



AGE AND GENDER DIFFERENCES IN PARKINSON'S DISEASE: A REVIEW

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ABSTRACT

Age and gender are two basic characteristics that may influence the clinical course of Parkinson's disease (PD). The impact of age on the clinical phenotype is considered suggestive of increased severity of PD, especially in older patients. The clinical performance is found worse on both motor indices and non-motor symptoms. Some studies demonstrate very clear sex-related differences in the epidemiological and clinical features of the disease. Parkinson's disease affects men twice more often than women, but women have a higher mortality rate and faster progression of the disease. Controversial data, concerning the impact of age on non-motor symptoms (NMS) of PD exist. Some studies have found an association between the increasing age and the total load of NMS. Several studies have reported a higher incidence of PD in men and also gender differences in relation to motor symptoms. However, a scant information concerning the gender differences of NMS in PD is available. It has been reported that nonmotor symptoms affect the quality of life (QoL) of PD patients to a greater extent as compared to the motor ones and that they more often lead to institutionalization, thus imposing a considerable economic burden on PD patients' families and the society as a whole.

Keywords: PD, NMSPD, QoL, age, gender, comorbidity and survival,

INTRODUCTION

Since the official and systematic inclusion of sex and gender in biomedical research, gender differences have been indicated as important determinants of both the susceptibility to develop neurodegenerative disease in the general population and the clinical and therapeutic management of patients with neurodegenerative diseases. Several data demonstrate that PD in women starts with a more benign phenotype, likely due to the effect of estrogens. However, as the disease progresses, women are at higher risk of developing severely disabling treatment related complications, such as motor and non-motor fluctuations [1]. Age in PD is a strong factor contributing to the disease severity, rather than the disease duration. Age and gender are two basic characteristics that may influence the disease phenotype, either through disease independent factors, or by the differences in underlying pathology [2].

1. Age and sex differences in PD.

1.1. Age influence in PD. In 2009 Levy G. proposed a model on the relationship between aging and PD [3]. According to this model aging may play an essential role in the pathogenesis of PD by an interaction of the disease process and by aging related degeneration of nondopaminergic structures [3]. Data on the increasing incidence of PD with age has been established in worldwide meta-analyses: from 41 /100 000 at 40-49 years to 1903/100 000 at the age of 80 [4]. In about 3-5% of the cases, symptoms of PD may start earlier, before 40 years, defined as "early-onset of PD" [4, 5]. The early onset of PD is subdivided in "juvenile parkinsonism" (arising before 21 years) and "young-onset PD (YOPD)" arising between 21-40 years [5], or before 50 years according to other authors [6]. Systematic studies on the incidence of PD reveal the increasing number of cases with aging with a peak of the 7th decade, while other studies have reported a continuous increase after the age of 80 years [4]. The clinical presentation of PD in patients with advanced age may lead to faster progression of the disease [6]. Worsening of the disease severity has been found in studies of late versus early onset of PD [3, 7]. It has been published also that age may contribute to more severe presentation of motor and non-motor symptoms of the disease that do not correspond with the medication dose, responsiveness to treatment or disease duration [2].

1.2. Sex influence in PD. Over the recent years, considerable attention has been paid to sex differences in the incidence, causes, symptoms, treatment response and outcome of neurological diseases, particularly of PD [8]. Several studies focus on the age and/or sex influence in PD [1-3, 8,-10]. Significant differences in the incidence of PD by sex has been found in patients of the age group 50-90 with a prevalence in men compared to women. Non-significant male predominance of PD has been found in the other age groups [4].

Some studies demonstrate clear sex related differences in the clinical and epidemiological presentation of PD. According to Georgiev D et al (2017) men are twice more often affected by PD, but women have a faster progression of the disease and higher mortality rate [11]. On the other hand, women, compared with men, have

shown differences in the pharmacological responsiveness, deep brain stimulation and the quality of life [10, 11]. Some data reveal a more benign start of PD in women probably due to the effect of estrogens, but with progression of the disease, women are at higher risk of developing motor and non-motor fluctuations and treatment related complications, compared to men. Women also have worse chance to receive better and more effective results after treatment with deep brain stimulation [11].

2. Age and sex differences in non-motor symptoms in PD (NMSPD).

2.1. Age influence on NMSPD. Controversial data concerning the influence of age on NMSPD exist [12-16]. Some studies have found an association between the increasing age and the total load of NMS. Data on age influence of NMS in PD are controversial, too. [12,13] Schrang A et al. (2003) reveals a more common moderate depression in 40% of the patients with young onset of PD (YOPD) compared to those with late onset (LOPD) [12]. In contrast, Spica V et al (2013) have found a higher dominance of NMS in LOPD [13]. Ruwei O et al (2014) have reported that in the four age group of PD patients (<50 to 70> years old) age has no essential influence; the severity of NMS progresses with the course of the disease [14]. The frequency of NMS increases along with the disease duration. With the course of the disease almost all PD patients display at least one or even more NMS [15, 16].

