study directions. Since there are disparities between men and women who have PD, the authors must take them into account. We also expect that future research will learn more about these variances. Above all, the writers of this editorial stress the need of paying attention to how different therapies' sex response profiles are [8-10].

In light of the inequality between the sexes, I think it is interesting to consider this. Particularly in pharmaceutical dose, where there are a variety of responses, tolerances, and pharmacokinetics. Additionally, paying close attention to this matter may enable better management of side effects such WO and the development of dyskinesias, which frequently impose restrictions on drug therapy.

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