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Review

Fatigue in Parkinson's disease: Motor or non-motor symptom?

G. Fabbrini [a,b], A. Latorre [a], A. Suppa [b], M. Bloise [a], M. Frontoni [a], A. Berardelli [a,b,*]

[a] Department of Neurology and Psychiatry, "Sapienza" University of Rome, Viale dell'Università 30, 00185 Rome, Italy
[b] Neuromed Institute (IRCSS), Pozzilli (IS), Italy

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ABSTRACT

Fatigue is one of the most disabling symptoms in patients with Parkinson's disease (PD), with a significant impact on patients' quality of life. Clinical studies using ad hoc questionnaires showed that in PD fatigue is associated with non-motor as well motor symptoms. Neurophysiological observations suggest that motor mechanisms play a role in the pathophysiology of fatigue but there is no clear correlation between fatigue measured with clinical instruments and fatigue assessed with neurophysiological tests. Neuroimaging studies show that fatigue is associated with an involvement of non-dopaminergic or extrastriatal dopaminergic pathways. It is conceivable that both motor and non-motor mechanisms underlie the pathophysiology of fatigue.

1. Introduction

Fatigue has been defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion [1]. It is characterized by difficulty in initiating and sustaining mental and physical tasks in the absence of motor or physical impairment [2–4] and consists of both a mental and physical component [5]. Mental fatigue occurs after sustained intellectual activity or emotional tension (hypervigilance), as well as after boring, repetitive tasks or lack of activity (hypovigilance or depressive state fatigue) [5]. Physical fatigue may be subdivided into a peripheral and central component [1,2,6]. Peripheral fatigue is a sense of exhaustion caused by repeated muscular contraction (thus called muscle fatigue or physical exercise fatigue). Central fatigue consists of both physical and mental components and is caused by the executing of attention-requiring exercises, such as counting or calculation, or sustained physical activity [2,3] (Table 1)

Fatigue may occur in several medical conditions [7–17]; as regards neurological disorders in particular fatigue have frequently been described in patients with Parkinson's disease (PD) [18–22]. Although several features of fatigue in PD have been described, it is still unclear whether fatigue can be considered a non-motor symptom, as has been suggested by some authors [23,24], or whether fatigue is a motor manifestation of PD. In addition the pathophysiology of fatigue is largely unknown [25]. The aim of this paper was, therefore, to review existing evidence of fatigue both as a motor and as a non-motor symptom as well as to review neurophysiological and neuroimaging studies designed to investigate the pathophysiology of fatigue in PD.

2. Clinical features and assessment

The earliest reference to fatigue in PD dates back to 1967 [26], but only in the last two decades has fatigue been increasingly recognized as an important symptom in PD [18,19,24]. Fatigue is more common in PD than in normal subjects [3,19,27] its prevalence in PD ranging from 37 to 56% [18,19,21,28]. Fatigue can be an early symptom in about 2% of patients [26] and actually precedes motor symptom onset in approximately 32% of cases [29]. Fatigue has been described as the most disabling symptom by 15–33% of PD patients and one of the three most disabling symptoms by 58% of PD patients [16], which highlights the impact this symptom has on patients' quality of life [30].

Several studies have reported a relationship between fatigue and gender, and fatigue and physical activity. Levels of fatigue are higher in women than in men, with female, though not male, PD patients displaying more chronic fatigue than the general population [31]. PD patients with higher levels of fatigue are less physically active [32], though it is unclear whether fatigue results from a sedentary lifestyle or is actually the cause of physical inactivity [33]. The relationship between fatigue and disease severity in

* Corresponding author. Department of Neurology and Psychiatry, "Sapienza" University of Rome, Viale dell'Università 30, 00185 Rome, Italy. Tel./fax: +39 06 49914700.
E-mail address: alfredo.berardelli@uniroma1.it (A. Berardelli).

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Table 1
Summary of results supporting fatigue as a non-motor or motor symptom.

Evidence supporting fatigue as non-motor symptom in PD	Evidence supporting fatigue as motor symptom in PD
Clinical features: • Comorbidity with: - Depression [18,19,27,28,41–44] - Anxiety [20,29] - Sleep disorders [11,28,29,44,47] • Correlation with cardiovascular sympathetic dysfunction [48] • No improvement after STN DBS [37] *Neuroimaging studies*: • Decreased cerebral blood flow in the frontal lobe [66] • Striatal dopamine transporter uptake concentration values similar in patients with fatigue and in those without fatigue [34] • Involvement of the non-dopaminergic basal ganglia pathways and dopaminergic extrastriatal projections [64]	*Clinical features*: • Possible relationship with disease severity [3,19,28,29,34,35,36] and motor complications [19,29] • Fatigue more severe when patients reach HY stage III [29]. • Fatigue more severe in patients with postural-gait symptoms [29] • Improvement with L-Dopa but not with placebo [34] *Neurophysiological studies*: • Reduced motor performance during finger-tapping task [53] • Increased post-exercise facilitation of motor evoked potentials [57] • Increased motor evoked potentials amplitude during fatiguing exercise [57] • Possible relationship with the sequence effect [63] • Improvement of the neurophysiological variables with L-dopa [52,53,57]

PD patients is controversial, as is demonstrated by the fact that some authors have found a correlation [19,28,29,34,35] while others have not [3,36,37].

