

Fatigue The Most Unattended Non- Motor Symptom In Idiopathic Parkinson's Disease – Review Report

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Abstract

Background: -Fatigue being the most unrevealed, unattended symptoms among the non-motor symptoms, has shown to be the most disabling element in the road to recovery and have a greater impact on the quality of life among patients with Parkinson's disease. Yet the concept of fatigue is poorly studied. **Objective:** - The article reviews known evidence about fatigue prevailing in Parkinson's Disease and outlines the importance of optimizing the qualitative assessment with a non-invasive biomarker and physical therapy intervention. **Major findings:** - This subjectively measured non-motor symptom greatly depends on the patient's response which varies from one person to person. A standard quantitative assessment is yet to be found to measure the level of fatigue pre and post-physical therapy intervention. It is often confused with cognitive or physical exertion. This has led to low-quality evidence or no proper treatment protocols **Conclusion:** -This study thus concludes that non-motor symptoms often resist recovery, among which fatigue is the most felt but not reported. Future studies are to be directed to focus on fatigue and more promising protocols to be studied for their frequency, duration, and application.

Keywords: Non – Motor Symptoms, Fatigue, Biomarker, Diagnosis, Physical Therapy Intervention

Introduction

Fatigue is a subjective description for the feeling of lack of energy which is one of the most common non-motor symptoms among patients with Parkinson's disease affecting from 32 to 68% of the patients. Fatigue has been first mentioned in 1967 and an article assessing fatigue was first published in 1993. But Parkinson's disease was first given a neurological syndrome in 1817 by James Parkinson. With the timeline, it shows that fatigue though one among the many non-motor symptoms has been very much an under-researched factor ⁽¹⁾. Fatigue is the most debilitating symptom which most of the time causes a delay in recovery of the patients, continuity of the therapy session, strain on the caregiver due to dependency this ultimately leads to a very poor quality of life. Many factors as sleep disturbances, tremor, depression, anxiety, gastrointestinal abnormalities, prolonged use of Parkinson's drugs, immobility have added to the fatigue values ⁽²⁾. One-third of the patients consider fatigue as one of the most debilitating symptoms.

Prevalence

The prevalence of Parkinson's Disease in Asian countries is about 15–119 per 100,000 and incidence ranges from 10 to 20 per 100,000. In south India, about 20% of Parkinson's Disease patients have Non-Motor Symptoms as presenting symptoms among which fatigue is the predominant symptom. Due to lack of awareness, patients keeping it unrevealed with themselves thinking it's not the need to be attended to during the process of rehabilitation have become the most disability factor in the road to recovery. The non-motor

symptoms have become a major cause of hospitalizations⁽³⁾. After nocturia and constipation, fatigue (50%) is the most severely affected common non-motor symptom reported among the patients with Parkinson's disease in the Indian population⁽⁴⁾.

Terminology

A common understanding of the definition is as follows, "fatigue is described by PD patients as a lack of energy or a need for the increased effort needed to attempt daily activities that are distinct from sleepiness, lack of motivation and depression"⁽⁶⁾.

A lack of proper definition to fatigue creates the greatest challenge to decide on outcome measurement in measuring the intensity of it and hence it lacks quality evidence. Current evidence suggests that there is limited evidence on the effect of exercise and physical activity on fatigue.⁽⁷⁾

Fatigue has been associated with depression and increased daytime sleepiness motor performance, to be an inability to sustain any form of physical activity.

Predicted Pathophysiology

Fatigue which is not related to the demographic and motor features is affected by sleep dysfunction, anxiety, and depression. The early presence of the Lewy body along with the neurodegeneration explain the early occurrence and persistence of fatigue in patients with Parkinson's disease. This explains the dopaminergic Nigrostriatal pathway involvement with disease course and disease severity.

The non-dopaminergic pathway involvement in fatigue is the decrease of serotonin transporter binding in the basal ganglia and limbic structures and lower cerebral spinal fluid concentrations of serotonergic metabolites. Dysfunction of frontal-basal ganglia circuitry and impaired integration of limbic input and motor functions explain the pathophysiology of fatigue⁽⁹⁾.

It is a complex syndrome emerging from dysfunction in the endocrine, nervous and immune systems. Underlying fatigue triggers an inflammatory cytokine network. This inflammatory process promotes glutamate dysregulation and influences neuronal activity and neuroplasticity thus impacting the neuronal circuits directing to distress. The hypothalamic-pituitary-adrenal system connects to the basal ganglia, amygdala, thalamus, and frontal cortex, and dysfunction in this system leads to fatigue⁽¹⁰⁾.

