Sex differences in movement disorders

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Abstract | In a range of neurological conditions, including movement disorders, sex-related differences are emerging not only in brain anatomy and function, but also in pathogenesis, clinical features and response to treatment. In Parkinson disease (PD), for example, oestrogens can influence the severity of motor symptoms, whereas elevation of androgens can exacerbate tic disorders. Nevertheless, the real impact of sex differences in movement disorders remains under-recognized. In this article, we provide an up-to-date review of sex-related differences in PD and the most common hyperkinetic movement disorders, namely, essential tremor, dystonia, Huntington disease and other chorea syndromes, and Tourette syndrome and other chronic tic disorders. We highlight the most relevant clinical aspects of movement disorders that differ between men and women. Increased recognition of these differences and their impact on patient care could aid the development of tailored approaches to the management of movement disorders and enable the optimization of preclinical research and clinical studies.

Sex-based differences with regard to demographics, clinical features and therapeutic response have been identified in a range of neurological diseases, including Alzheimer disease (AD)[1], ischaemic stroke[2] and migraine[3]. In movement disorders, sex-related distinctions are emerging but are not yet widely recognized[4–6].

Movement disorders are a heterogeneous group of neurological conditions that include hypokinetic and hyperkinetic disorders. The former are characterized by slowness and paucity of movements, whereas the latter manifest with excessive, abnormal involuntary movements and postures[7]. Corticothalamic–basal ganglia and cerebellar network dysfunctions are well recognized in the pathophysiology of these disorders. Sexual dimorphisms in the dopaminergic system have been found in the basal ganglia of both patients with Parkinson disease (PD)[8,9] and unaffected individuals[10–19]. Preclinical evidence suggests that sex steroid hormones modulate the dopaminergic pathways in both normal and pathological states[5,12,13], and a neuroprotective effect of oestrogens has been proposed in women with PD[5,14–16]. Sex hormone changes — for example, during pregnancy — seem to induce or exacerbate hyperkinetic states such as chorea[7], suggesting that they contribute to sex-related variability in movement disorders through effects on basal ganglia networks. Other factors, including genetics, brain structure and brain function, might also contribute to sex-specific disparities in movement disorders (FIG. 1).

Increased recognition of sex differences in movement disorders, particularly PD, could aid the stratification of patients for diagnosis, treatment and prevention in the context of a multifactorial precision medicine approach[17]. In this Review, we highlight current evidence in this field and emphasize the importance of considering sex disparities when devising patient management strategies, formulating public health policies and designing clinical trials for movement disorders. We provide a brief discussion about potential mechanisms by which sex might influence disease susceptibility, pathogenesis and clinical presentation of hyperkinetic and hypokinetic movement disorders. With regard to hypokinetic movement disorders, we focus exclusively on PD owing to a lack of literature about sex differences in other parkinsonian syndromes, but we cover several hyperkinetic movement disorders, including essential tremor (ET), dystonia, chorea and tics.

Following the recommendations of the American Institute of Medicine[18], we use the term 'sex' rather than 'gender' in this Review. Sex refers to the definition of an individual as either male or female on the basis of reproductive organs and functions assigned by the X and Y chromosomes, whereas gender also encompasses one's self and social identity, which is rooted in biology but also shaped by environmental factors.

Parkinson disease

PD is a common neurodegenerative disease[19] mainly characterized by α-synuclein pathology and loss of dopaminergic neurons in the substantia nigra pars compacta[20]. The classic motor symptoms of PD are bradykinesia, rigidity, resting tremor, and postural and gait impairment[7]. PD has also a constellation of non-motor symptoms (NMS), including depression, anxiety, pain, orthostatic hypotension, and urinary, gastrointestinal and sleep dysfunction, which can precede the motor features by more than a decade[21].

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Key points

- Sex differences in epidemiology, clinical features and/or response to treatment have been reported in several movement disorders, including Parkinson disease (PD), essential tremor, dystonia, Huntington disease, Sydenham chorea and tic disorders.
- In the case of PD, male sex is associated with higher incidence and prevalence, earlier disease onset, more severe motor symptoms and progression, and more frequent cognitive decline compared with female sex.
- Few data are available on sex differences in hyperkinetic movement disorders, although craniocervical dystonia is more 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 strategies for patients with movement disorders.

Epidemiology

Many studies have indicated that the prevalence and incidence of PD are lower in women than in men[22–37], with age-standardized male:female (M:F) incidence ratios ranging from 1.3 to 2.0 in Western and South American populations[27–32]. However, lower M:F incidence ratios (0.95–1.20) were reported in Asia[23–26], possibly reflecting methodological issues, genetics, ethnicity and/or sex differences in behaviour, such as smoking[33]. A systematic analysis[34] of worldwide epidemiological studies in 2016 reported a M:F age-standardized prevalence ratio of 1.40, consistent with previous data[23,24,27,32]. Environmental factors, such as occupational exposure, which tends to be higher in men, might partly account for the male predominance. Overall, both M:F incidence and prevalence ratios for PD tend to increase with age. However, this trend is more evident for incidence than for prevalence, probably because the mortality risk is higher in men — but not women — with PD than in the general population[35]. As men tend to show earlier PD onset than women[36,37], and PD mortality increases with disease duration, mortality from the disease could also explain the increased incidence without a parallel increase in prevalence in men[38].

Risk factors

Sex disparities in epidemiology support the idea of sex-related differences in risk factors for PD. Gonadal hormones and sex chromosomes might modulate disease risk by influencing epigenetic mechanisms[8,12,39]. Preclinical evidence[5,12,13] has suggested a potential neuroprotective effect of oestrogens against dopaminergic damage through anti-inflammatory, anti-oxidative, and anti-apoptotic mechanisms[40,41], in addition to possible inhibitory effects on the formation and stabilization of α-synuclein fibrils — a key pathological feature of PD.

