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Non-Motor Symptoms of Parkinson's Disease and Health-Related Quality of Life: A Mini-Review

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ABSTRACT

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting seven million people globally. While the association of motor symptoms of PD with health-related quality of life (HRQoL) is extensively investigated, the effects of non-motor symptoms of PD, such as cognitive and behavioural symptoms, are recently highlighted. HRQoL reflects the physical, mental, and social aspects of health and is an essential subjective and reliable outcome measure of the disease. The current narrative review analyses recent literature on this topic focusing on studies in which behavioural symptoms of PD were considered as the main determinants of HRQoL.

Keywords: Behavior; Psychiatric; Parkinson's disease; Quality of Life

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder causing motor, non-motor and behavioural symptoms. Affecting seven milion people globally, this disorder is recognized as the second most prevalent neurodegenerative disorder after alzheimer disease. The disease incidence is estimated to become doubled by 2030 from existing estimates of 5 million patients worldwide [1,2].

Currently, treatment of PD is mainly based on improving motor functions [3]. However, especially in advanced stages, PD is often complicated by some clinical patterns indicating nonmotor and neuropsychiatric manifestations in addition to its motor features such as cognitive and mood disorders, psychosis and sleep disturbances which could have a great impact on patients' health-related quality of life (HRQoL). HRQoL reflects the physical, mental, and social aspects of health and is an essential subjective and reliable outcome measure of the disease. It specifically focuses on the patients' perception of health and life satisfaction that may be linked with the World Health Organization definition of health as ''the state of complete physical, mental, and social wellbeing, and not merely the absence of disease and infirmity" [4-6]. Although the performed studies on HRQoL of PD always were about motor aspect of disease, recent works now are focusing on non-motor symptoms of disease, showing the fact that bahavioural disturbances play major role in determining HRQoL.

Clinical course of disease

Parkinson disease is chronic and slowly progressive, meaning that symptoms continue and worsen over a period of years. Parkisnon disease is not considered a fatal disease and the way that it progresses is different for everyone. The symptoms of the disease can be classified into motor and non-motor symptoms. A case-control study addressed the issue whether the nonmotor

symptoms of disease are different from normal aging or not. 174 patients with PD and 128 age-matched controls had been included in their study [7]. They concluded the frequency of nonmotor symptoms were meaningfully greater among patients with PD, which brings the fact that these symptoms are disease-specific and not purely a result of normal aging [2,7,8]. Of note nonmotor symptoms significantly impact QoL [9,10].

Non-motor symptoms as the early manifestations of disease usually are not diagnostic and patients almost will remain undiagnosed until they reveal motor symptoms like resting tremor, rigidity and bradykinesia [11-13].

Motor Symptoms

Treatment of motor symptoms, as the main symptoms of PD, is heavily under investigation and multiple treatment have suggested for it, yet. Motor and non-motor symptoms are linked together and insufficient treatment of motor symptoms may cause increase in non-motor symptoms while the patient is asymptomatic in terms of motor symptoms [14]. Consistently, there are known cases showing that disease treatment may also worsen some non-motor symptoms especially psychiatric-related symptoms like depression, dementia and similar symptoms. Initial therapy always should be considered once the motor symptoms have been manifested. The treatment priority is to immediately control the disease progression and so, Levodopa, the mainstay of PD treatment, here is helpful. Other options include monoamine oxidase type b(MAO-b) inhibitors and dopamine agonists. There is a place for amantadine usage particularly in patients with mild symptoms and also for use anticholinergics. However, their less indication for treatment, due to troublesome side effects, is similar to that of amantadine and same category of drugs [8]. Despite using levodopa for managing the motor symptoms of the disease, it might have some complications such as dyskinesia, resting tremor and motor fluctuations that should be considered for all patients. These complications are characterized by changeable on-off series of symptoms which often initiate within 5 to 10 years after levodopa begins [11,15]. They may be managed by changing the dosage or frequency of levodopa or addition of some other medications such as catechol-o-methyltranferase (COMT) inhibitors to avoid further metabolism of levodopda and prolonging its effect, MAO-b inhibitors and also using a dopamine agonist [16]. Along with the indicated methods to reduce motor complications and dyskinesia, amantadine currently is the only option which has been suggested because of its promising pharmacological effects [17]. It has been shown that complications of levodopa and gait disorders are the main motor factors of HRQoL [9].

Non-motor symptoms and Impact on Health Related Quality of Life

Autonomic dysregulation and related symptoms

These symptoms contain gastrointestinal tract related conditions such as constipation, drooling, dysphagia, neusea and vomiting, urinary symptoms (e.g. urgency, frequency, incontinence), cardiovascular conditions (e.g. orthostatic hypotention, erectile dysfunction) and thermodysregulation [11]. Drooling was noticed in majority of patients as the most important determinants of HRQoL in PD patients especially in gastrointestinal tract disorders. It is also known as sialorrhea which is presumed to be a result of patient's dysphagia rather than the exccesive saliva production [18]. Of note, when the disease advances, resulting in forward head posture and opened mouth, drooling might get worse in thease patients. There are simple techniques to reduce drooling for example, speech and swalloing therapy, chewing gum and sucking on hard candy. Beside, PD medications can be helpful especially if drooling primarily begins in medication "off" periods [19]. The controversy is truly remarkable for using anticholinergic agents or antihistamines as their efficacy has remained uncertain over the last years. There is also a study of botulinum toxin B on drooling where its efficacy was shown in both severity and frequency of sialorrhea, without worsening of dyphagia. It is important to note that the adverse effects such as dry mouth and gait disorders were seen by the botulinum toxin B [18]. Dysphagia may act like a beginer of consequence that led to aspiration, malnutrition, loss of weight gain and dehydration and result in increased risk of mortality [16]. Nausea and vomiting can be provoked by impaired gastric movements and are often related to PD's treatment as well, such that the levodopa absorption is likely to be impaired as a result of gastric motion impairment and then its intestinal absorption effects could increase the existing nausea [15]. It sould be noted that the anti-dopaminergic medications may deteriorate these symptoms, so they should not to be used.

