**Movement disorders and sex differences**

Sara Meoni1,2 , Antonella Macerollo3,4 , andElena Moro1,2\*

1Division of Neurology, Movement Disorders Unit, CHU of Grenoble, Grenoble Alpes University, Avenue Maquis du Grésivaudan, 38700 Grenoble, France

2INSERM U1216, Avenue Maquis du Grésivaudan, 38700 Grenoble, France

3 The Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool, L9 7LJ, United Kingdom

4 School of Psychology, Faculty of Health and Life Sciences, University of Liverpool Brownlow Hill, Liverpool, L69 3GB, UK

Corresponding author:

Elena Moro, MD, PhD

Movement Disorders Unit

Department of Psychiatry and Neurology

Centre Hospitalier Universitaire de Grenoble

BP217 38043 Grenoble CEDEX 09 France

E-mail: [elenamfmoro@gmail.com](https://autodiscover.chu-grenoble.fr/owa/redir.aspx?C=EBhblcvgNE2ylOXmc320V7bb6dH7c9EIuRq1JjnXQizq_dhgjtTjf8h1hqPOiPRh2udV0sDNRlE.&URL=mailto%253aelenamfmoro%2540gmail.com)

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**Key points**

* There are differences in epidemiology, clinical features, and response to treatment between women and men with several hypokinetic and hyperkinetic movement disorders.
* In Parkinson’s disease, male sex is associated with higher incidence and prevalence, earlier disease onset, more severe motor symptoms and progression, more frequent cognitive decline compared to female sex.
* Only few data are available on sex differences in hyperkinetic movement disorders. Craniocervical dystonia is prevalent in women, whereas most focal task-specific dystonias and tics are more frequent in men.
* Prospective studies specifically addressing sex differences in risk factors, symptomatology, disease progression, biomarkers and response to treatment are needed to develop tailored management of the movement disorders patients.

**ABSTRACT**

Relevant sex-related differences are emerging in brain anatomy and function, pathogenesis, clinical features, and response to treatment of several neurological conditions, including movement disorders. Oestrogens can influence the severity of motor symptoms in Parkinson’s disease, whereas elevation of androgens can exacerbate tic disorders. Nevertheless, the impact of sex differences in movement disorders remains under-recognized.

We here provide an updated review of sex-related differences in Parkinson’s disease, and the most common hyperkinetic movement disorders (essential tremor, dystonia, Huntington’s disease and other chorea syndromes, tics/Tourette syndrome). This review aims at highlighting the most relevant clinical aspects of movement disorders that differ between men and women. A better recognition of these differences and their impact on patients’ care represent a step forward a tailored approach in the management movement disorders. Moreover, this knowledge is essential to optimize preclinical research and clinical studies.

**Introduction**

Relevant sex-based differences regarding demographics, clinical features, and therapeutic response are emerging in several neurological diseases, such as Alzheimer disease1, ischaemic stroke2, and migraine3. In movement disorders, these sex-related distinctions are relatively unknown and underrecognized4–6.

Movement disorders are a heterogeneous group of neurological conditions, including hypokinetic and hyperkinetic disorders, the former characterized by slowness and paucity of movements, and the latter manifesting with excessive, abnormal involuntary movements and postures7.

Cortico-thalamic-basal ganglia and cerebellar network dysfunctions are well recognized in the pathophysiology of movement disorders. Sexual dimorphisms in the dopaminergic system have been found in the basal ganglia of both patients with Parkinson’s disease (PD)8-9 and normal subjects10–11, and in functional neuroimaging of healthy subjects12–19. Preclinical evidence suggests that sex steroid hormones modulate the dopaminergic pathways in both normal and pathological states5,20,21. A neuroprotective effect of oestrogens has been evoked in women with PD5,22–24. Sexual hormones changes (like during pregnancy) may also induce or exacerbate hyperkinetic states, such as chorea7, suggesting their contribute to sex-related variability in movement disorders through effects on basal ganglia networks. Several other factors, including genetics, brain structure and function, in addition to gonadal hormones, may contribute to sex-specific disparities in movement disorders (FIG. 1).

Similarly to Alzheimer disease1, the field of sex differences in movement disorders, particularly in PD, needs to be better acknowledged and studied as it could help stratification of subgroups of populations for diagnosis and treatment or prevention, in the context of a multifactorial precision medicine approach25.

The aim of this review is to highlight current evidence on this field, and propose sex disparities as important factors to consider in patient management and in future clinical trials for movement disorders. A brief discussion about potential mechanisms by which sex may impact disease susceptibility, pathogenesis, and clinical presentation of hyperkinetic and hypokinetic movement disorders is also provide. We believe that this knowledge is important to plan future research priorities and to influence public health policies. As recommended by the American Institute of Medicine26, in this review we use the term “sex” and not the term “gender.” Indeed, sex is intended to define either a male or a female based on reproductive organs and functions assigned by chromosomes X and Y. Gender encompasses one’s self and social identity as either male or female, which is rooted in biology but also shaped by environment. Concerning hypokinetic movement disorders, we have focused only on PD, whereas concerning hyperkinetic movement disorders, we have reviewed essential tremor, dystonia, chorea, and tics.