In some prospective and case–control studies, a longer lifetime exposure to oestrogens has been associated with reduced PD risk and milder symptoms at onset in women[14–16,42–52]. Consequently, the reduction in oestrogen levels after menopause has been suggested to increase the risk of PD in women[27,36,53]. However, a meta-analysis including 14 observational studies did not support a protective effect of hormone replacement therapy (HRT) on PD risk in women[54]. Caffeine is reported to have a protective effect with regard to PD risk, which might be attenuated by HRT in women[44,55]. Overall, however, no convincing evidence has been found for a link between reproductive factors such as age at menarche, age and type of menopause, fertile lifespan, pregnancy history and use of oral contraceptives and the risk of PD in women[33,56].

As regards potential environmental risk factors for PD, women tend to have a lower exposure to occupational toxins and a lower incidence of head trauma than men[57], reflecting differences in behavioural and social factors.

Biomarkers

Several potential biomarkers for PD diagnosis, prognosis and risk prediction have been identified in biofluids and peripheral tissues and through genetic and imaging studies[58]. Although several 'wet' biomarkers are thought to exhibit sex differences[59–61], only uric acid seems to have a strong sex specificity. Serum urate is an inverse risk factor for PD, particularly in men[62,63], and urate levels correlate negatively with disease severity in men but not in women[64–68]. In a large case–control study[63], higher uric acid levels predicted a lower risk of PD in men only, indicating a possible sex-related difference in purine pathways. Moreover, reduced levels of urate were found in post-mortem brain tissue from male patients with PD — but not in brain tissue from female patients — compared with brain tissue from individuals without neurodegenerative disease[68].

Few studies have examined sex differences in imaging biomarkers for PD. In one MRI study that measured sex differences in brain structures in patients with PD[69], reduced cortical thickness in multiple brain regions including the frontal, parietal, temporal and occipital lobes, associated with altered connectivity, was found in male patients in comparison with female patients. In a resting-state functional MRI study in drug-naive patients with early PD, sex-specific cortical and subcortical connectivity patterns within the sensorimotor network were reported, with connectivity being better preserved in women than in men[70], possibly related to sex-specific nigrostriatal dopaminergic pathways. Similarly, ^{123}I-FP-CIT nuclear imaging studies in patients with PD indicated higher physiological striatal dopamine levels in women than in men at symptom onset and throughout the disease course[36,71]. Moreover, in a ^{18}F-fluorodopa PET study[72], women with PD had 87% higher ^{18}F-fluorodopa uptake in the right dorsolateral prefrontal cortex than did their male counterparts.

Taken together, the neuroimaging findings support structural and functional signatures in women with PD, characterized by a better preserved presynaptic system and higher striatal dopaminergic levels at disease onset in comparison with men. These observations could explain sex differences in clinical symptoms, disease course and development of motor complications. In the near future, neuroimaging techniques could provide biomarkers to stratify patients according to the risk of disease progression and development of motor and non-motor complications over time.

Genetics

The interaction between sex and genetics is complex and poorly understood in the context of PD. Sex seems to influence the expression of several polymorphisms in PD[9,73–75], and genetic factors might differentially influence the manifestations of PD in men and women.

Mutations in the leucine-rich repeat kinase 2 (*LRKK2*) gene are a common cause of genetic PD. These mutations show autosomal inheritance and incomplete penetrance, and have been described predominantly in the North African Berber and Ashkenazi Jewish populations[76]. Some studies have found that male predominance in PD is not evident in some populations[77–82], possibly owing to a higher prevalence of *LRRK2* mutations among women than among men[83]. *LRRK2* mutations also show sex-specific effects on the manifestations of PD. In a large cohort study[81], men with PD who had the *LRRK2*^{G2019S} mutation had milder motor symptoms and higher cognitive function, a lower incidence of REM sleep behaviour disorder (RBD) and worse thermoregulation scores than men with idiopathic PD, whereas women with *LRRK2*^{G2019S} had worse motor complications than women with idiopathic PD. Moreover, among patients with *LRRK2*-associated PD, women had worse motor complications but better olfaction than men, suggesting that both sex and genetics influence the phenotype.

Mutations in the glucocerebrosidase (*GBA1*) gene have also been implicated in PD, although unlike the aforementioned *LRRK2* mutations, *GBA1* mutations do not seem to influence the sex ratio in PD[84]. Some evidence suggests an increased risk of neuropsychiatric comorbidities, such as anxiety and depression, in men but not women with *GBA1* mutations[85].

Sex might also contribute to the prediction of PD risk with high specificity as part of a combined genetic–clinical score, according to a population-based study[86]. Further studies are needed to fully elucidate the relationship between sex and genetics in PD.

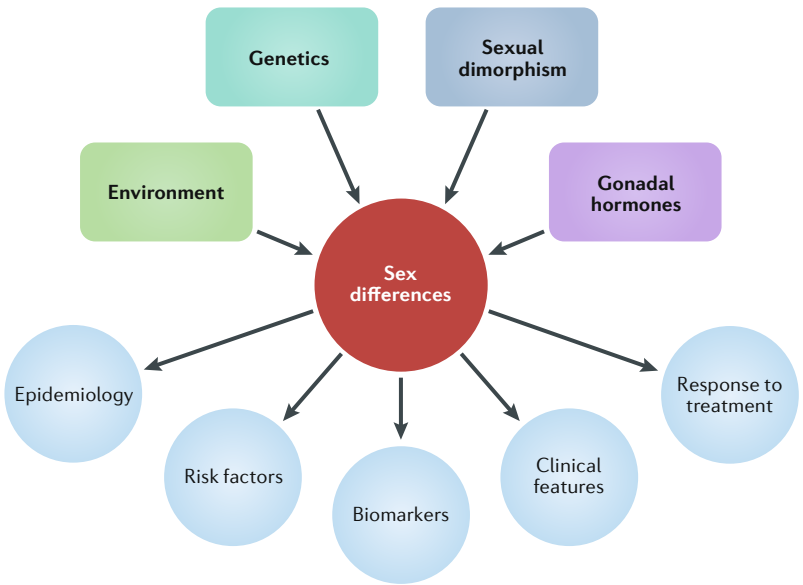

Fig. 1 | **Factors implicated in the genesis of sex differences in movement disorders.** Factors including genetics, gonadal hormones, sexual dimorphism and the environment are likely to interact to determine sex differences, which result in differences in epidemiology, risk factors, biomarkers, clinical features and response to treatment between men and women with movement disorders.