The Movement Disorder Society (MDS) recently commissioned a task force to assess the strength and weakness of the currently available clinical rating scales for fatigue in PD [38]. Only two scales were considered appropriate for rating fatigue severity: the Fatigue Severity Scale (FSS) and the Multidimensional Fatigue Inventory (MFI). The FSS is a self-administered unidimensional generic 9-item fatigue rating scale [1], that reveals the functional impact of fatigue. The FSS is the scale that is most commonly used to assess fatigue in PD. The strengths of this scale include its brevity, easy administration and good psychometric properties in PD. The MFI is a 20-item self-report measure with five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [39]. The strengths of the MFI include the presence of a subscale designed to measure mental fatigue whose validity has been demonstrated in both PD [40] and non-PD populations. According to Lou et al. (2001) [3], the MFI is an instrument that can be reliably used to distinguish mental from physical fatigue.

3. Evidence suggesting that fatigue in PD is a non-motor symptom

Fatigue has, like other symptoms such as apathy and depression, been considered a non-motor symptom [23,24], there being evidence of an extensive comorbidity between the different types of non-motor symptoms [20].

Several studies have reported a relationship between fatigue and depression [18,19,41–44]. One prospective longitudinal study showed, however, that fatigue can be independent of depression, and that non-depressed PD patients may exhibit more fatigue than depressed PD patients [28]. In addition, a recent multiple logistic regression analysis showed that depression was not a significant independent variable related to fatigue in PD patients [30]. Some reports have suggested that anxiety may also be associated with fatigue [20,29].

Fatigue has been correlated with sleep disorders, which are commonly present in PD patients [45]. Excessive daytime sleepiness (EDS) is present in up 50–75% of patients with PD [46,47] though its correlation with fatigue is debated [28,44]. A multiple logistic regression analysis, however, revealed that fatigue cannot be ascribed to EDS or poor sleep [29]. The characteristics of sleep disorder-induced fatigue and those of primary fatigue are different. EDS fluctuates over the course of the day, whereas fatigue is more constant during the day [33] and persists after naps [4]. Furthermore, EDS correlates with disease duration, whereas fatigue does not [47].

Lastly, autonomic dysfunction may be involved in the pathogenesis of fatigue in PD. In a study on 33 PD patients, Nakamura et al. (2011) [48] first demonstrated a close relationship between fatigue and cardiovascular sympathetic dysfunction in PD patients; fatigued patients had a higher pressure response to the dobutamine infusion test and a lower cardiac MIBG uptake than non-fatigued patients. One explanation for this finding is that cardiac sympathetic denervation may lead to failed increases in cardiac contractility during exercise, which may in turn lead to shortness of breath or a sensation of fatigue in PD patients. Increased orthostatic intolerance, which has been observed in patients with chronic fatigue syndrome [49], was also reported by Nakamura et al. (2011) [48] in a proportion of fatigued PD patients. These results suggest that patients with orthostatic hypotension may experience fatigue.

4. Evidence suggesting that fatigue in PD is a motor symptom

Two studies investigating the relationship between fatigue and motor complications in the advanced phase of PD reported conflicting results. Karlsen et al. (1999) [19] did not find differences in the frequency of motor fluctuations between patients with or without fatigue, whereas more recently Hagell and Brundin (2009) [29] found that 53% of the PD patients with fatigue had motor fluctuations and in 83% of these fatigue worsened during the off phase. No studies have addressed whether the presence of L-dopa-induced dyskinesias is associated or not with fatigue.

Neurophysiological investigations have provided important insights into the pathophysiology of fatigue. Single fiber electromyography (SFEMG) has shown that neuromuscular transmission in PD patients with fatigue is normal, which thus excludes an involvement of the cholinergic system at neuromuscular junction in fatigue [50]. The peripheral component of fatigue does not differ between PD and normal subjects, as demonstrated by the decrease in EMG amplitude and in the M-wave after repeated contraction [51]. On the other hand if PD patients perform repeated voluntary contractions fatigue is more evident in PD patients than in healthy controls. Using an automated system to measure muscle fatigability, Ziv et al. (1998) [52] showed that repeated contractions in PD patients induce a pathological reduction of strength, when compared with controls. Lou et al. (2003) [53] assessed physical fatigue by measuring finger-tapping parameters (dwell time and movement time), using an electronic keyboard equipped with musical digital interference technology, and a submaximal force exercise paradigm to test force generation. Dwell time was defined