**Parkinson’s disease**

**Epidemiology**

Many studies about PD prevalence and incidence have pinned down a decreased rate of women27–37. However, the age-standardized male to female (M:F) ratio incidence of PD spanning from around 1.3 to 2.0 has mainly concerned the Western countries and the South American population32–37. Lower incidence M:F ratios (0.95-1.2) have been recently observed in Asia28–31, but this might reflect methodological issues, genetics, ethnicity, and gender differences in behaviour, such as smoking38. A recent systematic analysis39 of epidemiological studies worldwide reported a M:F ratio of age-standardized prevalence at 1.40 in 2016, confirming previous data28,29,32,37. Environmental factors, such as occupational exposure which tends to be higher in men, might partly account for male prevalence in PD. Overall, both M:F ratio incidence and M:F ratio prevalence tend to increase with age. However, this trend is more evident for M:F ratio incidence rather than prevalence, likely related to the higher mortality rate for PD males compared to the general population, but not for PD females40. Moreover, the mild increased premature mortality risk over female patients30 could also account for such difference. Since men tend to have an earlier PD onset41,42, and PD mortality increases with disease duration, mortality from the disease could also explain the increased incidence in men without a parallel increase in prevalence43.

**Risk factors**

Sex disparities in epidemiology support sex-related differences in risk factors for PD. Gonadal hormones and sex chromosomes may influence epigenetics8,20,44 and modulate disease risk. Preclinical evidence5,20,21 evokes a potential neuroprotective effect of oestrogens against dopaminergic damage through anti-inflammatory, anti-oxidative, and anti-apoptotic mechanisms45,46, in addition to possible alpha-synuclein anti-aggregation and fibril destabilization properties. Interestingly, the protective effect of caffeine intake on PD risk may be attenuated by hormone replacement therapy (HRT) in women47,48. Despite conflicting data, a longer lifetime exposure to oestrogens seems to be associated with reduced PD risk and milder symptoms at onset in women22–24,47,49–58. Consequently the withdrawal of oestrogens after menopause might increase PD risk in women during this lifetime span32,41,59. Contradictory results emerge from epidemiological studies about the association between exogenous hormones, i.e. use of HRT, and the use of oral contraceptives (OCs) and risk for PD23,24,50–58. A recent meta-analysis on 14 observational studies does not support a protective role of HRT on female PD risk60. Overall, there is no convincing evidence between reproductive factors such as age at menarche, age and type of menopause, fertile lifespan, pregnancy history, use of OCs, and the risk of PD in women38,61. Concerning potential environmental risk factors, women tend to have a lower exposure to occupational toxics and lower incidence of head trauma compared to men62, reflecting differences in behavioural and social factors.

**Biomarkers**

Several potential biomarkers for PD diagnosis, prognosis and risk prediction have been identified in biofluids, peripheral tissues, genetics, and imaging63. Although there is some evidence that sex-differences may exist for some wet biomarkers64–66, only uric acid appears to have a stronger sex specificity. Serum urate is an inverse risk factor for PD, particularly in men67,68, and urate levels inversely correlate with disease severity in men but not in women69–73. In a large case-control study68, higher uric acid levels predicted a lower risk of PD only in men, indicating a possible sex-related difference in purine pathways. Moreover, lower levels of urate were found only in male autoptic PD brain tissue compared to healthy subjects73. The interaction between urate and oestrogens protective effects could result in lower PD risk in women.

There is no great evidence about imaging biomarkers assessing sex differences. In one MRI study assessing sex differences in brain structures74, reduced cortical thickness in multiple brain regions including frontal, parietal, temporal, and occipital lobes associated to an altered connectivity was found in male PD patients compared with females.

**Genetics**

The interaction between sex and genetics is complex, and not well known in PD. Sex may influence several polymorphisms’ expression in PD9,75–77. On the other hand, genetics may impact differently PD expression in males and females. One example can be the leucine-rich repeat kinase 2 (LRKK2) gene mutation. LRKK2 mutations are a common cause of genetic PD with autosomal inheritance and incomplete penetrance, mostly described in North African Berbers and Ashkenazi Jews78. Some studies report a possible role of LRKK2 gene mutation in reversing the M:F ratio in idiopathic PD79–82. Indeed, a recent meta-analysis83 has shown a higher prevalence of LRKK2 mutation among women, in contrast with previous data suggesting a similar prevalence in both sexes84. On the other hand, no influence of the glucocerebrosidase (GBA1) mutations has been described on PD sex ratio compared to the general population85. However, there is some evidence about an increased risk of neuropsychiatric comorbidity (anxiety, depression) in men but not in women with GBA1 mutation86.