Clinical features

Motor symptoms. Despite a lack of studies specifically addressing the effects of sex on PD symptoms, several sex-based differences in the clinical features of PD have been described (FIG. 2). In comparison with men, women are more likely to present with a tremor-dominant phenotype at disease onset and to show slower disease progression[36]. A slightly older average age and milder motor symptoms at PD onset[42] suggest a more benign PD phenotype in women than in men, probably related to higher baseline dopaminergic activity[36,87] and a possible protective effect of oestrogens. Deficiencies in access to medical care in women compared with men might also influence the relationship between sex and age at PD onset; for example, the tendency of women to seek medical care later than men could give a misleading impression of later disease onset in women[88,89]. Evidence from the Parkinson's Progression Markers Initiative (PPMI)[90] study supports an effect of sex on motor progression in newly diagnosed patients, with women showing slower progression than men. However, during the disease course, female sex seems to be independently associated with the development of motor fluctuations[91], with women tending to have an earlier onset of wearing-off periods and a higher risk of developing levodopa-induced dyskinesias[92–96], as well as a shorter time to dyskinesia occurrence[97]. By contrast, men seem to have more severe motor features throughout the course of the disease[98]. A study in autopsy-confirmed PD found that the diffuse malignant phenotype, characterized by severe motor symptoms, the presence of RBD, and autonomic and cognitive deficits at diagnosis, was more frequent in men than in women[99].

PD and hormone-related events in women. PD symptoms seem to be influenced by the menstrual cycle. Worsening of PD symptoms can occur just before the onset of menses, when oestrogen levels are reduced, whereas progressive improvement can be observed at the time of ovulation, when oestrogen levels are higher. These findings support a positive effect of oestrogens on the dopaminergic system[100–103]. Also consistent with this idea, in postmenopausal women with PD, HRT is associated with milder disease symptoms[104,105].

Pregnancy is not a frequent event in women with PD, as the disease usually manifests after the menopause. However, in women who develop the condition at childbearing age, PD symptoms have been reported to worsen during pregnancy and in the postpartum period[106–109], and some women present with new PD symptoms during pregnancy or shortly after delivery[108]. Permanent clinical deterioration that fails to resolve after delivery has been described in some women[107]. An increased requirement for levodopa during both pregnancy and the postpartum period has also been reported[106]. Of note, levodopa is a safe treatment during pregnancy, but amantadine should be avoided. Overall, PD does not seem to confer an increased risk of fetal or birth complications[109].

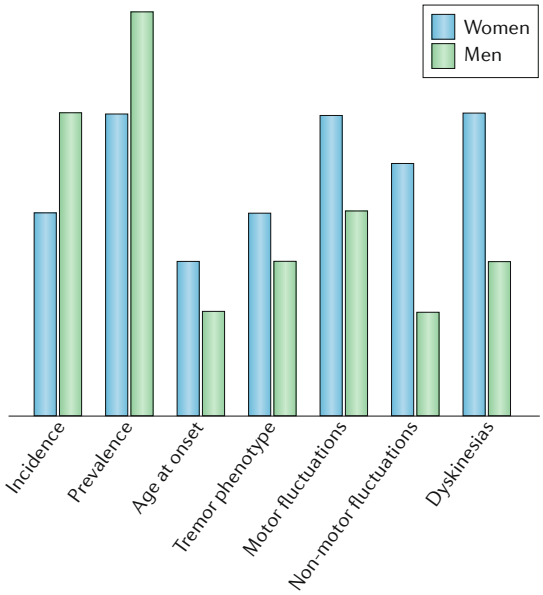

Fig. 2 | **Sex differences in Parkinson disease.** With respect to Parkinson disease, women (blue bars) tend to have later age at disease onset; lower prevalence and incidence; higher rates of tremor phenotype; and a greater likelihood of dyskinesia, and motor and non-motor fluctuations compared with men (green bars).

The mechanisms underlying the exacerbation of PD symptoms during pregnancy and in the early postpartum period are unknown. Several factors could interact, including alterations in medication metabolism related to physiological changes, diet and intestinal transit variation during gestation, physical and psychological stress, or — less likely owing to the relatively short time frame of pregnancy — disease progression[109]. The dopamine-sparing properties of oestrogens, including inhibition of dopamine uptake, synthesis and release[110], might justify the increase in levodopa intake that has been observed in the early postpartum period when oestrogen levels are rapidly declining.

Non-motor symptoms. The available data indicate sex differences in the prevalence and severity of NMS in people with PD[111]. Despite methodological differences in NMS assessment across PD studies, some NMS seem to be consistently associated with sex. Mood symptoms (sadness, nervousness, anxiety and lack of motivation), restless legs syndrome, constipation and pain are more prevalent in women[26,112–116], whereas sexual dysfunction (reduced or increased interest in sex, difficulty in having sex and erectile dysfunction), drooling, urinary symptoms and excessive daytime sleepiness are more common in men[113,115–122]. Sex differences are less evident for other NMS, such as sleep disturbances. Overall, women tend to have a higher NMS burden than men[113].

