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Comparison of Parkinson's Disease Features in Males and Females

Review Article

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Abstract

Differences of sex hormones in men and women cause differences in physiologic and pathologic process in two sexes, which makes the field of Women's Health. Parkinson's disease is one of the most common chronic, progressive and disabling disorders and this can reveal the importance of this disease in women. We did a literature review about the features of Parkinson's disease (PD) in men and women and found noticeable differences in prevalence, clinical presentations, and the course of disease and treatment. In addition, we identified female life events, such as menstruation, menopause, pregnancy and also medications (like oral contraceptives and hormone-replacement therapy), impacts women with PD. On the other hand, approximately 3-5% of women diagnosed with this disorder are under the age of 50 and a large number of these women are still experiencing regular menstrual cycles. So, being aware to these biological sex-specific differences can help improve the quality and individualization of care for women with PD and may provide insights into neurobiological mechanisms.

Keywords: Parkinson's Disease; Women; Hormone.

Introduction

It has been confirmed that there are numerous physiological and anatomical differences in organ systems of human body, depending on sex. Developing information about differences in various medical conditions between men and women have led to developing of the Women's health field. Many researches at this field have recognized that there are significant interactions between disease state and women's life changes and events like menstruation, pregnancy and menopause. Although these differences have been proven in many disorders in the field of Neurology, like Migraine and Epilepsy [2], there are few studies and reviews about movement disorders in women health. Among neurodegenerative disorders, Parkinson' disease is the most common disorder with motor presentations and the second one in the world after Alzheimer' disease [1]. Some studies have revealed significant differences in men and women with Parkinson' disease in various aspects of this illness like illness onset, prevalence, primary and late presentations, course, response to the medications, complications due to illness and treatments. High prevalence of PD and verity of its features in women show the importance of the studies on PD in women's health field. In this article, we tried to collect data from studies about Parkinson's disease in women by conducting a Medline literature search with focusing on Parkinson's disease, women health, estrogen, menstruation, pregnancy and menopause. In this article we will classify and discuss our findings in four sections: epidemiologic studies, clinical aspects of PD, management and treatment, and biochemical studies.

Epidemiologic Differences

Epidemiologic aspects of PD in male and female are usually the most recognized differences of PD between them. Many epidemiologic studies have demonstrated a decreased rate of Parkinson's disease in women, compared to men [4].

Baldereschi and Taylor during two large epidemiologic meta-analyses studies on age-adjusted male to female groups estimated that the incidence ratio of PD in male to female is almost 1.5 [5, 8]. Two longitudinal population studies in USA and Italy reported that the prevalence of Parkinson's disease is almost two-fold higher in men than women [3, 5].

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It seems that Parkinson's disease in women presents in older age than men. Alves et al., and Haaxma et al., showed the age of onset were approximately two years later in females [6, 9].

Lower incidence and older age of onset in women, can be due to female sex hormones, genetic factors and lower environmental risk factors in women such as head traumas and exposure to the occupational chemical materials like pesticides in rural areas. Existence of positive family history-especially early onset PD-is a very important factor, which can neutralize the differences of disease occurrence in men and women.

Estrogen has protective effect against Parkinson's disease and any reductions in estrogen level throughout the life such as; early menopause, fewer pregnancies, hysterectomy and oophorectomy are risk factors for developing of PD [7-12].

Savica et al., in an interesting study demonstrated that among environmental risk factors for PD, anemia is the strongest one in women, while pesticide exposure, head trauma and less caffeine intake are the major environmental risk factors in men [13].

Haaxma et al., and Lavalaye et al., in their biochemical studies found that general level of Dopaminergic activity in women significantly is higher than men. This difference might be the reason of later onset of Parkinson's disease in women comparing to men [9, 14].

Clinical Presentation

As regard of clinical presentation, various studies have shown some differences between men and women. Haaxma reported that Parkinson's disease in women mostly presents as tremor dominant type and shows a slower progression rate as well [9].

Kaplan in 2006 reported the same findings and showed that Parkinson's disease has less severe manifestations and slower progression rate in women compared to men at the equal time course of the disease. During this study, PD in both group of men and women had been assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) [17].

Miller et al., and Lyons et al., with two large studies reported that drug induced dyskinesia is more common in men than women [15-19].

Regarding cognitive and behavioral aspects of PD, there are difference between men and women. Investigations showed that women with PD have better condition in cognitive tests compared to men [15]. Also Joutsa et al., found that Dopa agonists cause less Impulse Control behaviors and Dopamine dysregulation syndrome in women than men [22].

One of the common non-motor symptoms of PD is rapid eye movement sleep behavior disorder (RBD). Bjornara et al., reported that frequency of RBD in men and women with PD are the same, but the presentation is different. While violent dreams with kicking out and fighting features are common in men, women show more sleep disturbances with less aggressive behaviors [21].

Among the non-motor and psychiatric symptoms of PD, women present depression and anxiety more than men [20]. On the other hand, Depression as a medication side effect appears more frequently in women than men. It should be kept in mind that women with PD are more likely to show certain medical complications like osteoporosis and bone fracture. It is clear that these types of complications could worsen the course of disease and its prognosis [23].

Management and Treatment

Regarding the management, researchers have found differences between men and women in terms of Parkinson's disease response to treatments. Shulman et al., reported that there is a greater bioavailability of L-dopa in women, which causes different metabolism and efficacy of L-Dopa in women compared to men [16].

Hariz et al., studied a large group of patients with PD, who underwent surgical treatment. They found out that women are selected for surgery less than men and in the later course of their disease [25, 26]. Generally the stereotactic surgical procedures for PD in women have had better outcomes comparing to men [24, 25].