Sex may also contribute to predict PD with high specificity in a combined genetic-clinical score, as recently shown by a population-based study87.

Further studies are needed to elucidate the relation between sex and genetics in PD.

**Clinical features**

*Motor symptoms*

Although the lack of studies specifically addressing the effects of sex on PD symptoms, several differences in clinical features based on sex have been described (FIG. 2). Women are likely to present a tremor-dominant phenotype at disease onset, with a slower progression41. Moreover, the slightly delayed age and the milder motor symptoms at PD onset42 suggest a more benign PD phenotype in women, probably related to baseline higher dopaminergic activity12,41, and to the evoked protective effect of oestrogens. However, the less frequent access to medical care in women compared to men may also influence the role of age at PD onset88,89. Evidence from the Parkinson’s Progression Markers Initiative (PPMI)90 study has supported the effect of sex on motor progression in newly diagnosed patients, with women progressing at a slower rate than men. Yet, during the disease course, female sex appears to be independently associated to the development of motor fluctuations91. Indeed, women tend to have an earlier onset of wearing off periods and a higher risk to develop levodopa-induced dyskinesias92–96, with a shorter time to dyskinesia occurrence97. Men appear to have more severe motor features during the course of the disease98. A recent study in autopsy-confirmed PD found that the diffuse malignant phenotype, defined on severity of motor symptoms, rapid eye movement sleep behaviour disorder (RBD), and autonomic and cognitive function at diagnosis was more frequent in men99. These findings do not support the neuroprotective role of oestrogens, and indicate that other factors may influence the disease severity and progression in both sexes.

Clinical features of PD women during hormone-related events are detailed in BOX 1.

*Non-motor symptoms*

Available data shows differences in non-motor symptoms (NMS) prevalence and severity between sexes100. Despite methodological differences in NMS assessment across PD studies, some NMS appear to be specifically associated with sex. Indeed, mood symptoms (sadness, nervousness, anxiety, lack of motivation), restless legs syndrome, constipation, and pain are more prevalent in women31,101–105, while sexual dysfunction (reduced or increased interest in sex, difficulty in having sex, erectile dysfunction), drooling, and excessive day time sleepiness are more common in men102,104–110. Regarding other NMS, such as urinary and sleep disturbances, sex differences are not evident. Moreover, women tend to have a higher NMS overall burden than men102.

However, the vast majority of the studies on NMS included patients already treated with dopaminergic agents, thus representing a major limitation given the different effects of dopaminergic treatment on several NMS111. Indeed, one study110 in 200 *de novo* untreated PD patients showed that women had the same prevalence of mood symptoms compared to PD men, in contrast with previous studies on treated patients. An important effect of sex has also emerged in several NMS present in the PD premotor phase, such as olfaction/taste difficulties, acting out during dreams and sadness, being more prevalent in men than women110. Moreover, a large cross-sectional study112 showed that in a combination of several NMS best predicting PD, dysautonomia was a predictor of PD only in men, while RBD only in women, suggesting that sex-based differences are present even in the preclinical phase of the disease. This should be kept in mind when designing clinical trials for early diagnosis biomarkers.

Unfortunately, there is a lack of longitudinal studies assessing the influence of sex on NMS, taking in account patient’s age, disease progression and severity, and medications. One prospective study showed no significant difference in NMS between sexes at baseline, while reporting a higher NMS prevalence at 2 years in men than women113.

Interestingly, non-motor fluctuations (NMFs) seem to be more frequent in women94,102,104,114. Only one study assessed prospectively NMFs in relation to sex115, reporting higher rate of NMFs in women. This could explain the higher prevalence of mood symptoms in women reported by several studies in patients on dopaminergic treatment irrespective of disease duration. The higher rate of NMS fluctuations in women, in addition to a different pathophysiology compared to men, may suggest also that they are underestimate and/or undertreated.

Moreover, an association between Health Related Quality of Life (HRQoL) and NMS116 emerges in PD. Indeed, fatigue and depression appear to be the main determinants of poor HRQoL in female patients even in the early stages, suggesting the importance of a gender-specific therapeutic management.

The role of sex in cognition has not been fully investigated. In a large PD longitudinal study, sex accounted for 2.6% of the predictive data provided by a clinical-genetic risk score for cognitive decline117. Dissimilar findings exist about the prevalence and the impairment in specific cognitive domains in men compared to women118–120, partly reflecting differences in neuropsychological assessment. Overall, male sex emerges to be associated with an higher prevalence and risk for cognitive impairment and dementia in PD108,112,121–126. A longitudinal study showed that the primary predictive factor in the transition from no cognitive impairment to PD-Mild Cognitive Impairment or PD-Dementia was male sex and that males progressed more rapidly than females126. However, recent evidence suggests that cognitive decline in PD women starts later than in men, but it reaches the male rate after 80 years old127. Interesting, a recent meta-analysis on non-demented PD patients, reported greater frontal executive deficits in men compared to women, with no significant differences in the visuospatial abilities and verbal memory118, in contrast with previous studies. These findings, along with a milder motor profile at PD onset in women, could be explained by a less severe impairment of the frontal striatal pathway in the early stages of the disease, possibly related to the oestrogens protective effect.