Of note, the vast majority of the studies on NMS included patients who had already received dopaminergic agents, which represents a major limitation given the differential effects of dopaminergic treatment on several NMS[123]. One study[121] in 200 untreated patients with de novo PD showed a similar prevalence of mood symptoms in women and men, in contrast with previous studies on treated patients. An important effect of sex has also emerged for several NMS that are present in the PD premotor phase, such as olfactory and gustatory impairments, and sexual dysfunction, which are more prevalent in men than in women[121]. Moreover, in a large cross-sectional study[124] in which several NMS were assessed for their capacity to differentiate people with early PD from controls, dysautonomia was a predictor of PD only in men, whereas RBD was associated with PD only in women, suggesting that sex-based differences are present even in the preclinical phase of the disease. These observations should be kept in mind when developing biomarkers for early diagnosis of PD.

Unfortunately, we lack longitudinal studies on the influence of sex on NMS that take into account the age of the patients, disease progression and severity, and medications. In a 2-year follow-up study, mood symptoms (sadness or blues) improved in both sexes after starting dopaminergic treatment. However, men developed more daytime sleepiness and increased sex drive than women, probably as adverse effects of dopaminergic treatment[125].

Interestingly, PD-related non-motor fluctuations (NMFs) seem to be more frequent in women than in men[94,113,115,126,127]. In particular, mood-related NMFs, such as pain, mood changes and anxiety, are more prevalent in women[98,128]. These findings could explain the higher prevalence of mood-related NMS in women found in several studies in patients on dopaminergic treatment, irrespective of disease duration.

An association between health-related quality of life (HRQoL) and NMS[129] has also emerged in PD. Fatigue and depression seem to be the main determinants of poor HRQoL in female patients even in the early stages of PD. By contrast, no association was found between NMS and HRQoL in male patients, highlighting the importance of sex-specific therapeutic management.

The relationship between sex and cognition has not been fully investigated in patients with PD. In a large longitudinal study in this population, sex accounted for 2.6% of the predictive data provided by a clinical–genetic risk score for cognitive decline[130]. Studies on the prevalence of cognitive decline and impairments in specific cognitive domains in men compared with women have produced conflicting results[128,131,132], partly reflecting differences in neuropsychological assessment. Overall, however, male sex seems to be associated with an increased prevalence and risk of PD-associated cognitive impairment and dementia[119,124,133–138]. A longitudinal study showed that the primary predictive factor in the transition from no cognitive impairment to mild cognitive impairment or dementia in patients with PD is male sex and that men progress more rapidly than women[138]. However, another study suggested that although PD-associated cognitive decline starts later in women than in men, the rates are similar in both sexes after the age of 80 years[139]. Interestingly, a meta-analysis of studies investigating cognitive impairment in PD patients without dementia found greater frontal executive deficits in men than in women but, in contrast with previous studies, found no significant differences in visuospatial abilities and verbal memory between the sexes[131]. These findings, along with

a milder motor profile at PD onset in women, could be explained by less severe impairment of the frontal striatal pathway in the early stages of the disease, possibly related to the protective effect of oestrogens.

Larger and prospective studies are needed to clarify whether the higher prevalence of cognitive impairment in men with PD is sex-related or whether it mirrors sex differences in cognitive function in the general population[100].

Response to treatment

Medical treatment. The response to dopaminergic medications differs between men and women, according to data obtained from retrospective and prospective studies that were originally designed to measure other outcomes. Numerous studies have pointed to the use of a higher dopaminergic dosage, expressed as levodopa equivalent daily dose (LEDD), in men than in women[98,140,141]. Evidence suggests that this sex difference in LEDD is related to differences in levodopa pharmacokinetics and pharmacodynamics between the sexes[142–147], with body weight playing a key role. Compared with men, women show higher levodopa plasma concentrations, related to lower body weight[145] and reduced rates of levodopa clearance[147], resulting in greater levodopa bioavailability[144,146]. This finding could partly explain the sex discrepancy in levodopa-related complications[126], such as the higher rate of dyskinesia and the greater severity of motor fluctuations and NMFs in women than in men, as discussed above. However, factors other than body weight, including abnormal plastic responses to levodopa and differences in energy metabolism[148], might interact and contribute to the differences in levodopa complications that have been observed between the sexes. In addition, some genetic factors could modulate the risk of levodopa-induced dyskinesia; for example, a dopamine receptor D2 (*DRD2*) polymorphism[81,95] is associated with a protective effect on dyskinesia development in men but not in women. Moreover, recent data suggest a sexual dimorphism in genes implicated in dopamine metabolism, which could explain the need for higher doses of levodopa in men who carry the G allele of the monoamine oxidase type B (*MAOB*) gene[149].

No data are yet available about sex difference in the response to non-oral dopaminergic treatment, such as infusional dopaminergic treatments, or other classes of anti-PD medications, such as anticholinergics, catechol-*O*-methyltransferase inhibitors and MAOB inhibitors. Also, to date, no recommendations have been formulated about the sex-specific management of medical treatment in PD[150,151].

Deep brain stimulation. Deep brain stimulation (DBS) is a well-established treatment for PD, but only a few studies on sex differences in the response to this intervention have been conducted. Some studies have found reduced utilization and later access to surgery in women than in men[152–154], despite the higher burden of motor complications in the former group. Several hypotheses have been put forward to explain this discrepancy, including more severe anxiety related to surgery and a lower DBS referral rate among women in countries with low socioeconomic status. The benefits from DBS are similar between sexes, although women tend to show better quality-of-life outcomes[155–157]. Moreover, DBS seems to be safe and effective during pregnancy[158].