Clinical Types

Fatigue can be seen as physiological which is induced due to prolonged physical activity and pathological which never goes off with rest. It is also recognized as central fatigue, where it is the involvement of the central nervous system which is exhibited by a sense of exhaustion involving both mental and physical domains whereas peripheral fatigue is more involving the physical domain of reduced muscle mass, inability to do motor performances in the presence of motivation.⁽⁵⁾ Central fatigue is sometimes referred to as cognitive fatigue and peripheral fatigue is termed as motor fatigue.

Kluger and colleagues proposed the fatigue symptom as a syndrome, they differentiated Parkinson's fatigue from other conditions causing fatigue. they also provided a detailed recommendation to report Parkinson's – related fatigue⁽⁸⁾. Fatigue is incorporated with many neurobiological features and the underlying pathophysiology which can form the basis for the development of appropriate biomarkers and development of targeted interventions. Till now the patients have characterized this fatigue qualitatively and is different from the normal physiological fatigue experienced by the general population.

Diagnosing Fatigue

With the lesser-known evidence of pathophysiology, it has become very difficult to diagnose fatigue. In accordance with the *Diagnostic and Statistical Manual IV* style used for defining cancer-related fatigue and chronic fatigue syndrome, the Parkinson's disease foundation working group developed a case definition of PD-related fatigue. A daily or nearly daily feeling of significantly diminished energy or an increased perception of effort disproportionate to attempted activities or general activity level forms the basis of this diagnosis. The criteria have yet to be validated. There are 9 validated scales as which have been critiqued according to the movement disorder society task force they are, The Fatigue Severity Scale (FSS) the Fatigue Assessment Inventory (FAI), the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F), the Multidimensional Fatigue Inventory (MFI), the Parkinson's Fatigue Scale (PFS), the Fatigue Severity Inventory (FSI), the Fatigue Impact Scale for Daily Use (D-FIS), Visual Analogue Scale (VAS), and the Clinical Global Impression Scale (CGIS).

Potential Biomarkers

Studies have shown that biomarkers for cognitive decline can lead to early diagnosis and can be a breakthrough for indicating treatment prognosis. inflammatory markers higher serum levels of IL-6, IL1-Ra, sIL-2R, and VCAM-1 were associated with higher fatigue levels promote glutamate dysregulation and negative effect on neuroplasticity and neuronal activity. hypothalamic-pituitary-adrenal system involvement shows cortisol levels as biomarkers from saliva for fatigue. ⁽⁹⁾C-reactive protein and cytokines are potential biomarkers for subjective fatigue ⁽²⁾. Biomarkers are very essential, especially when there are no clear diagnostic criteria. Higher levels of inflammatory molecules alter the immune response thus leading to fatigue ⁽¹²⁾.

Increased salivary cortisol levels can be a cause of dysfunctional pituitary – hypothalamic – axis, this pathway also results in fatigue symptoms. Hence salivary cortisol can be a non-invasive biomarker to measure fatigue. The activation of the inflammatory cytokine network leads to sickness behavior. Cortisol in urine levels can also be analyzed for fatigue and stress-related.

Studies of changes in human saliva during prolonged physical exertion have been reported many times. The ratio of the ion intensities of these two peptides, referred to as the fatigue biomarker index can also be taken as a choice to conducted studies as a tool for measuring the fatigue levels and also a treatment index to assess the benefits of the exercise interventions ⁽¹³⁾

Managing Fatigue

There are numerous pharmacological and non-pharmacological intervention studies, non-pharmacological studies have shown no or fewer effects, studies carried with drugs like modafinil, methylphenidate, pergolide, bromocriptine, etc have no effect on fatigue. Whereas levodopa showed some benefits when fatigue was one of several nonmotor symptoms assessed in randomized, placebo-controlled trials, where nonmotor symptoms were not the primary endpoints of the study ⁽¹⁴⁾.

Non- pharmacological treatments as exercise, pacing daily activities, involvement in social activities, group therapy, a Nordic walking program, energy conservation techniques, dance interventions, cognitive behavioral therapy, acupuncture, and many more. Among these exercises have shown to be promising if done patient-tailored. This is lacking in the present clinical approaches. Hence a customized tailored protocol is the need to handle fatigue in Parkinson's disease ⁽¹⁵⁾. Forced or assisted exercises that can exceed their threshold voluntary intensity level should be added as part of the treatment regime.

Conclusions

Finally, concluding that there are only insights into the concept of fatigue from its definition, patient's perspective, diagnosis to its management. There no evidence-based guidelines nor clinically established approaches to the management of fatigue. Till now fatigue is mostly a patient-explained subjective symptom and the responses cannot be generalized post-intervention as each patient has a different perspective about their fatigue, also a standard intervention is not established due to no proper outcome measures. Many treatment protocols have been put forwards and proved their effects on the reduction of symptoms and improved quality of life but there is no open literature yet proved to have a robust regime of duration, frequency, time, outcomes measures to quantify fatigue levels, etc over each treatment. Hence, the choice of the administration of the treatment varies from therapist to therapist.

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