REVIEW

CME

Movement Disorders in Women: A Review

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ABSTRACT: The field of women's health developed based on the recognition that there are important sex-based differences regarding several aspects of medical illnesses. We performed a literature review to obtain information about differences between women and men for neurological movement disorders. We identified important differences in prevalence, genetics, clinical expression, course, and treatment responses. In addition, we found that female life events, including menstruation, pregnancy, breast feeding, menopause, and medications prescribed to women (such as oral contraceptives and hormone-replacement therapy), have significant implications for women with movement disorders. Understanding this biological sex-specific information can help improve the quality and individualization of care for women with movement disorders and may provide insights into neurobiological mechanisms.

Key Words: movement disorders; women; gender

The field of women's health evolved from the recognition that a number of medical conditions differ in presentation, course, and therapeutic response between women and men. It is known that distinct physiological and anatomical differences occur in a variety of organ systems, depending on whether an individual has two X chromosomes or one X and one Y chromosome. Furthermore, it has been recognized that there are important interactions between disease states and uniquely female life events, such as menstruation, pregnancy, and menopause. The Institute of Medicine has recommended exploration of the biological contributions of sex to human health.[1] It is well known by neurologists that there are clear sex differences and specific women's issues in a variety of neurological conditions, such as headache, pain, stroke, and epilepsy. Although women's issues have been mentioned widely in the literature on neurological movement disorders, this is the first review article that attempts to synthesize the information.

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We conducted a Medline literature search for the years 1970 to 2013, focusing on the most common movement disorders along with the key words gender, sex, women, female, estrogen, progesterone, hormones, menstruation, pregnancy, breastfeeding, and menopause. Resulting articles were reviewed and are summarized below, organized according to the type of movement disorder. We have focused on sex differences in prevalence, genetics, clinical expression, and course treatment; on the influence of female life events, such as menstruation, pregnancy, lactation, and menopause; and on medication for women, including oral contraceptives and hormone-replacement therapy. Following the recommendations of the Institute of Medicine, we use the term "sex" as opposed to "gender." Sex is the classification of either male or female based on reproductive organs and functions assigned by chromosomes. Gender encompasses one's self and social identity as either male or female, which is rooted in biology but also shaped by environment.[1]

Parkinson's Disease

A decreased rate of Parkinson's disease (PD) among women has been reported in many prevalence and incidence surveys, and this difference persists across age groups.[2] These results have been confirmed in two published meta-analyses, which reported age-adjusted

male-to-female incidence ratios of 1.46 and 1.49.[3,4] The prevalence of PD was approximately two-fold lower for women than for men in the Northern California population study and in the Italian longitudinal study.[3,5] The latter study reported a prevalence rate of 8.8 to 9.9 cases per 100,000 for women compared with 13.0 to 19.0 cases per 100,000 for men.[5] Age at onset appears to be later in women compared with men. Two studies found consistently that age at onset was approximately 2 years later for women.[6,7]

A lower preponderance of PD in women and later age at onset could reflect differences in risk factor exposure, such as lower occupational exposure to environmental chemicals or a lower rate of head trauma. Alternatively, sex hormones or the sex chromosomes themselves could affect the expression of PD-related genes (epigenetics) or disease risk. Although there is an increased risk of PD if a blood relative has the illness, there is no reported evidence of any difference if the relative is female or male.[8] This suggests that sex does not influence hereditary factors. Data supporting a potential protective role of endogenous estrogens come from research indicating that lifetime reduction in estrogen levels (early menopause, fewer pregnancies, hysterectomy/oopherectomy) appears to be a risk factor for the development of PD.[9-12] An analysis of potential environmental risk factors for PD indicated that, among men, the absence of coffee consumption, a history of head trauma, and pesticide exposure were the strongest factors identified; whereas, among women, anemia was the strongest factor.[13] Women may have reduced access to medical care, which could influence assessed age at onset. Two studies found higher baseline levels of dopaminergic activity in women compared with men, which might explain the later age at onset.[7,14]

The clinical manifestations of PD reportedly differ somewhat based on sex. At onset, compared with men, women are more likely to have a tremor-dominant phenotype of PD, which has been associated with a slower rate of decline.[7] At equivalent points in the time course of the illness, it has been observed that women have less severe symptoms, as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), suggesting that, in general, women do have a more slowly progressing course of PD.[15] However, women generally report greater disability and worse quality of life when surveyed.[16] Women tend to have more drug-induced dyskinesias than men.[17-19]