Essential tremor

ET is an isolated tremor syndrome characterized by bilateral, largely symmetric, postural or kinetic tremor involving the upper limbs[7]. ET has a variable frequency range (4–12 Hz) and can also involve the head, vocal cords and lower limbs, in the absence of other neurological signs, such as dystonia, ataxia or parkinsonism[159].

Epidemiology

The most robust findings on sex differences in the epidemiology of ET came from a meta-analysis[160] that included 28 population-based prevalence studies from 19 countries and two large community-based studies[161,162]. This study found M:F prevalence ratios ranging from 0.78 to 1.19, with a median of 0.95, suggesting no overall sex differences in ET prevalence. However, some individual population-based studies have found a significantly higher prevalence of ET among men than among women[163–165]. This male predominance might be attributable to clinical and pathological associations between ET and PD, which is also more prevalent in men[166]. High levels of heterogeneity in methodology, diagnostic criteria, clinical assessment and ethnicity among the available studies might partly account for the observed discrepancies in M:F prevalence ratios. Interestingly, although no substantial sex differences were found in adults, in the paediatric population, ET seems to be more common in boys than in girls[167,168].

To date, no data are available concerning sex differences in the genetics of ET.

Clinical features

Some evidence suggests that men develop ET earlier than women. For example, a community-based epidemiological study in Sweden published in 1960 found that 3% of men in the general population had tremor onset by the age of 18 years, compared with 0% of women[169].

Some studies have demonstrated a specific sex-related phenotype for ET. Compared with women, men seem to be affected by more severe postural hand tremor[170], and head tremor tends to be more prevalent in women than in men with ET[170–172]. Moreover, the coincidence of female sex and severe hand tremor increases the odds of additionally developing the combination of head and voice tremor[172].

Response to treatment

No studies are available regarding the impact of sex on medical treatment for ET. We also lack evidence about ET treatment during pregnancy; however, the most commonly used medications for ET, primidone and propranolol, are contraindicated in pregnancy owing to their known teratogenic potential. Similarly, both topiramate and gabapentin should be avoided during pregnancy as they have been associated with congenital malformations and toxicity in animal studies[173–175]. In most cases, women prefer to manage their tremor

without medication during pregnancy to minimize the risk of fetal malformations and developmental disorders.

One study examined the effects of sex on the outcome of DBS therapy for ET, and no differences in outcome between the sexes were found for either thalamic or subthalamic stimulation[176].

Dystonia

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements and/or postures. Dystonic movements are typically patterned and twisting and can be tremulous[177].

Epidemiology

Dystonia encompasses a group of clinically and aetiologically heterogeneous diseases, the most common types being the adult-onset focal dystonias (AOFDs)[178,179]. Conflicting data on AOFD prevalence have been reported, probably reflecting non-uniform methodologies in epidemiological studies[179]. Nevertheless, a clear female predominance has emerged in all types of craniocervical dystonia, namely, blepharospasm, oromandibular dystonia, Meige syndrome, cervical dystonia and spasmodic dysphonia. The M:F ratio ranges from 1:1.6 to 1:3.8 depending on the type of dystonia[180–186], with the peak age at onset in the sixth decade. Focal task-specific dystonias (FTSDs) such as writer's cramp[187,188], musician's cramp and golfer's cramp[189,190] are more frequent in men than in women[191]; however, typist's cramp has been described more often in women[185,192]. These discrepancies in FTSD prevalence could be linked to differences in daily life activities, including jobs and hobbies, between women and men.

With regard to generalized dystonia, no sex predominance has been reported in either idiopathic or inherited dystonias — that is, dystonias associated with *DYT1* or *DYT6* gene mutations, or myoclonus–dystonia (also known as DYT11). The one exception is dopa-responsive dystonia (DRD), which is caused by autosomal dominantly inherited GTP cyclohydrolase 1 (*GCH1*) deficiency and is more frequent among girls and women than among men[193].

Acute dystonic reactions are known to be more frequent in men than in women[194], whereas tardive dystonia is more frequent in women[195].

Risk factors

The most common AOFDs, cervical dystonia and blepharospasm, are believed to result from the interaction of susceptibility genes with genetic and environmental risk factors[196]. One study[197] showed abnormal temporal discrimination time (TDT; the shortest time interval at which two separate stimuli are perceived as asynchronous) in unaffected female first-degree relatives of patients with cervical dystonia. The TDT is abnormal in patients with cervical dystonia[198] or other types of focal and generalized dystonia[197,199–201] and could be a subclinical marker of carrier status for mutations linked to these conditions. Abnormal TDT might reflect structural and functional changes resulting from inherited defective inhibition within the network connecting the superior colliculus, basal ganglia and sensorimotor cortex[202]. The findings of abnormal TDT in unaffected female relatives of patients with cervical dystonia suggest that the penetrance of the causative mutations is greater in female than in male carriers. These results could partly explain why cervical dystonia is more prevalent in women than in men. The involvement of nuclear hormone receptors in epigenetic programming has been suggested as an explanation for these observations but remains speculative[203].

Epidemiological and clinical data suggest that sex hormones influence dystonia. The oestrogens could modulate the nigrostriatal dopaminergic system[5,12,13], thereby exacerbating involuntary motor function. However, the correlation between dystonia and hormone-related events in women remains to be elucidated. The menstrual cycle might result in subjective changes in dystonia symptoms, as shown by two surveys conducted in large cohorts of premenopausal women, which reported worsening of dystonia during menses in around 40% of patients[103,204]. Anecdotal reports and small case series suggest that pregnancy has variable effects on dystonia symptoms, with improvement, worsening and no effect all being reported in the literature[175,204,205]. The menopause and HRT do not seem to substantially influence dystonia[204,206].

