How much does sex matter in Parkinson disease?

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Sex and gender differences denote the biological and the sociocultural differences, respectively, between men and women. Conceivably, along with many other modifying factors (e.g., aging), male and female brains respond to neurodegenerative processes in different ways, thus contributing to distinct clinical expressions. Parkinson disease (PD) is not an exception as, for instance, the incidence is approximately twofold higher in men.[1] Differences in motor symptoms have been extensively analyzed, showing that women with PD have a more benign phenotype, with milder progression but higher incidence of levodopa-induced dyskinesias.[2]

In recent years, a steadily increasing number of studies are addressing the prevalence, pathophysiology, and importance of nonmotor symptoms (NMS) in PD.[3] Although only a handful of studies have addressed this topic, NMS are more likely to be sex- or gender-sensitive than motor symptoms, in light of the profound effect of biological and social factors. The few available data are mainly focused on treated patients and do not enroll healthy controls (table); only one study examined the sex differences in NMS prevalence among de novo patients with PD and controls.[4]

In this issue of *Neurology*®, Liu et al.[5] analyze the sex-related differences in the expression of NMS of more than 400 early, drug-naive, patients with PD and almost 200 healthy controls. Participants were enrolled in the Parkinson's Progression Markers Initiative (PPMI) study, which is an ongoing, international multicenter study designed to identify biomarkers of PD progression.[6] Built on the strength of both the PPMI data and a comprehensive statistical analysis, the authors show that men with newly diagnosed PD present with poorer olfaction and less trait anxiety as compared to women. Furthermore, women outperform men on the Montreal Cognitive Assessment (MoCA) (a measure of global cognition) and verbal memory, but underperform on visuospatial tasks. Interestingly, similar sex-related discrepancies in cognitive performances were observed in the control group as well, suggesting that these are intrinsic differences. Even more interestingly, Liu et al. describe a combination of NMS that can best differentiate PD from controls. Remarkably, in both men and women, poor olfaction is the most powerful NMS predicting PD diagnosis, followed by the MoCA score. Once again, sex makes a difference, since dysautonomia is a predictor of PD diagnosis only in men, while REM sleep behavior disorder is a predictor only in women.

This study is limited by its cross-sectional design and by the relative small sample when compared to a very recent dataset. Schrag et al.[7] have recently analyzed the NMS spectrum during the premotor phase of 8,166 individuals with and 46,755 individuals without PD, without focusing on sex-related differences. Longitudinal data from the PPMI cohort are warranted to clarify the influence of sex (or gender) on NMS over time and especially after the introduction of dopaminergic replacement therapy. Perhaps the first hint of sex-related differences in NMS expression came from observations of patients with impulse control disorders: it is now well-known that hypersexuality is more common in men whereas pathologic shopping affects women more.

Nevertheless, the study by Liu et al.[5] provides us with a number of important practical conclusions. First, men with newly diagnosed PD have poorer olfaction at presentation and less trait anxiety than women. Second, the cognitive profile at disease onset is also influenced by sex. Third, in keeping with a large amount of previous observations[8] and regardless of sex, olfaction impairment is the most consistent NMS predicting PD diagnosis. Finally—and more important—it is advisable that future strategies aimed at identifying patients with PD in their premotor phase should take potential sex differences into account in order to increase sensitivity. A sex-related effect has been described for both gene expression patterns[9] and biologic biomarkers, e.g., serum urate.[10]

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Table Studies addressing sex differences in nonmotor symptoms of Parkinson disease

Reference	No. of patients	No. of controls	Men, %	Disease duration, y	Drug-naive	Evaluation of NMS	Main findings	
							Men	Women
11	950	NA	62.6	7.9 ± 5.7	No	NMSS	Daytime sleepiness, sialorrhea, altered interest and problems in sex	Fatigue, restless legs, constipation, feeling of nervousness and sadness
12	156	132	58.3	6.3 ± 4.4	No	FAB, MINI, MoCA, NMSS	Altered interest in sex	Fatigue, lack of motivation, depression and anxiety
4	195	93	63	0.9 ± 0.7	Yes	NMSQ	Sex difficulties and taste/smell impairment	
13	533	NA	56.7	4.4 ± 4.1	No	NMSS	Urinary frequency and problems in sex	Difficult falling asleep, feeling of nervousness and sadness, anhedonia, apathy, abulia, pain
14	134	NA	64.2	3.2 ± 0.9	No	NMSQ	Swallowing, sadness and anxiety prevalence was reduced; urgency, daytime sleepiness, and weight change prevalence increased[a]	Sadness and dizziness prevalence was reduced[a]
15	490	176	62.4	3.2 ± 2.4	No	ESS, MoCA, RBD-Q, semantic and phonemic fluency	Lower MoCA and fluency scores, more RBD, daytime sleepiness, sexual dysfunction, and orthostatic hypotension	Pain
5	414	188	64.9	1.1 ± 1.1	Yes	ESS, GDS-15, HVLT-R, JOLO, LNS, MoCA, RBD-Q, SCOPA-AUT, SDMT, semantic fluency, STAI, UPSIT	Poorer olfaction, higher visuospatial performances	Higher trait anxiety, better global cognition and memory performances

Abbreviations: ESS = Epworth Sleepiness Scale; FAB = Frontal Assessment Battery; GDS-15 = Geriatric Depression Scale; HVLT-R = Hopkins Verbal Learning Test–Revised; JOLO = Benton Judgment of Line Orientation; LNS = Letter Number Sequencing; MINI = Mini International Neuropsychiatric Inventory; MoCA = Montreal Cognitive Assessment; NA = not applicable; NMS = nonmotor symptoms; NMSQ = Nonmotor Symptoms Questionnaire; NMSS = Nonmotor Symptoms Severity Scale; RBD-Q = REM sleep behavior disorder questionnaire; RBD = REM sleep behavior disorder; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Questionnaire; SDMT = Symbol Digit Modalities Test; STAI = State-Trait Anxiety Inventory for Adults; UPSIT = University of Pennsylvania Smell Identification Test.
Data are expressed as mean ± SD.
[a] As compared to the baseline assessment. Study comparing the effect of dopaminergic treatment and disease progression in the same cohort of the study by Picillo et al.[4]

Since diagnosing PD at prodromal stages is our next challenging mission, one of the PPMI study purposes is to find reliable and widely applicable diagnostic biomarkers.[6] In this context, Liu et al. remind us that sex matters, even in PD.

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