There are sex differences in cognitive and behavioral aspects of PD. Women tend to perform better on cognitive testing.[17] When treated with a dopamine agonist, women reportedly have fewer impulse control problems than men.[20] Rapid eye movement sleep behavior disorder, which is commonly associated with PD, appears to occur with equal frequency between sexes but is often expressed differently. Men reportedly experience more violent dreams, causing them to kick out or fight, whereas women have less aggressive behavior but more disturbed sleep.[21] In patients with PD residing in nursing homes, it was observed that women more often had wandering behavior and reported more depressive symptoms,[22] and they developed depression more frequently as a side effect of treatment. It also should be noted that women with PD are more likely to have certain medical comorbidities, such as osteoporosis and bone fractures, which may influence the course of their illness.[23]

Some studies have identified sex differences related to the treatment of PD. A difference has been observed in the metabolism of levodopa (L-dopa), with a greater bioavailability in women.[16] One review indicated that women are less likely than men to undergo surgical treatments for PD,[24] and another study found that the use of surgery was delayed in female patients.[25] Some studies have reported that women with PD have better outcomes than men after stereotactic surgical procedures.[25,26] Investigators in the Stalevo Reduction in Dyskinesia Evaluation PD (STRIDE) study analyzed their data and observed that female sex was a risk factor for the development of both L-dopa-induced dyskinesias and wearing-off motor fluctuations.[27]

The influence of female life events on PD has received some attention in the literature. One study examined how hormone fluctuations in women affected their symptoms of PD.[28] Although no substantial changes were observed during menstruation or menopause, a significant increase in PD symptoms was identified while women were taking oral contraceptives.[28] In another study that involved 19 women with PD, 17 reported regular, natural menstruation, and 15 noted a significant worsening of menses-associated pain and fatigue after disease onset.[29] Two of those patients required hysterectomy. Most of the women also noted a worsening of their PD symptoms during menstruation as well as an attenuated effect of their antiparkinsonian medications with increased *off* time. The investigators believed that this clinical worsening was caused in part by the low estrogen levels during menstruation, because low estrogen levels have been associated with worsening of PD symptoms. This suggests that estrogen supplementation may help with symptomatic treatment of PD (see below).

Although pregnancy (when estrogen levels are high) appears to be an uncommon event in women with PD, it has been associated with either no change or a worsening of the illness.[30] One case study described a woman aged 33 years with PD who experienced a substantial worsening of her symptoms during pregnancy; and, 15 months after delivery, she still had not experienced any improvement.[31] Eight of 14 women with PD who became pregnant experienced a worsening of their symptoms, and some did not return to baseline after delivery.[32] In a report of 35 pregnancies

among 26 women with PD, 16 (46%) experienced a worsening or the appearance of new symptoms during or soon after delivery.[33] The use of L-dopa generally appears to be safe during pregnancy.[34] In contrast, studies in rats suggest that amantadine and selegiline can have teratogenic effects.[33]

Animal models that use selective neurotoxic insults to simulate PD have demonstrated that estrogen influences the synthesis, release, and breakdown of dopamine by increasing dopamine uptake sites and receptor expression and by increasing the electrical excitability of dopaminergic neurons.[35] Recent research has indicated that estrogen plays a role in gene expression by acting as a transcription factor in neuronal cell nuclei. In addition, it has been demonstrated that estrogen has neuroprotective effects in animal models of PD. One study reported a loss of greater than 30% of substantia nigra dopaminergic neurons in estrogen-deprived, nonhuman primates and a restoration of dopaminergic function in rats chronically treated with estrogen.[16] Another study demonstrated that, in rats, toxin-induced nigral dopaminergic cell death was reduced significantly by estrogen replacement.[36]