2.2. Sex influence on NMSPD. Anatomical and physiological differences of brain structure and function not only influence the clinical presentation of neurological disorders, including PD, but also age and sex-related differences. Sex related differences in PD motor symptoms are well known and have been reported in many studies [1,2,3,8,9], but data on sex influence on NMSPD are still scant [17,18,19]. Martinez-Martin P et al (2012) have performed an extensive study of 951 PD patients to assess the predominance and severity of NMS and have found significant differences between males and females concerning the prevalence and severity of NMS. The most common NMS for both sex groups are sleep/fatigue in 84.02% and miscellaneous in 82.44%. In the female group prevail the feeling of sadness, nervousness and fatigue, constipation, restless legs and pain. In the male group more common and severe are drooling saliva, daytime sleepiness and sex dysfunction [17]. Nicoletti A et al (2017) in a study of 585 PD patients have found significantly sex-related differences compared with the general population [19]. Both PD men and women have been recorded with higher frequency of hallucinations, sleep disturbances and cognitive impairment compared to the general population. Women with PD have shown higher prevalence of urinary incontinence and depression, while PD men more commonly have sleep disorders, hallucinations and cognitive impairment. Compared to the general population the higher prevalence of NMS has been closely related with male gender [19]. The reason of this male-female differences in the clinical presentation of PD is the possible

effect of estrogen on dopaminergic structures and pathways of the brain [20, 21].

2.2.1. The role of estrogens. It has been established in animal models that estrogen may prevent the depletion of neurons in brain dopaminergic structures thus playing neuroprotective role [20]. Such results suggesting the possible protective role of estrogen on brain dopaminergic system and function in PD are controversial [20, 21, 22]. Some studies put emphasis on the protective effect of estrogen on brain dopaminergic structures and the diminished risk for PD and less severe motor or non-motor symptoms of PD in women [20, 22.] As it has been previously noted that cognitive impairment is more common in male PD patients [19]. Janowsky (2006) in a review has reported that higher levels of estrogen may play neuroprotective role in men with low levels of testosterone. Androgen deprivation leads to noticeable loss of synapses in the hippocampus in animal models, and these changes lead to cognitive deprivation, respectively. The restoration of testosterone to its androgen metabolites may play protective role in the cognitive deprivation [21]. In another study it has been found, that in male PD patients with higher rate of testosterone deficiency, the supplemental testosterone replacement therapy has not lead to remarkable improvement of motor and non-motor PD symptoms [23].

2.2.2. Sex influence on the quality of life (QoL) of PD patients. Nowadays, PD is considered a neurodegenerative disease clinically presented with motor and non-motor symptoms. In all stages of the PD non-motor symptoms are present in 90-95% of the cases. The list of NMS is variable, including cognitive deprivation, autonomic dysfunctions, neuropsychiatric disorders, sleep disorders, gastrointestinal disturbances, pain, olfaction impairment and many others [15,16,17]. It has been documented that many of the NMS have a greater impact on the worsening of the quality of life of PD patients than the motor symptoms [15, 16, 17]. This influence of NMS may also lead to problems on caregivers; to arise economic problems on PD patients' families and the society as a whole [15, 16]. An universal definition of health related quality of life (QoL) is not accepted yet. The term QoL is relevant to the patient's self-assessment of the disease impact and includes some physiological, physical and social aspects [24]. The assessment of QoL in PD patients contributes to complete information about disease complications and the impact of burden on healthcare system. The impact of motor symptoms on impaired QoL has been well understood and estimated. Lately, the impact of NMS on QoL attracts the attention of neurologists [15-17, 25, 26.] Not only motor symptoms, but non-motor symptoms have a direct negative influence on the health-related quality of life in PD [25, 26]. Some studies demonstrate the sex differences in NMS relevant to QoL. Sexual problems, daytime sleepiness and drooling were found as most common in men PD patients. Conversely, fatigue, depression, restless leg, pain, constipation, and disability contribute to the impairment of QoL in women with PD [25, 26, 27].

