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Review article

Sex differences in Parkinson's disease: Features on clinical symptoms, treatment outcome, sexual hormones and genetics

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ABSTRACT

Parkinson's disease (PD) is the second most frequent age-related neurodegenerative disorder. Sex is an important factor in the development of PD, as reflected by the fact that it is more common in men than in women by an approximate ratio of 2:1. Our hypothesis is that differences in PD among men and women are highly determined by sex-dependent differences in the nigrostriatal dopaminergic system, which arise from environmental, hormonal and genetic influences. Sex hormones, specifically estrogens, influence PD pathogenesis and might play an important role in PD differences between men and women. The objective of this review was to discuss the PD physiopathology and point out sex differences in nigrostriatal degeneration, symptoms, genetics, responsiveness to treatments and biochemical and molecular mechanisms among patients suffering from this disease. Finally, we discuss the role estrogens may have on PD sex differences.

1. Introduction

Parkinson's disease (PD) is the second most frequent age-related neurodegenerative disorder, which affects about 3% of the population by the age of 65 years of age and 5% of the people over the age of 85 (Lang and Lozano, 1998a, 1998b; Moghal et al., 1994). It is characterized by neuronal loss and formation of Lewy bodies (α-synuclein accumulation in neurons) in the pars compacta of the substantia nigra, thus causing degeneration of the basal ganglia circuitry (Heller et al., 2014; Milanov et al., 2001; Schrag et al., 2000). Oxidative stress, excitotoxicity and neuroinflammation play an important role in neuronal death in PD (Albarracin et al., 2012; Leszek et al., 2016; Sutachan et al., 2012; Cabezas et al., 2014), being important the involvement of nitric oxide (NO) and other reactive nitrogen species (Fukae et al., 2007; Mosley et al., 2006). Furthermore, the identification of gene mutations that induce impairment of mitochondrial energy production and oxidative stress has highlighted the importance of mitochondrial abnormalities in PD pathogenesis (Misiak et al., 2010).

PD causes clinical symptoms such as bradykinesia, rest tremor, rigidity and postural instability (Dos Santos et al., 2014; dos Santos et al., 2015; Hughes et al., 1992). PD patients suffer also from non-motor symptoms, which are significant determinants of disability and quality of life. The most common non-motor symptoms in PD patients are cognitive abnormalities, from mild cognitive impairment to dementia, vegetative dysfunctions, sensory symptoms as well as psychiatric symptoms like depression, anxiety, sleep disorders, apathy and constipation (Picillo et al., 2014; Jankovic, 2008). It has been shown that dopaminergic treatment improves some of these symptoms, but may worsen others, suggesting the need of novel therapies without such side effects (Picillo et al., 2014).

It has been suggested that sex is an important factor in the development of PD. This neurodegenerative disease is more common in men than in women by an approximate ratio of 2:1, and there is a higher risk for PD in men (Baldereschi et al., 2000; Solla et al., 2012). Nevertheless, women have a greater mortality and earlier nursing home placement than men (Dahodwala et al., 2016). There have been reported sex differences in the onset of symptoms, type of motor and non-motor symptoms, medication use, the effect size of PD risk factors, levodopa bioavailability, neuropsychiatric and cognitive changes, development hallucinations, caregiver utilization and reliance, and quality of life

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(Cabezas et al., 2014; Colombo et al., 2015). For instance, women with PD have better motor scores in Unified Parkinson's Disease Rating Scale (UPDRS), but higher prevalence of dyskinesia (Chandran et al., 2014). It has been shown that sex differences in PD are determined by the nigrostriatal dopaminergic system, which arises from genetic, environmental and hormonal influences (Gillies et al., 2014). Other factors such as socioeconomic differences, gender bias and differences in access to specialty care may also be important (Dahodwala et al., 2016).

In women, the age of PD onset has shown a positive correlation with the duration of fertile life (Misiak et al., 2010). Sex hormones, specifically estrogens, influence the PD pathogenesis and might play an important role in PD differences between men and women (Gillies and McArthur, 2010a, 2010b). Estrogens have neuroprotective effects on the nigrostriatal dopaminergic system and can modulate monoamine oxidase (MAO) Kelada et al., 2002. The neuroprotective effect of estrogens might also be partially mediated by inhibition of interleukin 6 production (IL-6), increases inflammation and plays a key role in PD development (Ray et al., 1997; Vegeto et al., 2001). Furthermore, some studies have suggested that modulation of neuroinflammatory response by estrogens is involved in the neuroprotective effects, and other studies have shown that neuroinflammation and microglial activation play a major role in the progression of PD (Gerhard et al., 2006; Rodriguez-Pallares et al., 2007; Suzuki et al., 2007; Tripanichkul et al., 2006). Nevertheless, women present later age at PD onset, tremor- predominant PD, increased depression, decreased capacity for daily activities and severe levodopa-induced dyskinesia (Song et al., 2014). Furthermore, normal human basal ganglia are sexually dimorphic, which might influence the onset and progression of PD (Smith and Dahodwala, 2014). Sex differences could also be due to differences in life style, exposure to risk factors for PD, and cultural and social effects (Chandran et al., 2014; Accolla et al., 2007). There are also differences in the response to oral dopaminergic therapy with men needing higher doses of L-dopa than women, to achieve optimal therapeutic control (Accolla et al., 2007). In this regard, our hypothesis is that chromosomes genes and sexual hormones play an important role in sex differences in PD. These include differences in mitochondrial function and neuroinflammation, as well as in the action of genetic factors. The aim of this review is to highlight PD characteristics by sex and point out sex differences in nigrostriatal degeneration, symptoms, genetics, responsiveness to treatments and biochemical and molecular mechanisms, among patients suffering from this disease. Furthermore, we deepen our knowledge into the role of estrogens on PD sex differences.