There have been some studies examining the effects of estrogen therapy on PD.[37,38] One study indicated that estrogen therapy reduced symptoms in women with early, untreated PD.[39] A study of 138 postmenopausal women with PD found that those who had received estrogen hormone-replacement therapy before diagnosis had an average age at onset that was 5.6 years later than those who had not received such therapy ($P = 0.0004$).[39] Another study involving postmenopausal women also reported a lower risk of PD among women on estrogen-replacement therapy,[40] whereas a third study reported either no difference (for those with natural menopause) or a higher risk of PD (for those with surgically induced menopause).[12] The randomized, double-blind POETRY trial assessed the effects of estrogen-replacement therapy on 23 postmenopausal women with PD and found that it was safe and well tolerated, with evidence of an improvement in motor symptoms.[41] Another clinical trial indicated that low-dose estrogen therapy improved motor fluctuations in treated women.[42] One large-scale observational study involving nursing home residents found that women with PD who were receiving estrogen-replacement treatment were less likely to have dementia compared with women who were not receiving this therapy.[22]

Tourette's Syndrome

Gilles de la Tourette syndrome (TS) has a well-established male predominance, and most studies have reported a prevalence ratio between 2:1 and 5:1,[43] although one reported a ratio closer to 10:1.[43] Consequently, most studies on TS have substantially higher enrollment rates for males than for females.[43]

It is now generally recognized that TS is a neuropsychiatric spectrum disorder in which most patients exhibit some features of obsessive-compulsive disorder and attention deficit hyperactivity disorder.[43-45] When considering the spectrum, evidence indicates that there is sex-specific clinical expression, with males exhibiting tics and attention deficit disorder more often and with females more likely to exhibit obsessive compulsive disorder. [46,47] It has been suggested that, when considering the full clinical spectrum, the condition is almost equally as common among males and females.[43] One study compared adult men versus adult women with TS and reported that the women were more likely to experience depression and anxiety.[48]

Family studies have indicated that maternally transmitted TS is associated with earlier age at onset, greater motor tic complexity, and more frequent compulsive rituals, whereas paternal transmission is linked to greater vocal tic severity, earlier onset of vocal tics, and more severe attention deficit hyperactivity disorder symptoms.[49,50]

Regarding therapy for TS, females reportedly have a better response to the antipsychotic drug haloperidol, whereas males often need more medication adjustments.[46] Because tics tend to be more prevalent in boys than in girls, it has been suggested that higher estrogen levels in females may protect against the development of tics and that estrogen therapy may be useful in the treatment of TS.[46] This possibility is supported by the observation that females typically describe an increase in tics at the time of menarche (when estrogen levels are the lowest). However, no studies regarding the influence of estrogen therapy on tics have been published. It has also been suggested that higher androgen levels in males may influence brain development and contribute to the greater prevalence of the condition in this sex[51] and that the use of anti-androgen therapy may be rational.[52] An open-label study involving two adult patients with TS[53] and a controlled clinical trial involving 13 adult patients with TS tested the anti-androgen drug flutamide and reported a modest reduction in motor tics, but not in vocal tics.[54]

Complications during the mother's pregnancy have been linked to a higher occurrence of TS in her offspring. One study from Sweden demonstrated that mothers of children with TS were two times as likely to have had complications during their pregnancies as control mothers. Furthermore, mothers of children with TS were significantly younger when giving birth than months in the control group.[55] Another study reported that mothers of children with TS were 1.5 times more likely to have had complications with pregnancy and birth.[49] Maternal prenatal smoking, extreme nausea and vomiting during the first trimester, and high stress all have been implicated as risk factors for the occurrence of TS.[49,56] Prenatal maternal use of tobacco and nicotine has been associated

with an eightfold increase in the risk of comorbid obsessive compulsive disorder in children with TS.[57] Greater than 50% of 180 mothers of children with TS noted at least one adverse perinatal event. Approximately 25% of girls with TS, but only 11% of boys with TS, were products of unplanned, emergency cesarean sections. Forceps delivery and maternal use of coffee, alcohol, and tobacco also were associated with an increased risk of obsessive compulsive disorder in patients with TS; whereas increased paternal age, low Apgar scores, and low birth weight were associated with greater tic severity.[57]

Hormonal events in females with TS reportedly have an impact on symptoms. In one survey, 26% of women with TS reported an increase in tics before menstruation.[46] Other hormonal changes, such as premenstrual syndrome, oral contraception use, pregnancy, and menopause, appeared to cause no change in the frequency or severity of tics, obsessive compulsive disorder, or attention deficit hyperactivity.[46] One case report emphasized that TS during pregnancy can present technical difficulties in the performance of regional anesthesia and cesarean section.[58]