Larger and prospective studies are needed to clarify if the higher prevalence of cognitive impairment in PD men is sex-related or if it mirrors the sex-differences in cognitive function in the general population100.

**Response to treatment**

*Medical treatment*

Response to dopaminergic medications differs between men and women. However, this evidence comes from both retrospective and prospective studies aimed at studying other outcomes. Numerous studies pointed at the use of higher dopaminergic dosage, expressed as levodopa equivalent daily dose (LEDD), in males compared to women98,129,130. Evidence suggests that this sex difference in LEDD is related to differences in levodopa pharmacokinetics and pharmacodynamics between sexes131–136, with body weight playing a key role. Indeed, women show higher levodopa plasma concentrations related to a lower body weight134, and a lower levodopa clearance136, thus resulting in a greater levodopa bioavailability compared to men133,135. This could partly explain the sex discrepancy in levodopa-related complications114, i.e., the higher rate of dyskinesia, and the greater severity of motor and non-motor fluctuations in women compared to men, as discussed above. However, other factors in addition to body weight, including abnormal plastic responses to levodopa and differences in the energetic metabolism137, may interact and account for the differences in levodopa complications between sexes. In addition, some genetic factors could modulate the risk of levodopa induced dyskinesia, such as the DRD2 polimorphism95, associated to a protecting effect on dyskinesia development only in men. Moreover, recent data suggests also a sexual dimorphism in genes implicated in dopamine metabolism, which could explain the need for higher doses of levodopa in males carrying the *MAO‐B* G allele138.

To note, no data are available about the sex difference in response to non-oral dopaminergic treatment, such as infusional dopaminergic treatments, or other class of anti-PD medications (i.e., anticholinergics, COMT-I, MAOB-I).

To date, no recommendations are available about the sex-specific management of medical treatment in PD139,140. This might be important for tailoring medical treatment in men and women.

*Deep brain stimulation therapy*

Deep brain stimulation (DBS) is a well-established treatment for PD, but there are only few studies about sex-differences. Some studies have reported a reduced utilization and later access to surgery in women141–143, despite the higher burden of motor complications compared to men. Several hypotheses have been made to explain this discrepancy, including more severe anxiety related to surgery, and a lower referral for DBS in countries with low socioeconomic level in women. The benefit from DBS is similar in both sexes, but women tend to show better outcome in quality of life144–146. Moreover, DBS appears to be safe and effective during pregnancy147.

However, no conclusion can be drawn because of lack of ad-hoc studies.

**Essential tremor**

**Epidemiology**

Although there are few studies available, results concerning epidemiological studies regarding sex differences in essential tremor (ET) are inconclusive. One meta-analysis and other studies did not find sex difference in ET concerning the M:F ratio prevalence (ranging from 0.78:1 to 1.19:1; median = 0.95:1)148–150. However, some other studies found a significant higher prevalence among men151–153. These opposite results are likely related to methodological differences among these studies as well as dramatic differences in sample’s size of these studies. Indeed, Louis et al.149 performed a community-based study in northern Manhattan, New York, on the base of neurological examination as well as handwriting samples on 1965 participants. Gilk et al.150 used a door to door survey in North Israel Arab villages on 900 people. Both groups did not find gender differences in ET.

Mancini et al.151 presented positive results in their study administered by family doctors specifically trained to identify ET. Moreover, they examined a sample of 13.604 individuals for a period of 12 months. This longer period of observation gave the opportunity to register more ET cases due to the increase of incidence with age. Dotchin et al.152 used a screening questionnaire in their door-to-door survey and the neurological examination was performed only on the positive responders producing a selective participants group. Tan et al.153 performed a study on 15.000 people with a screening questionnaire for Parkinson’s disease. Consequentially, they investigated the presence of ET in a selected population of neurological patients and this might have contribute to their positive results.

It has been hypothesized that the possible male predominance in ET patients highlighted by some authors might be due to the possible clinical and pathological associations between ET and PD, which is highly prevalent in men154. Interestingly, in the paediatric population ET is definitely three times more common in male population155.

Other studies have demonstrated a specific sex-related phenotype for ET. Head tremor seems to be more prevalent in female than in male with ET156,157.

**Genetics**

To date, no data is available concerning sex differences in genetics for ET.

**Clinical features**

Some evidence suggests that men develop ET earlier than women, as reported in a community-based epidemiological study in Sweden in which 3% of males had tremor onset by age 18 versus 0% of females158. In a American study, although no sex differences were found in adults, the incidence of ET in children was 42% higher in males than in females (2.7 vs. 1.9 cases per 100.000)159.

