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Sex Differences in the Therapy of Advanced Movement Disorders

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Abstract - The influence of sex differences in movement disorders is still under-recognized. There are significant sex differences in the pathophysiology, epidemiology, clinical manifestations, and treatments outcome of many of movement disorders especially Parkinson's disease. Importance of sex specific differences in invasive treatment outcomes emphasize the importance of their considering when devising patient's individual management strategies. Increased recognition and future prospective studies specifically addressing sex differences in invasive treatments' outcomes may help and provide a tailored therapeutic and precision medicine approach to movement disorders. We highlight the most relevant invasive treatment's effects in advanced movement disorders that differ between men and women. But also, the differences in selection of invasive methods. Increased recognition of sex differences and their impact on treatment of advanced phase of movement disorders, that are very disabling, is very important for future studies and precise and personalized medicine. In this article, we provide a review of sex- related differences in treatment of advanced movement disorders, mostly Parkinson's diseases.

Key words: therapeutics; sex characteristics; movement disorders

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Introduction

Movement disorders are a heterogeneous group of a of nervous system conditions that cause either increased movements or reduced or slow movements [1]. The main pathophysiology of movement disorders is network dysfunction of corticothalamic-basal ganglia and cerebellar network dysfunction. These movements are voluntary or involuntary [2]. The influence of sex differences in movement disorders is still under- recognized. There are some evidence that structural differences in the dopaminergic pathways between men and women underline the magnitude and severity of motor and non-motor symptoms associated with these disorders. Also, the sex differences in epidemiology and pathophysiology were noticed [3]. Although the reason is not known, it is thought to be caused by sex hormones especially oestrogens with their neuroplastic role on the dopaminergic system and releasing and the postsynaptic effect of neurotransmitters, including dopamine [4]. We highlight the most relevant treatment effects in advanced movement disorders that differ between men and women. But also, the sex differences in selection of invasive methods. Increased recognition of sex differences and their impact on treatment of advanced phase of movement disorders that are very disabling is very important for future studies and precise and

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personalized medicine [5]. Sex differences are the most studied and described in Parkinson's disease (PD), so the largest part of this manuscript will be devoted to it. In this article, we provide a review of sex- related differences in treatment of advanced movement disorders, mostly Parkinson's diseases.

Parkinson's disease

PD is the second most common neurodegenerative disease and is characterized by α-synuclein pathology and loss of dopaminergic neurons in the substantia nigra pars compacta [6]. The cardinal motor symptoms (MS) of PD are bradykinesia, rigidity, resting tremor, and postural and gait impairment. Non-motor symptoms (NMS) that can be present more than 10 years before motor symptoms are: depression, anxiety, pain, orthostatic hypotension, and urinary, gastrointestinal and sleep dysfunction [6]. Treatment is still symptomatic. The disease has no cure and brings a progression of symptoms and the development of new symptoms over time. There are several groups of antiparkinsonian drugs and plenty of options for the treatment of non-motor symptoms. For good treatment of PD, a multidisciplinary team is crucial. Over time, symptoms develop that are less responsive to medication, such as freezing of gait, falls, etc. [6-8]. The main sex difference considering PD are that 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 [9,10]. Very well-known different genetic, hormonal, neuroendocrine and molecular factors are important for sex differences in PD (in phenotypic variations, onset, progression, and management) [11]. Like in all other diseases, data available for therapeutic management of PD in females is limited although there are some evidence that women suffer more from the side effects of antiparkinsonian drugs [12]. There is an unmet need for novel therapeutic strategies that will involve sex differences and specific treatment of PD.

Advanced Parkinson's disease

Management of this stage of PD is a challenge. To have a good management of the disease in that stage we must treat appropriately MS and NMS. The definition of advanced Parkinson disease (APD) is still unclear. There are different definitions based on some consensus and expert opinions for the stage when conventional treatment does not provide an adequate level of symptoms control. Some are based on disease duration, some on time spent in OFF phase and ON phase with dyskinesia (used for invasive methods), some on Hoehn and Yahr stages and some on clinical phenotype: presence of severe motor fluctuations, dyskinesias, falls, axial motor symptoms resistant to levodopa, and cognitive decline [13,14]. Patients usually don't like this term APD so there is a group of clinicians suggesting the term "complex phase" instead of ADP [15]. Motor symptoms in advanced PD are dyskinesias, motor fluctuations, and symptoms that respond poorly or not at all to dopaminergic treatment like gait problems, postural disorders, lack of stability, dysphagia, dysarthria, falls and freezing of gait (FOG). Non-motor symptoms are usually severe in advanced stage and influenced the most quality of life patients and their caregivers. They are usually the most responsible cause of premature institutionalization and hospitalization in this stage [16]. Symptoms like sleep problems (mostly REM sleep behaviour disorder (RBD), cognitive and autonomic impairments, neuropsychiatric changes (visual hallucinations, impulse control disorders (ICD) like gambling, pathological shopping, hypersexuality, behavioural changes: performing complex stereotyped tasks, psychotic symptoms) are often present in this stage. Other psychiatric problems are often depression, anxiety, and apathy. Pain could be very hard symptom especially in OFF periods and we can differentiate musculoskeletal pain, dystonic pain, neuropathic pain, and central pain syndrome. Autonomic symptoms like orthostatic hypotension may increase risk for falls. RBD, age, disease's duration, visual hallucination are the most powerful predictors