Chorea

Sydenham's or rheumatic chorea is a disorder that occurs mainly in childhood and is considered an autoimmune neurological manifestation of acute rheumatic fever. It occurs twice as often in girls as in boys.[15] Sydenham's chorea is very rare in adults[59] and, when it does appear in adults, it usually has its onset during pregnancy and is referred to as chorea gravidarum (CG).[60] CG can be the initial manifestation of Sydenham's chorea or it can represent a recurrence of childhood Sydenham's chorea. In a study that monitored the subsequent course of women who had previously suffered Sydenham's chorea, 20 of 66 women became pregnant, and 15 women (75%) developed CG.[61] It is not believed that infectious or autoimmune processes are involved in CG but, rather, that it arises as a result of activation of subclinical damage to the basal ganglia from prior rheumatic fever, likely because of the hormonal changes associated with pregnancy.[59,61] Most of the time, chorea arises after the first trimester of pregnancy. In a study of 15 patients with CG, generalized chorea was identified in 67%, focal or multifocal chorea was identified in 20%, and 13.4% had hemichorea.[61] Many of these patients experienced complications, including spontaneous abortion in 2 patients. The severity of chorea tends to decrease as the pregnancy progresses. Another study demonstrated that approximately one-third of patients with CG go into remission after delivery; however, in others, chorea may last for several months afterward. Severe CG has been associated with hyperthermia, rhabdomyolysis, myoglobinuria, and even death.[30]

Drug treatment for CG is recommended only for those situations in which the health of the mother or fetus is threatened. The use of dopamine receptor blockers—the most common drugs for suppressing chorea—typically are not advised during pregnancy and are labeled a category C risk, meaning that animal studies have demonstrated a small, undefined risk to the fetus. However, no studies have been done in humans. If treatment is indeed necessary, then high-potency neuroleptics (butyrophenones) have been recommended.[62] There appears to be little published experience with the newer, atypical antipsychotics.

Oral contraceptives can cause chorea in women, even those with no history of Sydenham's chorea or CG.[39,59,62] Two patients with CG had chorea that persisted while they were taking oral contraceptives after pregnancy.[59]

In Huntington's disease (HD), the sex of the parent transmitting the mutation has a major influence on the clinical manifestations of affected offspring. Juvenile-onset HD, which typically manifests as a parkinsonian condition rather than the usual choreic disorder, is usually linked to paternal inheritance, and maternal transmission is generally associated with later age at onset. The majority of late-onset (age >50 years) HD cases are inherited from the mother.[63] Paternal age at the time of conception is inversely related to age at onset, whereas no such correlation has been demonstrated for maternal age.[63] This may be because, as males age and the male germ cells continue to undergo divisions, the amount of male germ cell DNA that is methylated decreases, causing the expression of sequences that were previously silenced and resulting in the transmission of a greater number of abnormal trinucleotide repeats.[63]

Prenatal testing for the HD genetic mutation has been available since 1986. The locus on chromosome 4 was identified in 1983, and the HD gene was identified in 1993. Women at risk for HD who are contemplating pregnancy can be gene tested to determine whether they might pass the illness on to a child. At-risk women can also undergo in utero genetic testing of their fetus through amniocentesis. A study involving 868 at-risk couples found that only 5% requested testing of the at-risk parent, and 9% underwent in utero testing.[30] Even when the results were positive, most couples continued the pregnancy. Preimplantation genetic testing is a technique in which embryos are formed in vitro and tested for the HD gene in the eight-cell stage. Embryos without the HD gene can then be selected for implantation. The increased failure rate of pregnancy with in vitro fertilization, however, may act as a deterrent to preimplantation testing for some people.[30]

Dystonia

Focal craniocervical dystonias are more common in women than in men. The overall female-to-male ratio

has varied from 16:1 to 33:1, depending on the population studied.[64] Twice as many men have writer's cramp, whereas typist's cramp occurs more often in women, a finding that may be attributable to differences in activities engaged in by men and women.[64] The National Hospital and King's College observed a female-to-male ratio of 261:163 for cervical dystonia (torticollis), 68:34 for blepharospasm, 23:7 for oromandibular dystonia, 26:10 for spasmodic dysphonia, and 63:124 for writer's cramp.[64]