Some studies have demonstrated a specific sex-related phenotype for ET. Head tremor seems to be more prevalent in female than in male with ET156,157,160. Compared to women, men seem to be affected from more severe postural hand tremor157. Moreover, the presence of both female sex and severe hand tremor increased the odds for having in addition the combination of head and voice tremor160.

**Response to treatment**

No study is available concerning the impact of sex on medical treatment for ET.

Concerning the sex effects in DBS therapy, no differences have been found for both thalamic and subthalamic stimulation in one study specifically addressing this topic161.

**Dystonia**

**Epidemiology**

Dystonia concerns a group of clinically and aetiologically heterogeneous diseases, the most common types being the adult-onset focal dystonia (AOFD)162,163. Largely conflicting AOFD prevalence data have been reported so far, likely reflecting a non-uniform methodology in epidemiological studies world-wide163. A clear female prevalence emerges in all types of craniocervical dystonias (blepharospasm, oromandibular dystonia, Meige syndrome, cervical dystonia, spasmodic dysphonia). The M:F ratio ranges from 1:1.6 to 1:3.8 according to the type of dystonia164–170, with the peak age at onset in the sixth decade. Focal task-specific dystonia (FTSD), such as writer’s cramp171,172, musician’s cramp and golfer’s cramp173,174, are more frequent in men175. Nevertheless, the typist’s cramp has been described more often in women169,176. The different prevalence of FTSD between sexes could be linked to different gender-related daily life activities (job, hobbies) in women and men.

Regarding to generalized dystonia, no significant sex prevalence has been reported nor in idiopathic neither in inherited dystonia (associated to DYT1 or DYT6 gene mutations, myoclonus dystonia and Dopa-Responsive Dystonia).

It is known that acute dystonic reactions are more frequent in men177, whereas tardive dystonia is more frequent in women178.

**Risk factors**

The most frequent AOFD, cervical dystonia (CD), and blepharospasm (BSP) are believed to result from the interaction of susceptibility genes with genetic and environmental risk factors179. A recent study171 has showed a female sex-effect on abnormal temporal discrimination time (TDT) in unaffected female first degree relatives of CD patients. The TDT, the shortest time interval at which two separate stimuli are perceived as asynchronous, has been found abnormal in CD180 and in other types of focal and generalized dystonia181–184, thus assuming the possible role of mediational endophenotype (subclinical marker of gene carriage). Abnormal TDT may reflect structural and functional changes as results of an inherited defective inhibition within the network connecting superior colliculus, basal ganglia and sensorimotor cortex185. The findings of abnormal TDT in unaffected relatives of CD patients suggest that inherited gene expression becomes fully penetrant only in female carriers, while remaining at reduced penetrance in male carriers. These results could partly explain the higher prevalence of CD in women. A likely role of nuclear hormone receptors on epigenetic programming has been suggested, although it remains speculative186.

Indeed, a possible influence of sexual hormones on dystonia arises from epidemiological and clinical data. The oestrogens may modulate the nigrostriatal dopaminergic system5,20,21, and thus the involuntary motor function in dystonia. However, the correlation between dystonia and hormone-related events in women remains to be elucidated. Sparse and contradictory literature is available about this topic. Menstrual cycle may result in subjective worsening of dystonia symptoms in some patients.187,188 Anecdotal reports suggest that pregnancy may affect differently dystonia symptoms, with improvement, worsening, or no effect in generalized and focal/segmental dystonia187,189,190. A case of CD onset during pregnancy with spontaneous resolution after the second trimester, defined as ‘dystonia gravidarum’, has also been described.189 In addition, menopause has been suggested as a factor predisposing to BSP in older women191. Indeed, the peak age of craniocervical dystonia in the sixth decade in women may suggest that lowering of circulating oestrogens levels after menopause could play a role on symptoms onset in some patients. However, menopause and HRT seem not to impact significantly dystonia in other reports187.

**Genetics**

Sex may affect the penetrance of some genetic dystonia. Myoclonus dystonia (DYT11), associated to epsilon- sarcoglycan (SGCE) gene mutations, shows reduced penetrance on maternal transmission of the disease allele, through a maternal genomic imprinting of the SGCE gene192. Thus, most affected subjects inherit the disease gene from their fathers. A reduced penetrance especially in males has also been described in DRD with heterozygous mutations in the GTP cyclo-hydrolase I gene193. Concerning X-linked dystonia-parkinsonism (DYT3, Lubag disease), there are some reports of women affected, suggesting that several molecular mechanisms involving X chromosome may occur in determining phenotype expression and severity in female carriers194.

**Clinical features**

Specific studies assessing sex differences regarding clinical features in dystonia are lacking. Available literature suggests that motor symptoms in isolated dystonia tend to develop earlier in men, with a shorter time to diagnosis and a greater severity compared to women195–197.