of dementia [17,18]. Terminal symptoms of APD cause hard disability requiring help for the activities of daily living due to limitations to perform basic activities, severe dysphagia, recurrent falls, and dementia. This is a main cause of caregivers' burden [19].

Invasive treatments

In APD we can see a poor level of motor control with alternating periods of good and deficient control over symptoms (motor fluctuations with delayed onset of response, end-of-dose deterioration, dose failures, and unpredictable responses). Nevertheless, these periods may be accompanied by sever non-motor symptoms. The fact that motor fluctuations are result from the short half-life and irregular plasma fluctuations of oral levodopa is well known. In APD we try in the beginning with adopting dosage of medicine, adding other antiparkinsonian medications and increasing number of taking medicines to improve motor fluctuation and dyskinesias. When strategies of providing more continuous dopaminergic stimulation by adjusting oral and transdermal medications are still not enough to improve quality of life and everyday functioning we must think about invasive treatment. In advance invasive treatment are included three device-aided therapies: deep brain stimulation (DBS), continuous infusion therapy with levodopa-carbidopa intestinal gel, levodopa-carbidopa-entacapone intestinal gel or apomorphine in this stage. Also, physical therapy, speech therapy, occupational therapy, physical activity, and psychological and psychiatric support are very important. Modern treatment of APD is holistic, individual, personalized and symptom orientated [20]. A holistic modern treatment includes appropriate treatment of motor and non-motor symptoms, especially those influencing the quality of life the most. Good effect of different treatment in APD is influenced by a lot of nondrug-related issues like age, personality, preferences for treatment, cultural beliefs, lifestyle, pharmacoeconomics, pharmacogenetics, and comorbidity [20]. So, in holistic plan we must consider all this factors and watch every patient and patient's most problematic symptoms individually. Today, the main aim in treatment of APD is personalized medicine. It can include all pharmacological and non-pharmacological strategies to suit the need and requirements of individual patients. It's called symptom tailored medicine. But there is also personalized and precision medicine that will be helpful to those PD resulted from specific gene mutations. Then the goal of treatment could be attempted to prevent or enzyme replacement [21]. These therapies differ in some element like invasiveness, side-effect profile, and the need for nursing care. For appropriate treatment it is necessary to know and have experience with all three methods and understand the clinical characteristics defining patients who are candidates for certain invasive treatments [22,23]. Knowing differential beneficial effects on specific motor and non-motor symptoms of the currently available invasive methods for advanced PD is necessary for personalized management [24].

Deep Brain stimulation

Deep brain stimulation (DBS) is present in PD for more than 35 years and is STN-DBS is the best-studied intervention for advanced PD. Evidences from previous studies have shown that DBS of either the subthalamic nucleus (STN) or the internal globus pallidus (GPi) have beneficial effect on motor fluctuations and dyskinesia associated with advanced PD-increased ON time without troubling dyskinesia by a mean of 4.6 hours per day, reducing medications more than 50 %, reducing OFF time for 67 %, reducing dyskinesias for 70 % and increasing quality of life for 50 - 70 % [25]. The mechanism is still unknown. It's thought that high frequency modulates neural circuits [26]. DBS makes no major lesion and is adjustable and reversible. It requires intensive adjustments in the postoperative period and coming to centre of excellency to manage parameter stimulation and adjustment of medical treatments. It is rather safe methods and adverse events recorded during first 6 months were generally not serious compering to group on

medications [27]. The adverse events could be due to operative procedure like intracerebral haemorrhage, infections etc., but cognitive and behavioural complications were infrequent and not significantly different between DBS and medical treatment groups [28]. The long-term studies have shown persistent effect after 5 or 10 years [29,30]. Compering studies of STN DBS or GPi DBS effectiveness in APD have shown that in the off-drug phase assessment, STN DBS led to significantly greater improvements compared with GPi DBS in mean change in the UPDRS motor examination score, disability score, and levodopa equivalent drug reduction but in the on-drug phase assessment, GPi DBS was associated with greater reduction in dyskinesia compared with STN DBS. So, STN as target is better for more medication reduction, less-frequent battery changes, and a more favourable economic profile and GPi is better for more-robust dyskinesia suppression, easier programming, and greater flexibility in adjusting medications. But in the end the conclusion is that the decision which target place (STN or GPI) must be individual patient and symptoms tailored [30,31]. Factors that predict benefit of DBS are preoperative levodopa responsiveness, age, duration of OFF time, dyskinesias, and psychiatric symptoms [32].