2. Sex differences in Parkinson's disease in humans

2.1. Sex differences in basic disease characteristics and in nigrostriatal degeneration in Parkinson's disease

There are sex differences related to the age at onset of PD and to the amount and progression of nigrostriatal degeneration. To assess these differences, Haaxma et al. (2007) studied 253 patients with a disease duration of less than 10 years and who were not treated with levodopa or dopamine agonists. According to these researchers, age at onset was 53.4 years old in women and 51.3 years old in men. Furthermore, they measured the amount and progression of nigrostriatal degeneration using [^{123}I]FP-CIT single-photon emission computed tomography, and found that women had a 16% higher mean striatal dopamine transporter (DAT) binding than men (Haaxma et al., 2007). Importantly, this study showed that increasing cumulative estrogen levels and a later menopause in women delayed the age of PD onset (Haaxma et al., 2007). Additionally, in patients without PD there is a higher striatal DAT binding than in women. According to Wong et al., who carried out an evaluation for sex effects on DAT binding in normal subjects through DAT [^{11}C]2-β-carbomethoxy-3β-(4-fluorophenyl) tropane (β-CFT) positron emission tomography (PET) imaging, young-to-middle age women have higher levels of DAT binding compared to men (Wong et al., 2012). In PD, there is a progressive decline in the DAT binding of the brain. Through [^{123}I]FP-CIT single-photon emission computed tomography, Kaasinen et al. investigated the effects of sex on brain dopamine and serotonin transporter binding in 231 PD patients and 230 controls. These authors found that women had higher binding of DAT in the caudate nucleus compared with males, with a similar near-significant difference in the right putamen, and furthermore, female subjects had higher caudate nucleus dopamine transporter binding in both normal and degenerated dopamine systems (Kaasinen et al., 2015).

To understand the risk factors for this neurodegenerative disease and its natural history, Hirsch et al. examined the incidence of PD and its variation by age and sex. These authors found a rising incidence with age in both sexes and higher incidence of PD in males between 60 and 79 years old (Hirsch et al., 2016). Furthermore, they found that the incidence rate in women and men at 40 years and older was 37.55 and 61.21 per 100,000 person-years, respectively (Hirsch et al., 2016). In another study, Caslake et al. examined the effect of sex in the incidence of PD in 363 patients from North-East Scotland. They found that among this population, PD was more common in men in a ratio of 1.87:1 (Caslake et al., 2013). Moreover, Das et al. examined average annual incidence rates (AAIRs) of PD in a South Asian Indian population, finding that AAIRs peaked earlier for males than females, at 60–69 years, whereas female AAIRs continued to rise 70–79 years before dropping off in the 80+ age group (Das et al., 2010).

Due to the formation of Lewy bodies in the neurons of the pars compacta of the substantia nigra and the ability of its component the alpha-synuclein to pass from the brain to the blood, plasma α-synuclein concentration is an important biological marker of PD (Tokuda et al., 2006; Hong et al., 2010). For example, Caranci et al. compared total plasma α-synuclein concentrations in 69 PD patients and 110 control subjects, finding that these concentrations decreased in men when measured in a more advanced stage of the disease. Indeed, the authors found that only in men with PD, plasma α-synuclein concentration was related to hallucinations, sleep disorders and cognitive impairments; they concluded that plasma α-synuclein expression is a potential biological marker for PD progression in men (Caranci et al., 2013).

2.2. Sex-related differences among motor symptoms in PD

PD researchers have found that the expression and severity of motor symptoms in this neurodegenerative disorder is affected by sex. For example, Solla et al. assessed sex differences in motor symptoms between Sardinian patients with idiopathic PD by using the Unified Parkinson's Disease Rating Scale (UPDRS), and found that women presented tremor as initial symptom of PD and worse UPDRS instability score in comparison with men (Solla et al., 2012). Furthermore, higher motor scores, levodopa dosage, younger age at onset and female sex are risk factors for the development of motor fluctuations (Picillo et al., 2016). Using the UPDRS-III, Haaxma et al. also found that women presented tremors more often than men did, not only as initial symptom, but also throughout all the duration of the disease (Haaxma et al., 2007). Moreover, through the UPDRS-III, Lubomski et al. examined the motor symptoms in 129 men and 81 women with PD attending specialist neurological clinics across three centers, finding that men presented a greater disease burden and more pronounced motor symptoms (Lubomski et al., 2014). Furthermore, Szewczyk-Krolikowski et al. investigated sex differences in motor symptoms among 490 PD patients within 3 years of diagnosis. The authors found that there was a pattern of increased severity and greater alterations of symmetricity in the face, arms and neck in men than women, and more postural problems in women (Szewczyk-Krolikowski et al., 2014). On the other hand, Song et al. reported that total UPDRS scores were not significantly different between men and women with PD, whereas neither they found significant sex differences on scores in four cardinal motor signs and on motor subtypes (Song et al., 2014).