Saunders-Pullman et al., revealed that estrogen therapy could reduce symptoms of PD in women with early, untreated PD [36]. They studied on 138 postmenopausal women with PD and found that the patients who had received estrogen replacement therapy before beginning of PD had an average age of onset that was 5.6 years later than those, who had not received such therapy [36]. Similarly, Currie et al., studied postmenopausal women and revealed a lower risk of PD among women, who are taking estrogen-replacement therapy [40]. Rocca et al., in another study reported either there is no difference in risk of PD occurrence (for those with natural menopause) or a higher risk of PD (for those with surgically induced menopause) [12]. The POETRY trial was one of the major studies about hormone replacement therapy in PD. This randomized, double blind trial studied the effects of estrogen-replacement therapy on 23 postmenopausal women with PD and revealed that it is safe and well tolerated, with evidence of an improvement in motor symptoms [35]. Tsang et al in another clinical trial showed that low- dose estrogen therapy improves motor fluctuations in treated women with PD [42]. One large-scale observational study involving nursing home residents elderly patients revealed that the rate of dementia in women with PD, who were receiving estrogen-replacement treatment was lower than women who were not receiving this therapy [20].

Biochemical Factors

All of these differences of PD in women and men show the effects of female biochemistry and physiology. So, many researchers have evaluated the influence of female body events on PD. Kompoliti studied how female hormones fluctuations can affect their symptoms of PD [27]. According to Kompoliti's study, although no substantial changes are found during menstruation or menopause, an obvious increase in PD symptoms is identified in women, who are taking oral contraceptives [27].

Tolson et al., during their study on 19 women with PD, reported a significant worsening of menses-associated pain and fatigue

in 15 women after onset of PD [28]. Two of these patients underwent hysterectomy. Majority of the women also showed an obvious worsening of PD symptoms during menstruation as well as a decreased effect of their antiparkinsonian medications with prolonged off time. The investigators believe that lower estrogen level has been associated with worsening of PD symptoms. Lower estrogen level during menstruation might be responsible for this clinical worsening. These findings strongly suggest that estrogen supplement can help to improve of PD symptoms [28]. Pregnancy during PD is a rare phenomenon. Although studies have reported that there is an increased rate of both motor and non-motor symptoms during pregnancy in spite of the higher level of estrogens, however; it is rarely significant enough to impact the women's overall level of functioning [30]. Shulman in a case study reported a 33-year old woman with PD who experienced a significant worsening of PD symptoms during her pregnancy. She did not experience any improvement in her postpartum follow up visits until 15 months [33]. Golbe reported a group with 14 women with PD. Eight of them got pregnant and showed a worsening of PD. Some symptoms never returned to the baseline after delivery [32]. Non-motor symptoms (such as fatigue, constipation and depression) seem to improve after delivery but the progression of motor symptoms (rigidity, slowness of movement and tremor) usually persists [32]. Hagel reported 35 pregnancies among 26 women with PD. 16 persons (46%) had experienced a worsening or the appearance of new symptoms during or soon after delivery [31]. While data has shown that increasing length of estrogen exposure (the time from puberty to menopause) decreases risk of developing Parkinson's disease, pregnancy seems to increase the risk of developing Parkinson's disease. This seems contradictory but it might be due to the differences between the types of estrogen. Estriol is the main form of estrogen during pregnancy while Estradiol is the main form of estrogen in normal menstrual cycle.

The other concern of pregnant women with Parkinson's disease is the risk of birth defects, which can be caused by antiparkinson medications. The dopamine agonists, bromocriptine and pergolide, are considered relatively safe during pregnancy, though they block milk production and breast-feeding [35]. The remainder of antiparkinson's medications carries a category C, meaning that animal studies suggest some increased risks but human studies are not available or have not confirmed that risk. Basically the use of L-dopa during pregnancy is safe [34]. Studies on Levodopa with or without carbidopa (Sinemet) suggest increased risk in animal studies but there are no reported birth defects in newborns in the small number of investigated pregnancies [35]. In contrast, studies in rats have shown teratogenic effects of amantadine and Selegiline [31].

Amantadine is the only antiparkinson's medication that has resulted in heart malformations in babies with first trimester exposure. There is no data available about the COMT inhibitors so far [35].

Noticeable effects of estrogen and female hormonal cycle on PD has pushed the scientists to evaluate the therapeutic effects of estrogen on PD. Using selective neurotoxins in animal models to simulate PD has demonstrated that estrogen influences the synthesis, release, and breakdown of dopamine by increasing dopamine uptake sites, receptor expression, and increasing the electrical excitability of dopaminergic neurons [41]. Some of recent studies have revealed. that estrogen plays a role in gene expression by acting as a transcription factor in neuronal cell nuclei. On the other hand, multiple studies demonstrated that estrogen has neuroprotective effects in animal models of PD. One of these studies revealed a loss of greater than 30% of dopaminergic neurons of substantia nigra in estrogen-deprived, nonhuman primates and a restoration of dopaminergic function in rats chronically treated with estrogen [16]. Another study showed that toxin-induced nigral dopaminergic cell death in rats, was reduced significantly by estrogen replacement [39].

Conclusion

All of these findings show the differences of Parkinson's disease presentation in men and women and the role of female sex hormones especially estrogen, in all aspects of PD. Considering these facts may help to better management of Parkinson' disease in women in various stages with different complications. Young women with PD should receive enough information about the teratogenic effects of medications as well as clinical course, complications, and prognosis of PD in case of pregnancy. We recommend more studies regarding Parkinson's disease in women and to better understanding of female sex hormones impact on PD.

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