Non-motor features, including pain, sensory, and neuropsychiatric abnormalities have been increasingly described in all types of isolated dystonia198–201. Psychiatric disorders, especially major depressive disorders and anxiety disorders, are more frequent in AOFD. The association of specific psychiatric features and the higher female prevalence in craniocervical dystonia suggests a common underlying sex-related physiopathology, which still remains poorly understood.

**Response to treatment**

No studies specifically addressing sex differences in medical treatment of dystonia are available so far. A recent, large cross-sectional analysis202 from the Project 1 Dystonia Coalition showed no sex differences in the use of oral medications (anticholinergics, benzodiazepines, muscle relaxants, dopaminergics, baclofen), and botulinum toxin treatment in all types of dystonia lumped together. Evidence based recommendations indicate botulinum toxin treatment as a potential contraindication during pregnancy and lactation in women with CD203.

*Deep Brain Stimulation*

Sex does not appear to impact differently the response of globus pallidus internus stimulation. DBS surgery has been described safe in case series of dystonic women during pregnancy147,204,205. When proposing DBS to young dystonic women, a rechargeable battery might be encouraged to avoid surgery scars related to repeated replacement. A subclavicular placement for battery instead of abdominal in women planning a pregnancy would be preferred.

**Huntington’s disease**

**Epidemiology**

Huntington’s disease (HD) is caused by a polyglutamate triplet expansion (CAG) in Huntingtin (HTT) gene on chromosome 4206. It shows equal penetrance and prevalence in both sexes on the autosomal dominant inheritance. Nevertheless, data from HD animal models207–209 and epidemiological cohorts210,211 suggest that sex may account for some variability in disease expression between men and women. A recent large American cohort study212 found that the age‐adjusted diagnostic frequency was higher among women than men (7.05 per 100,000 vs. 6.10 per 100,000; *P* < 0.01), suggesting that several sociodemographic factors, including sex, may influence HD epidemiology.

**Risk factors**

Triplet CAG expansion length is recognized to be the strongest risk factor for developing HD, with greater numbers of repeats predicting an earlier age of onset206,213. Nevertheless, there is evidence suggesting that other factors could contribute to HD phenotype expression. Sex-specific influence of apolipoprotein E ε2ε3 genotype on the age of onset has been described214. This genotype is associated with significantly earlier age of onset in male than in female patients, suggesting that it may be a risk factor for earlier onset in men.

Sexual hormones may account for a small portion of the phenotypic variance in HD. Scientific evidence from animal models suggesting a protective effect of oestrogens in HD is preliminary207–209. Inconclusive data are available about a possible protective role of female sex in HD215,216.

**Biomarkers**

No studies specifically investigating sex differences in HD biomarkers for disease progression and prognosis are available.

**Genetics**

Sex differences on normal neurodevelopment have been recently described in children at-risk for HD (having a family history of HD)217. In particular, the number of repeats in HTT gene, below disease threshold, conferred to females advantageous changes in brain structure and general intelligence compared to males.

The sex of the affected parent seems to predict the intergenerational CAG repeat instability of mutant *HTT*218, which tends to be higher with paternal transmission. This could be related to repeat size increases occurring more in the course of spermatogenesis than oogenesis219. Another possible explication is that a massive expansion of CAG could destroy the oocyte resulting in impaired fertilization220. Moreover, it is known that Juvenile-onset HD, manifesting with parkinsonian features rather than with chorea, tend to be linked to paternal transmission, while maternal inheritance is more frequently associated to a later onset of the disease221.

**Clinical features**

A few studies have investigated sex effects on clinical features in HD.

In a large European cohort study, women had more severe disease phenotype and faster progression particularly in the motor and functional domains, despite no differences in age of onset215. On the other hand, other studies have found that women had a later age of onset and longer disease course216. Men inheriting HD from affected mothers seem to have a slower course222.

The investigation of a possible correlation between clinical features and lifetime oestrogens exposure and the HRT in HD women is limited, mainly because of the young age of onset of the disease. However, plasma levels of the androgens total testosterone and dehydroepiandrosterone sulfate were related to the presence of depression but not dementia in female patients223. Meanwhile, low plasma testosterone levels have been associated to high disease severity and dementia in male patients, but not with depression or psychotic features224.

Yet, women showed a significantly higher prevalence of a history of depressive episodes, but not of suicidal ideations or attempts, obsessive-compulsive disorders, or psychotic symptoms. Additionally, there were more current or past abusers of nicotine or alcohol among men compared to women215.

A few studies have investigated the differences related to sex in body composition of HD patients. Women have lower body mineral density than both healthy controls and affected men, whereas men show a significant reduction of lean body mass. Overall, women tend to be less affected than men regarding body composition225, thus suggesting a different impact of the disease in energy expenditure and metabolism between sexes.

**Response to treatment**

No specific studies are available addressing sex differences in medical treatment for both movement and psychiatric disorders in HD.