Genetics

Sex might affect the penetrance of some forms of genetic dystonia. DYT11, which is associated with ε-sarcoglycan (*SGCE*) gene mutations, shows reduced penetrance on maternal transmission of the disease allele owing to maternal genomic imprinting of the *SGCE* gene[207]. Thus, most affected individuals will have inherited the disease allele from their father. As mentioned above, reduced penetrance in men has also been described in DRD associated with heterozygous mutations in the *GCH1* gene[208].

X-linked dystonia–parkinsonism (also known as DYT3 or Lubag syndrome) is caused by a mutation on the X chromosome and, therefore, is primarily observed in men. However, some affected women have also been reported, suggesting that several molecular mechanisms involving the X chromosome, such as homozygosity for the disease-causing change, non-random X chromosome inactivation or mosaic monosomy X, determine phenotype expression and severity in female carriers[209].

Clinical features

The available data from large epidemiological studies suggest that motor symptoms in isolated dystonia tend to develop earlier in men, with a shorter time to diagnosis and a greater severity than is observed in women[187,210,211]. However, DRD associated with autosomal dominant *GCH1* deficiency seems to have a more benign motor phenotype and a later onset in men than in women[193].

Non-motor features, including pain, and sensory and neuropsychiatric abnormalities, are increasingly recognized in all types of isolated dystonia[212–215]. Psychiatric disorders, especially major depressive disorders and anxiety disorders, are more frequent in AOFD than in generalized dystonia. The combination of specific psychiatric features and female predominance in craniocervical dystonia suggests a common underlying sex-related pathophysiology, which remains poorly understood.

Response to treatment

A large international cross-sectional analysis[216] from the Dystonia Coalition Project 1 found no sex differences in the use of oral medications (anticholinergics, benzodiazepines, muscle relaxants, dopaminergics and baclofen) or botulinum toxin treatment when all types of dystonia were combined. However, according to evidence-based recommendations, botulinum toxin treatment is contraindicated during pregnancy and lactation in women with cervical dystonia[217].

Sex does not seem to influence the response to globus pallidus internus stimulation, and DBS surgery has been found to be safe during pregnancy in case series of women with dystonia[158,218,219]. When proposing DBS to women with dystonia, a rechargeable battery might be encouraged to avoid surgery scars related to repeated replacement. In women planning a pregnancy, subclavicular rather than abdominal battery placement would be preferred.

Huntington disease

Huntington disease (HD) is a rare, progressive neurodegenerative disorder that is inherited as an autosomal dominant trait and is characterized by a variable combination of movement disorders, cognitive impairment and behavioural symptoms[220].

Epidemiology

HD is caused by a polyglutamine triplet (CAG) repeat expansion in the huntingtin (*HTT*) gene on chromosome 4 (REF.[221]). The condition has an autosomal dominant pattern of inheritance and shows equal penetrance and prevalence in both sexes. However, data from HD animal models[222–224] and epidemiological cohorts[225,226] suggest that sex accounts for some variability in disease expression between men and women. A large American cohort study[227] found a slightly higher HD prevalence among women than among men (7.05 versus 6.10 per 100,000; $P<0.01$), suggesting a possible relationship between sex and HD.

Risk factors

CAG repeat expansion length is recognized to be the strongest risk factor for developing HD, with greater numbers of repeats predicting an earlier age of onset[221,228]. However, evidence suggests that other factors contribute to HD phenotype expression. For example, the apolipoprotein E ε2ε3 genotype is associated with a significantly earlier age of HD onset in male than in female patients[229], indicating that this genotype is a risk factor for earlier onset in men.

Sex hormones might account for a small portion of the phenotypic variance in HD, with preliminary evidence from animal models suggesting a protective effect of oestrogens on neurodegeneration related to HD progression[222–224].

Genetics

Sex differences in normal neurodevelopment have been described in children who have a family history of HD but have *HTT* CAG repeat lengths below the threshold for disease development[230]. Longer repeats are associated with advantageous changes in brain structure and IQ that are more pronounced in girls than in boys.

The sex of the affected parent seems to predict the intergenerational CAG repeat instability of mutant *HTT*[231], which tends to be higher with paternal transmission, possibly because repeat size increases occur more in the course of spermatogenesis than in oogenesis[232]. Another possible explanation is that a massive expansion of CAG could destroy the oocyte, resulting in impaired fertilization[233]. Moreover, juvenile-onset HD, manifesting with parkinsonian features rather than with chorea, tends to be linked to paternal transmission, whereas maternal inheritance is more frequently associated with later onset of the disease[234].

Clinical features

Several studies have investigated sex effects on the clinical features of HD. On the basis of two large, international cohort studies[235,236], women have a more severe disease phenotype and faster progression, particularly in the motor and functional domains, than men, and they tend also to have a longer disease duration, despite no significant differences in the age of onset[235]. Men who inherit HD from an affected mother seem to have a slower disease course than men who inherit the condition from an affected father[237]. No sex differences have been reported in the clinical phenotype at onset (usually characterized by motor symptoms) or in the distribution across stages of the disease[235].

A large study[238] based on the REGISTRY database found that HD motor symptoms have a stronger impact on functional ability and independence in women than in men, but no sex differences were found in the effects of functional disability on quality of life.

Investigations of a possible correlation between clinical features and lifetime oestrogen exposure and HRT in women with HD are limited, mainly because of the young age of onset of the disease. Reduced plasma levels of total testosterone and dehydroepiandrosterone sulfate have been linked to the presence of depression but not dementia in female patients with HD[239]. Low plasma testosterone levels have been associated with high disease severity and dementia but not with depression or psychotic features in men with HD[240].

Evidence is emerging for a reduced disparity in the prevalence of depression between women and men in the HD population compared with the general population[235]. A large European cohort study found no independent effect of sex on depression in HD after controlling for other variables using an interviewer-rated measure[241]. Similarly, another European population study[242] found no significant sex differences in anxiety and depressive symptoms in HD. In contrast with findings in the general population, the similar prevalence in depressive symptoms between men and women with HD could be related to the higher levels of disability and functional impairment in the HD population. No differences in suicidal ideations or attempts, obsessive–compulsive disorder (OCD) or psychotic symptoms have been described between men and women with HD[235]. A higher prevalence of current or past nicotine[235] or alcohol[235,242] abuse has been reported in men than in women in this population[235].