In reviewing the influence of female hormones on dystonia, one article concluded that there was no correlation between pregnancy, menopause, or postmenopausal hormone-replacement therapy and the worsening of dystonic symptoms.[65] However, other publications have reported effects. One woman with generalized dystonia reportedly had low circulating estrogen levels and exacerbations of dystonia that responded to estrogen-replacement therapy.[66] Another study described the course of 10 pregnant women with dystonia, including one woman with generalized dystonia and nine women with focal or segmental dystonia. During pregnancy, 3 of those patients experienced a partial or complete remission of their dystonia, 2 had an exacerbation, and the remaining 5 had no notable change.[67] There is one reported case of cervical dystonia that emerged during pregnancy and resolved without treatment after the second trimester.[67] The term *dystonia gravidarum* was used to describe this phenomenon. Complications associated with using L-dopa to treat dystonia during pregnancy have been described, including spontaneous abortion, teratogenicity, and intrauterine growth retardation.[30]

Deep-brain stimulation (DBS) targeting the globus pallidus internus has been used to treat patients with dystonia, particularly the generalized form. Sex does not appear to be a prognostic factor in the response of generalized dystonia to DBS.[66] A case series has been published describing women with dystonia who became pregnant during treatment with DBS.[66] Overall, pregnancy was well tolerated. In one woman, the stimulator located in the chest caused discomfort during breastfeeding. Fetal ultrasound does not appear to have any adverse effects on the function of DBS equipment.[66] It is recommended that women who are receiving DBS should give birth in a hospital rather than at home. If a cesarean section is required, then the use of electrocautery should be used in the bipolar mode and should be performed with caution. There is no evidence that general, regional, or epidural anesthesia adversely affects pregnancy or delivery in the presence of a DBS system.

Restless Legs Syndrome

Restless leg syndrome (RLS) is more prevalent among women.[68] Furthermore, RLS often presents for the first time during pregnancy, usually during the second or third trimester, and it often resolves after delivery.[69] RLS has been associated with neuropathy, malignancy, uremia, and, most importantly, anemia, which might explain its greater prevalence among women and its appearance during pregnancy. Close links between RLS and iron deficiency (with or without anemia) or changes in iron metabolism have been recognized.[70] Some patients improve after blood transfusion or iron supplementation.[30]

The use of estrogens has also been associated with a significantly higher incidence of RLS.[71] This suggests that high estrogen levels may be another factor in the increased prevalence of RLS among women and the appearance of RLS during pregnancy. Menopause does not appear to lower the incidence of RLS, however, suggesting that the role of hormones, and specifically estrogen, in RLS is complex.[71] When used during pregnancy to treat RLS, the dopamine agonists pergolide and ropinirole reportedly caused intrauterine growth retardation, finger (digit) malformations, and fetal deaths, whereas L-dopa has been used safely.[30]

Wilson's Disease

In Wilson's disease, women generally develop the neuropsychiatric form of disease almost 2 years later than men. This may be because of the protective effect of estrogens and sex differences in iron metabolism.[72]

One study described the course of pregnancies in 16 women with Wilson's disease. Although there was no apparent worsening of clinical features, 24 spontaneous abortions and 3 stillbirths were observed.[30] One case report described a woman who had untreated Wilson's disease during her pregnancy. In that patient, copper accumulation was found on the maternal side of the placenta along with elevated copper levels in the umbilical serum and amniotic fluid that were two to seven times higher than normal. Her infant was followed for one year after birth; and, although normal general development was observed, liver enzymes were elevated.[62] There have been reports of 2 women with Wilson's disease who had successful pregnancies and deliveries of healthy children while they were receiving standard chelation therapy during their pregnancies.[30]

Conclusions

It is clear that sex differences are common throughout the spectrum of neurological movement disorders. The incidence and prevalence of several movement disorders differ substantially between men and women. Sex also appears to have important correlation with both environmental and genetic etiological factors. Women often have different clinical presentations and manifestations, different courses, and may respond differently to treatment. The symptoms of several

movement disorders are clearly influenced by female life events centered around changes in sex hormone levels.

In this review, we covered a wide breadth of movement disorders. It is our hope that this review will serve as a stimulus for further research aimed at exploring how sex influences movement disorders. Knowledge of these sex-specific influences can help improve the quality and individualization of care provided to women as well as men with movement disorders. Research into the underlying neurobiological basis of sex differences is likely to provide important insights into the causes of and best therapies for movement disorders in general. ■

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