**Sydhenam’s disease and chorea gravidarum**

**Epidemiology**

Sydenham’s or rheumatic chorea is considered an autoimmune neurological manifestation of acute rheumatic fever, occurring mainly in childhood. The prevalence is higher in females than males (3:1)226. Chorea gravidarum (CG) can be the initial manifestation of Sydenham’s chorea or it can represent a recurrence of childhood Sydenham’s chorea during pregnancy227. CG could be induced by the interaction of hormonal changes related to pregnancy with basal ganglia damage from prior rheumatic fever228. However, other causes have been reported underlying this form of chorea, such as systemic lupus erythematosus, primary antiphospholipid antibody syndrome, syphilis, and encephalitis. Moreover, oral contraceptives can cause chorea in women, even in absence of history of Sydenham’s chorea or CG.

**Clinical features**

CG arises mostly after the first trimester of pregnancy, with a prevalent generalized pattern, even if focal, multifocal and hemi-chorea have been reported228. Frequent complications, including spontaneous abortion, could occur during CG. With the progression of the pregnancy, the severity of choreic movements tends to decrease. The disease can resolve after delivery in up to one-third of patients but it can last for several months afterward.

**Response to treatment**

No sex differences are available concerning the treatment of SC. Medications for CG are recommended only for those situations in which the health of mother or fetus is threatened.

**Tics/Tourette syndrome**

**Epidemiology**

Chronic Tics disease (TD), including Tourette syndrome (TS), is recognized to have a M:F ratio estimated to be approximately 2:1 to 5:1, up to 10:1229–236. The different M:F ratio across studies might be related to differences in the used methods. Eremberg et al. 229 performed an epidemiological study using a questionnaire on 99 TS patients. Jankovic et al. 230 studied 112 TS patients with detailed neurological examination collecting several phenotypes of TS. Comings et al. 231 described a larger cohort of 250 consecutive cases seen over a period of 3 years and this gave the opportunity to observe changes of the clinical features over a specific interval of time. A similar approach of studying consecutive patients from a TS clinic was adopted by Eapen et al.232 Differently, Freeman et al233 performed a multicentre study including 3500 TS patients. These authors confirmed that the male excess occurs in each centre.

The striking male prevalence in TD patients is consistent across nationalities237. The male preponderance seems to decrease in adulthood238, with a females preponderance after the age of 30 reported in German administrative data239.

**Risk factors**

Overall, there is evidence supporting the role of an increased exposure to androgenic steroids during the very early phases of neural development. Patients with TS exhibit an enhanced reactivity of the hypothalamic–pituitary–adrenal axis to external stressors, although they exhibit a normal diurnal cortisol rhythm and a normal restoration of the baseline activity of the axis following the acute stress response. Additionally, oxytocin is another hormone possibly implicated in disorders related to the TS spectrum, especially non-tic-related Obsessive Compulsive Disorders240.

Complications during mother’s pregnancy, maternal prenatal smoking, and high stress all have been implicated as risk factors for the occurrence of TS241,242. Further, maternal prenatal use of nicotine has been associated to an eightfold increased risk of developing OCD associated to TS242.

Among the risk factors for tics disorders, the involvement of abnormal innate and adaptive immune responses constitutes a significant ongoing research field243. Indeed, a dysfunctional neural-immune cross-talk has been observed in patients with TS, in analogy to other neurodevelopmental disorders243.

**Biomarkers**

Some brain structural characteristics such as thinning of the fronto-parietal cortex have been found in TS boys compared to TS girls244.

**Genetics**

Maternal transmission has been found associated with earlier age at onset of tic disorders, greater motor tic complexity, and more frequent compulsive rituals. Paternal transmission seems to expose to greater vocal tic severity, earlier onset of vocal tics, and more severe ADHD241,245.

The potential interaction between genetic and environmental susceptibilityfactors is still poorly understood. A heritability of TS has been evaluated to be 0.77 in a large scale multigenerational family study246. However, a twin-family study247 found a lower heritability, estimated between 0.25 and 0.37, suggesting a significant role for an interaction between genes and environmental factors. No differences in familial risk or heritability of TS between male and female patients seem to emerge246.

TS as other neuropsychiatric disorders has a polygenic aetiology, and the genome-wide association studies (GWAS) are the current approaches in the study of this movement disorder. Recently, one genome-wide significant locus within FLT3 on chromosome 13, rs2504235, has been found associated to TS248. However, it has not been found a specific gender difference in the genetic expression of tics disorders.

**Clinical features**

Oestrogens are known to influence the severity of tics. An increase in tic frequency during the estrogenic phase of the menstrual cycle has been reported249, although lessening of tics with increasing age has also been found229.

Gender may play a role in determining the clinical comorbidities in TS patients, especially at the onset of the disease. To this regard, some studies have found a sex-specific clinical expression in the spectrum of neuropsychiatric disorders associated with TS250. TS onset with compulsive tics is more typical in female than male patients, while the onset with behavioural issues is more frequent in male patients251. Males have more frequent onset of rage, that can be correlated to the higher prevalence of Attention Deficit Hyperactivity Disorder (ADHD) comorbidities in men with TS compared to TS females as well as general population251, especially ADHD associated to depression252. Furthermore, women are significantly more likely to report a previous history of depression and non-OCD anxiety253.