A few studies have investigated sex differences in body composition in patients with HD. Women with HD have lower bone mineral density than both healthy controls and affected men, whereas men with the condition show a significant reduction in lean body mass. Overall, women tend to be less affected than men with regard to body composition[243], suggesting a different impact of the disease on energy expenditure and metabolism between the sexes.

Response to treatment

No studies have specifically addressed sex differences in medical treatment for movement disorders in HD. However, in two randomized, double-blind, placebo-controlled studies[244,245] and one open-label, long-term, follow-up study[246], the dopamine receptor antagonist tetrabenazine showed similar therapeutic efficacy and rates of adverse events between men and women who were receiving the drug to treat choreic symptoms. In another study[247], from the Enroll-HD database, no sex differences in the efficacy of olanzapine, risperidone and tetrabenazine for HD chorea were found.

With regard to the treatment of mood disorders, the PREDICT-HD study, which mostly involved prodromal carriers of the *HTT* repeat expansion, found a sex difference in the use of antidepressant medication, with women being more likely than men to be prescribed serotonergic antidepressants[248]. However, in another study[242], mostly involving symptomatic patients with HD, in comparison with men, women had higher rates of current use of anxiolytics but not antidepressants, although they were more likely than men to have used both anxiolytics and antidepressants in the past. The discrepancy between these two studies might reflect increased rates of prescription of antidepressants in men as the disease progresses. The past use of anxiolytics and antidepressants in women might suggest that they are more likely than men to seek help for depression, probably related to greater disease severity and faster progression.

Most of the literature on pregnancy and HD to date has focused on genetic counselling in pre-symptomatic women, which is beyond the scope of this Review. However, as the mean age at pregnancy is rising in Western countries, the need to manage symptomatic women during pregnancy is likely to increase. Therefore, studies specifically addressing treatment during pregnancy in HD are needed. Of note, dopamine receptor blockers are classified according to the FDA Use-in-Pregnancy Ratings as category C ("Risk cannot be ruled out. Human studies are lacking … However, potential benefits may justify the potential risk.")[249] in pregnancy and are contraindicated in the first trimester. Haloperidol is generally preferred over the other typical neuroleptics because of the lower risk of maternal adverse effects[250]. With respect to second-generation antipsychotics, a clinical review found that in utero exposure to aripiprazole, olanzapine and quetiapine is not associated with increased risks of major congenital malformations, whereas risperidone might carry a slightly increased risk of such malformations[249]. Tetrabenazine has been classified as class C in pregnancy. Among the tricyclic antidepressants, desipramine and nortriptyline are preferred in pregnant women owing to their minimal adverse effects. The selective serotonin reuptake inhibitor fluoxetine also seems to be safe in pregnancy[174].

Sydenham chorea and chorea gravidarum

Epidemiology

Sydenham chorea, also known as rheumatic chorea, is considered to be an autoimmune neurological manifestation of acute rheumatic fever, occurring mainly in childhood. The prevalence of this condition is three times higher in women than in men[251]. Chorea gravidarum can be the initial manifestation of Sydenham chorea or can represent a recurrence of childhood Sydenham chorea during pregnancy[252]. Chorea gravidarum might be induced by the interaction of hormonal changes related to pregnancy with basal ganglia damage from prior rheumatic fever[253]. However, other causes have been reported to underlie this form of chorea, including systemic lupus erythematosus, primary antiphospholipid antibody syndrome, syphilis and encephalitis. Moreover, oral contraceptives can cause chorea in women, even in the absence of a history of Sydenham chorea or chorea gravidarum.

Clinical features

Chorea gravidarum arises mostly after the first trimester of pregnancy, with a prevalent generalized pattern, although focal and multifocal chorea and hemichorea have also been reported[253]. Complications, including spontaneous abortion, frequently occur during chorea gravidarum. With progression of the pregnancy, the severity of choreic movements tends to decrease. The disease resolves after delivery in up to one-third of patients but can last for several months afterwards.

Response to treatment

No sex differences have been reported with regard to the treatment of Sydenham chorea. Medications for chorea gravidarum are recommended only in situations where the health of the mother or fetus is threatened.

Tic disorders

Tic disorders are neurodevelopmental conditions with onset in the first two decades of life and may or may not persist into adulthood[254]. Tics, which represent the core defining feature of these disorders, are defined as recurrent, patterned, usually rapid, non-rhythmic movements and vocalizations, which can be suppressed voluntarily to a variable degree. Among the tic disorders, Tourette syndrome (TS) is characterized by the coexistence of multiple motor and vocal tics with onset in childhood and adolescence and lasting for more than 1 year[254].

Epidemiology

Chronic tic disorders, including TS, affect men more than women, with M:F prevalence ratios ranging from 2 to 10 (REFS[255–262]). The striking male predominance in tic disorders is consistent across nationalities[263] but seems to decrease in adulthood[264], with a female preponderance being reported above the age of 30 years in German administrative data[265].

Risk factors

Some evidence supports a role for increased exposure to androgenic steroids during the very early phases of neural development in the pathophysiology of tic disorders. Patients with TS show enhanced reactivity of the hypothalamic–pituitary–adrenal axis to external stressors, although they exhibit a normal diurnal cortisol rhythm and normal restoration of baseline activity of the axis following the acute stress response. Oxytocin is another hormone that has been implicated in disorders related to the TS spectrum, in particular non-tic-related OCD[266].