3. Age and sex related differences in comorbidity and survival in PD. Parkinson's disease is one of the worldwide most common neurodegenerative diseases, the second after Alzheimer disease. About 10 million people in the world and 1 million Americans are affected by PD. The perspective expects a doubling of this number next decades [28, 29]. PD is the disease of the middle and advanced age. With aging, elderly people suffer from many other chronic and degenerative brain disorders, gastrointestinal, urinary and musculoskeletal systems disturbances, auditory and visual dysfunctions [30-36]. Some studies concerning the comorbidity and mortality of PD have been published recently [37-41]. As the PD progresses patients suffer not only from motor and non-motor symptoms, but from many other chronic age-related comorbid diseases, too. The burden of comorbidity is less investigated [31, 32, 33]. A population-based cohort study of Leibson, et al. (2006) has revealed a significant PD comorbidity. The spread and type of comorbidity has been related to the duration and age of onset of PD [35]. Such motor symptoms of PD as gait disturbances and rigidity are commonly accompanied by falls that may cause many comorbid complications of the musculo-skeletal system as "lower extremity fractures", "osteopathies, chondropathies, and acquired musculoskeletal deformities" [35]. Gutman M, et al. (2004) in a large study of 15,000 PD patients and 30,068 controls have estimated the comorbidity in hospitalized patients for 6 years. The most common comorbidities as a cause for hospital admission, compared with the controls are aspiration pneumonia, psychoses, hip fractures, urinary disorders and infections including septicemia and fluid disorders [34]. Pressley J, et al. (2003) have reported comorbidity in 791 elderly PD patients (with mean age (78,5 \pm 7,6) . The study reveals remarkable differences in the comorbidity and health care between elderly patients with and without parkinsonism. Among PD patients fractures of extremities are more common in men and woman compared to the patients without PD. On the other hand, the pattern of fractures in patients with parkinsonism differs from that found in patients without PD, a difference related probably to the motor and gait disturbances and to the frequency and characteristics of falls [36]. Fullard M, et al. (2018) have studied sex differences in the comorbidity of newly diagnosed PD patients in a six years period and a sex related differences on the comorbid burden has been established. Men have a higher prevalence of lung cancer, ischemic heart disease and myocardial infarction, chronic obstructive pulmonary disease, diabetes, colorectal cancer, transient ischemic attack and stroke and chronic kidney disease. Conversely, the frequency of depression and dementia, cataracts and glaucoma, diseases of musculoskeletal system as osteoporosis, rheumatoid arthritis and osteoarthritis, fractures of extremities and congestive heart failure are higher in women

[38]. Hassan A, et al. (2015) have evaluated the profile of long-term PD survivors with 20 years disease duration in 187 PD patients (55% men). About 75% of the patients have 20-25 years of PD duration; the longest duration is 49 years. They have surprisingly mild cognitive impairment for the age, with deficits in the verbal fluency and delayed recall. These PD patients with 20 and more years survival reflect an elite group of PD patients with early-onset disease and relatively mild cognitive impairment, despite long disease duration [39]. Forsaa E, et al. (2010) have performed a community-based assessment of 230 PD patients for 13 years. During the study period 211 (92%) patients have lethal outcome. It has been found that male sex, age of onset, motor severity, dementia, psychotic symptoms and chronological age are independent predictors of mortality during the study period. The antiparkinsonian and antipsychotic treatment has not been found to significantly impact the survival rate. They have also concluded that the early prevention of psychoses and progression of motor symptoms may increase the survival in PD [37]. Early predictors of mortality have been investigated by Backstrom D, et al. (2018) in 178 PD patients with new-onset of the disease. The investigation has been performed using a multimodal protocol for 13.5 years, 109 of the patients have lethal outcome. Cerebrospinal fluid (CSF) has been analyzed in 99 patients. In early PD, mild cognitive decline, hyposmia, gait disturbance and reduced dopamine transporter activity, have been found to influence the shorter survival. A low-grade inflammatory reaction in the cerebrospinal fluid of 13.1% PD patients with strongly relation to the shorter survival is an interesting finding that may have clinical implication [40]. Marras C, et al. (2005) also have investigated predictors of survival in PD in a group of 196 PD patients. No age or gender differences have been found in the mortality ratio. Increased mortality is strongly associated with the bad response to levodopa, independent of disease severity or levodopa dosage. The severity of PD disease and response to levodopa are strongly related to the short survival [41].

CONCLUSION

Although PD is the most investigated movement disorder, studies on age and gender differences in NMSPD are insufficient. Future prospective longitudinal studies on the impact of age and gender of the clinical presentation of PD are needed in order to improve the therapeutic strategy and prognosis of the disease.

Abbreviations:

PD - Parkinson Disease,
NMSPD - Nonmotor symptoms in Parkinson disease,
QoL - Quality of life,
HRQoL - Health Related Quality of Life,
YOPD - Young Onset of PD.

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