Yet, sex plays a role in the neuropsychological profile of these patients. Girls have been found specifically slower than boys on the Letter Word Fluency, and this task appeared the only task on which there was greater TS-related deficit in girls than in boys254. However, girls with TS plus ADHD were less impaired that than males in the Letter Word Fluency254. Interesting, the gender is thought to have a role in the clinical manifestations of TS/TD patients’ relatives. Female relatives of are more likely to exhibit OCD without tics, whereas male relatives are more likely to exhibit tics255–257.

Tics manifestations (type, number, frequency, complexity) do not show significant gender difference. However, an increase in tic frequency during the estrogenic phase of the menstrual cycle has been reported249.

Women may experience greater functional interference from tics than men253. Interestingly, TS/TD showed a divergent course after adolescence characterized by tic improvement in men with a greater likelihood of tic worsening in women245. Additionally, female patients showed relative spreading of motor tic distribution in adulthood245.

**Response to treatment**

Women have shown better response to haloperidol than men, the latter often requiring medication changes249. No sex differences in treatment-seeking behaviour or attitudes towards treatment have been reported253. Further, the modality of intervention, perceived benefit of the treatment, or perceived duration of benefit did not differ between sexes. Equal results were found regarding the pharmacotherapy253. On the contrary, a long-term follow up of the North Dakota childhood study showed that males demonstrated more variability in improvement over time but more improvement overall than females258.

**Conclusions**

Sex differences seem to play an important role in the pathogenesis, risk factors, clinical features, and overall management of various movement disorders. Sex also appears to have relevant and complex correlations with both environmental and genetic factors. Sexual dimorphisms and sex hormones influence the dopaminergic system; oestrogens seem to decrease the risk of PD in women but also predispose to hyperkinetic conditions such as chorea. Women tend to have later age at PD onset, lower PD prevalence and incidence rates, higher rate of tremor phenotype, less diffuse malignant subtype, more dyskinesia, motor and non-motor fluctuations compared to men. Focal dystonia is more frequent in women, whereas tics are more frequent in men.

These sex-related differences are still poorly studied and understood. Especially in hyperkinetic movement disorders literature is scarce and controversial. Nevertheless, it is obvious that a better knowledge of the mechanisms of action of sex hormones in the basal ganglia, the sex differences in brain structure and function, the interaction between genes and sex, will likely help diagnosis and prognosis, differentiate phenotypes, develop innovative therapeutic options to treat and possibly modify the progression of some movement disorders. Improved knowledge about women and men differences in movement disorders is of utter importance to design clinical trials for neuroprotection drugs, risk prevention, and treatment.

**Box 1. PD and hormone-related events in women**

PD symptoms seem to be influenced by the menstrual cycle. A worsening of PD symptoms can occur just before the onset of menses when oestrogen levels are lower, whereas a progressive improvement can be observed at the time of ovulation, when oestrogen levels are higher. These findings can support the positive effect of oestrogens on the dopaminergic system188,259–261. Similarly, PD post-menopausal patients on hormone replacement therapy had milder symptoms of disease than those who were not262,263.

Pregnancy is not a frequent event in women with PD since the disease become manifested mostly after the menopause. During pregnancy and in the post-partum PD symptoms can worsen264–267. Some women may even present new PD symptoms during pregnancy or shortly after delivery266. Moreover, a permanent clinical deterioration without returning to baseline after delivery has also been described265. An increased levodopa requirement during both pregnancy and postpartum has been reported264. To note, levodopa is a safe treatment during pregnancy, while amantadine should be avoided. Overall, PD women appear not to be at higher risk of fetal or birth complication267. The mechanism underlying the deterioration of PD symptoms during pregnancy and in the early postpartum period is unknown. Several factors could interact, such as medication metabolism alteration related to physiological changes, diet and intestinal transit variation during gestation, physical and psychological stress, or less likely disease progression267. The dopamine-sparing properties of oestrogens including the inhibition of dopamine uptake, dopamine synthesis and dopamine release268 might justify the increase in levodopa intake observed in the early postpartum period when oestrogen levels are rapidly declining.

**Figure Legend**

**Figure 1.** **Factors implicated in the genesis of sex differences in movement disorders.**

Several factors (genetics, gonadal hormones, sexual dimorphism, environment) likely interact in determining sex differences resulting in divergent epidemiology, risk factors, biomarkers, clinical features and response to treatment between men and women with movement disorders.

**Figure 2.** **Sex differences in Parkinson’s disease.**

Women tend to have later age at PD onset, lower prevalence and incidence rates, higher rate of tremor phenotype, more dyskinesia, motor and non-motor fluctuations compared to men.

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