Complications during pregnancy, maternal prenatal smoking and high stress have all have been implicated as risk factors for the occurrence of TS in the offspring[267,268]. Furthermore, maternal prenatal use of nicotine has been linked to an eightfold increased risk of developing OCD associated with TS[268].

Among the risk factors for tic disorders, the involvement of abnormal innate and adaptive immune responses is the subject of ongoing research[269]. Dysfunctional neural–immune crosstalk has been observed in patients with TS, in analogy to other neurodevelopmental disorders[269].

Biomarkers

In young people (aged 10–25 years) with TS, thinning of the frontoparietal cortex has been observed in males relative to females[270]. Moreover, a negative correlation between tic severity and pre-central and post-central cortical thickness has been found to be more prominent in boys than in girls with TS. These findings could suggest that these brain areas are important players in the pathogenesis of tics, especially in male patients. In girls with TS, frontoparietal cortex morphology seems to be associated with tic control, suggesting underlying adaptive plastic changes.

Genetics

Maternal transmission is associated with an earlier age at onset of tic disorders, greater motor tic complexity and more frequent compulsive rituals. By contrast, paternal transmission seems to result in greater vocal tic severity, earlier onset of vocal tics and more severe attention deficit–hyperactivity disorder (ADHD)[267,271].

The potential interaction between genetic and environmental susceptibility factors in tic disorders is still poorly understood. The heritability of TS was calculated to be 0.77 in a large-scale, multigenerational family study[272]. However, a twin family study[273] found a lower heritability (0.25–0.37), suggesting a prominent role for environmental factors. No differences in familial risk or heritability of TS between male and female patients have emerged[272].

Like other neuropsychiatric disorders, TS has a polygenic aetiology, and genome-wide association studies are currently being used to study this movement disorder. One genome-wide significant locus within the *FLT3* gene on chromosome 13, rs2504235, was found to be associated with TS[274]. No sex differences in the genetic expression of tic disorders have been found.

Clinical features

Tic manifestations (type, number, frequency and complexity) do not show significant sex differences. However, tic frequency has been reported to increase during the oestrogenic phase of the menstrual cycle[275]. In addition, female patients seem to have less spreading of motor tic distribution in adulthood compared with men[271]. Lessening of tics with increasing age has been found in both sexes[255].

Sex might have a role in determining clinical comorbidities in patients with TS, especially at the onset of the disease. Some studies have found sex-specific clinical expression in the spectrum of neuropsychiatric disorders associated with TS[276]. For example, onset with compulsive tics is more typical in female than in male patients, whereas onset with behavioural issues is more frequent in males[277]. Men more frequently exhibit rage, which correlates with a higher prevalence of ADHD — especially ADHD associated with depression — in men than in women with TS, as well as in the general population[277,278]. Furthermore, among individuals with chronic tic disorders, women are more likely than men to report a history of depression and non-OCD anxiety[279].

Sex also influences the neuropsychological profile of patients with tic disorders. Among children with TS, girls were slower than boys on a letter–word fluency task[280] — seemingly the only task on which girls showed a greater TS-related deficit than boys. However, girls with TS plus ADHD were less impaired than their male counterparts on this task[280]. Interesting, sex is also thought to influence clinical manifestations in the relatives of patients with TS or other tic disorders. Female relatives of these individuals are more likely to exhibit OCD without tics, whereas male relatives are more likely to exhibit tics[281–283].

Women might experience greater functional interference with their social lives from tics than men. An exploratory research found that women reported increased rates of tic-related interference with their social, leisure and domestic activities compared with men. Moreover, women reported greater public avoidance behaviour, lower quality of life and diminished physical well-being due to tics[279].

Response to treatment

Among individuals with TS, women have shown a better response to haloperidol than men, with the latter often requiring medication changes[279]. In one study, no sex differences in treatment-seeking behaviour or attitudes towards treatment were reported in people with tic disorders[279]. Furthermore, the modality of intervention, perceived benefit of the treatment and perceived duration of benefit did not differ between the sexes. A long-term follow up of the North Dakota childhood study showed that men demonstrated more variability in tic improvement related to treatment over time but more improvement overall than women[284].

Neuroleptic drugs are generally contraindicated during pregnancy, and fluoxetine is preferred for the treatment of TS-associated OCD during pregnancy[250].

Conclusions

Through complex correlations and interactions with environmental and genetic factors, sex differences seem to influence multiple facets of movement disorders, including pathogenesis, risk factors, clinical features

and overall management. Sexual dimorphisms and sex hormones modulate the dopaminergic system, and oestrogens seem to predispose to and/or exacerbate hyperkinetic conditions such as chorea, dystonia and tics, although overall, tic disorders are more frequent in men than in women. By contrast, oestrogens might have a protective effect against PD: compared with men, women tend to be older at disease onset, exhibit lower PD prevalence and incidence and are less likely to develop the diffuse malignant subtype. However, women also show a higher rate of the tremor phenotype and more dyskinesia, motor fluctuations and NMFs in comparison with men.

Sex-related differences in movement disorders are still insufficiently studied and poorly understood. In hyperkinetic movement disorders in particular, the literature is scarce and controversial. Better knowledge of the mechanisms of action of sex hormones in the basal ganglia, the sex differences in brain structure and function, and the interaction between genes and sex is likely to aid diagnosis and prognosis, differentiation of phenotypes, and development of innovative therapeutic options to treat and possibly modify the progression of some movement disorders.

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Author contributions

E.M. and S.M. conceived the paper. All authors contributed to the literature search and to the writing. S.M. designed the figures. E.M. provided guidance for specific areas of competence and the overall manuscript outline.

Competing interests

E.M. has received honoraria for lecturing from Medtronic and for acting as a consultant from Medtronic and Newronika. She has received research grants from Merz and educational grants from Boston, Homeperf and LVL. The other authors declare no competing interests.

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