Constipation as another complication could occur in up to 60% of patients, same as what happens in nausea and vomiting and could be managed with routine therapies. Altering daily exercise and regimens with full-fiber diets, increased fluid intake and increased workout in addition to laxatives or stool softeners, if needed, are the mainstay therapies in such settings [16,20]. Regarding Urinary complications, they initially present

with nocturia as a most common complaint in almost above 60% of PD patients and while the disease advances other symptoms such as urinary urgency, frequency and incontinence become more prominent. In case of detrusor overactivity signs and symptomes (e.g. urinary frequency and urgency) urinary tract infections and prostate issues must be considered as the most important causes. Urinary issues, presenting during "off" periods may have a desirable response to PD medications and anticholinergics as well [21].

There is a bundle of the PD cardiovascular complications inwhere orthostatic hypotension, defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position, is reported as the most common feature of disease. Dizziness, lightheadedness, cloudy thinking, weakness and syncope are the clues leading physicians to consider orthostatic hypotension in PD patients [22]. Mainly, hydration with an daily intake of 2 liters of water and 8 grams of salt [16], changing the bed-time position in case of non-problematic orthostatic hypotension, reducing in antihypertensive therapy and diuretics (if avoiding these agents is not possible) in challenging situations are recommended. Of note in severe cases mineralocorticoids or the alpha-adrenergic medications might be needed [8]. Poor response to mentioned tratments arises the need for decreasing in dopaminergic agents [8,20]. An investigation on early initiation of carbidopa/levodopa with or without entacapone in patients with PD, showed an increased risk of cardiovascular events in patients under treatment with COMT inhibitors [23]. Patients with PD also may experince a new condition named "Thermodysregulation" which recognized by intolerance to heat and cold, along with excessive sweating [24]. These situations are more common while there is an association of cardinal motor symptoms and particular autonomic dysregulations (e.g. constipation) especially throughout the "off" period of disease. Botulinum toxin B, by probable reduction of sweating, and deep brain stimulation, maybe with the mechanism of decreasing in levodopa-induced complications, are adjustments to motor symptoms treatment [25].

Sexual system commonly may be influenced, as the disease could impact on that of males and females sexual function by diminshed libido, arousal, drive and orgasm as a common manifestation of disease. Meanwhile, the most annoying problem regarding these sexual effects is erectile dysfunction [26]. Although patients with PD are prone to get sexual dysfunction, however, there are multiple reasons (e.g. neurosychological issues, medications for mood disorders and cardiac problems) which should be considered, along with the disease itself, as a cause for sexual dysfunction. Thus, disease progression and also implemented treatments must be reviewed, and probable causes should be resloved. There are a need for re-assessment of neuroscychiatric issues as well.

Neuropsychiatric manifestations

Previously, depression have been discussed in the literature as a measure of HRQoL. In accordance with former findings [27], there is a consensus on depression importance as a neuropsychiatric symptom affecting HRQoL [10,28-34]. Because of some common symptoms of depression and Parkinson's for example loss of appetite, lack of motivation, slowed movement, slowed thinking or confusion, and sleep disturbances; the diagnosis of depression during the disease course may be missed. Ii is also important to know that the depression may be worsen throughout the "off" periods so the PD symptoms in these times must be controlled [11]. There are studies on efficacy of antidepressants for managing of depression but based on a recent Cochrane review there is e lack of evidence on the topic and data are inadequate for efficacy and safety of these agents [35]. These agents, as the most common medications for depression therapy, are include both TCAs and SSRIs. Complications due to these agents reported as the minimal in the trials; except with confusion and hallucination [35]. Other agents such as bupropion, venlafaxine and mirtazapine were evaluated and have shown to be helpful in a recent investigation [36]. Lastly, it has shown by several studies that pramipexole, an agonist of dopamine receptors, can relief depression in particular cases as well [37]. Depressive disorder is known to be associated with poor HRQoL. HRQoL offers an almost complete perception of the patient's disaese by illuminating discrepancies concerning disease and health-care team in recognizing priorities for management strategies and quality of care, and is a appropriate means of outcome measurement in medical researches [38]. Of note, the term determinant in these topics refers to factors influencing HRQoL at both indivisualy and population levels [39]. HRQoL also determines the efficacy of therapies for diseases at all demographic levels [40]. In other hand, there are several studies recognized anxiety as the robust determining factor of HRQoL even though depression was evaluated in their analysis [34,41,42]. Some have believed that the depression and anxiety have equal impact on

HRQoL [43].

There are also specific symptoms of the disease identified as HRQoL determinants while may not affect HRQoL in other disorders even with their presence. In the case of PD examples are include axial impairment [44], syncope, cardiovascular dysfunction, impulse control disorders [45], behavioural disorders linked to nonmotor fluctuations, fatigue [46], the whole of nonmotor symptoms [47], and decline in societal role participation.

Generally we should know the nonmotor symptoms, particularly depression, anxiety, insomnia, and other mental health factors, seem to have a greater adverse impact on HRQoL than motor deficits.

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