Male sex was identified as a predictor of STN DBS-induced improvement in camptocormia, but quality of life measures improved more in women than in men especially mobility, stigma, and cognition [33,34]. Other predictors for posture improvement after STN DBS were motor response to and pre-surgical dosage of levodopa, and shorter PD duration [33]. DBS STN is twice more common in men and women are still strongly under-represented for DBS consideration. Also, patients who underwent DBS for medication refractory tremor were predominantly men [34,35]. Sex specific influence has been established in regard to selection and outcome of deep brain stimulation for PD. Study has shown that men with advanced PD are likely to be maintained on lower doses of antiparkinsonian drugs. It is probably to an adjustment for the propensity of women to have more dyskinesia. This may also contribute to more functional impairment and reduced emotional well-being in women compared to men with similar duration and severity of motor symptoms and would therefore benefit from early surgical interventions when dyskinesias becomes dose-limiting [36]. We must have that in mind and suggest then earlier DBS as sort of individualized but sex dependent approach. Changes in personality are very important in PD patients. It is interesting that female patients seem to profit more from STN-DBS in reducing depressive symptoms, so in the future, more focus should lie on sex-related effects on NMS [37]. Males had improvements in total and musculoskeletal scores and chronic pain another NMS symptom. All of them had less low-back disability after DBS [38]. These facts could have important implications on selection for DBS. The investigations have shown a gap in referrals of deep brain stimulation for PD. Women were disproportionally underrepresented, but more likely to be approved for DBS [39]. We need to put more focus toward the implementation of equity as both sexes could benefit from DBS.

Pumps

There are no specific studies with sex differences regarding pumps as invasive methods. In the main studies, we can look if there is a difference between the sexes. In both the phase III program of the GLORIA registry with safety and effectiveness of levodopa-carbidopa intestinal therapy, more men than women required the ≥ 2000 mg/day dosage and discontinuations due to non-procedure or device-associated adverse effects were slightly higher in the ≥ 2000 mg/day group [40,41]. Considering the hardest symptoms that bother patients with PD before and 3 months after Deep brain stimulation and Continuous infusion of levodopa-carbidopa intestinal therapy (LCIG) in our research we found that before DBS and LCIG the most troublesome symptoms and problems of PD patients were similar in both sexes: slowness, gait, tremor, rigidity, falls and unpredictable response to their medication. But, in women after DBS, apathy and worry about lon-

gevity of DBS's good effects were higher than in men and weight gain and coping with pump and maintenance were higher in men than in women. After LCIG in women, weight loss and weakness were higher and burning and pricking in legs in men [42]. Although DBS and LCIG in PD are successful in reducing motor symptoms, our study has shown that we must pay more attention to assess and control non-motor symptoms, sex differences in outcome and psycho-social factors after them because they may impact patients' ability to access and continue successful therapy. More future studies will be useful in decision making on advanced therapy for individual patients.

In our other investigation, we correlated association between NMSs in DBS and levodopa/carbidopa intestinal gel and found in female patients, that quality of life after both invasive methods was highly correlated with depression, and moderately associated with fatigue but no correlation in men [43]. In our practice we had 5 men with Apomorphine pumps and pen who developed symptoms of impulse control disorders and dopamine dysregulation syndrome (unpublished data) and 1 with dyskinesia-hyperpyrexia syndrome after apomorphine pump but no women [44].

Other movement disorders

There is a lack of literature about sex differences in other parkinsonian syndromes and hyperkinetic movement disorders, including essential tremor (ET), dystonia, chorea and tics, especially about invasive methods. We found data about dystonia patients after DBS as a treatment in advanced or medication refractory phases. A craniocervical dystonia is more prevalent in women, whereas most focal task-specific dystonias and tics are more frequent in men. There are no sex differences in response to globus pallidus internus stimulation, and DBS surgery has been found to be safe during pregnancy in case series of women with dystonia [4,45]. A useful suggestion is that when proposing DBS to women with dystonia, a rechargeable battery might be encouraged to avoid surgery scars related to repeated replacement- Also, in women planning a pregnancy, subclavicular rather than abdominal battery placement should be preferred.

Conclusion

There are significant sex differences in the pathophysiology, epidemiology, clinical manifestations, and treatments outcome of many of movement disorders especially PD. Importance of sex differences in invasive treatment outcomes emphasize the importance of their considering when devising patient's individual management strategies. Increased recognition and future prospective studies specifically addressing sex differences in invasive treatments' outcomes may help and provide a tailored therapeutic and precision medicine approach to movement disorders.

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Conflict of interest

None to declare.

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