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Physiopathology and treatment of fatigue in multiple sclerosis

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Abstracts Fatigue is a common symptom of patients with multiple sclerosis (MS). It is reported by about one-third of patients, and for many fatigue is the most disabling symptom. Fatigue may be associated with motor disturbances and/or mood disorders, which makes it very difficult to determine whether the fatigue is an aspect of these features or a result per se of the disease. Although peripheral mechanisms have some role in the pathogenesis of fatigue, in MS there are clear indications that the more important role is played by "central" abnormalities. Neurophysiological studies have shown that fatigue does not depend on involvement of the pyramidal tracts and implicate impairment of volitional drive of the descending motor pathways as a physiopathological mechanism. Metabolic abnormalities of the frontal cortex and basal ganglia revealed by positron-emission tomography and correlations between fatigue and magnetic resonance imaging lesion burden support this hypothesis. Some recent studies also suggest that pro-inflammatory cytokines contribute to the sense of tiredness. No specific treatments are available. Management strategies include medications, exercise, and behavioural therapy; in most cases a combined approach is appropriate.

Key words Fatigue · Multiple Sclerosis

Introduction

Fatigue is a common symptom in patients. It is a frequent complaint in infectious disorders, tumours, systemic diseases, depression and dysfunctions of the motor system. The occurrence of fatigue in such different disorders is partially due to the fact that the term fatigue is used to describe various physical and psychological conditions. Fatigue is a highly subjective and non-specific symptom which can be easily confused with weakness, on the one hand, and with depressed mood, the other. The fact that in some disorders, such as multiple sclerosis (MS), fatigue may be associated with motor disturbances and/or mood disorders makes it very difficult and sometime impossible to determine whether fatigue is an aspect of these features or a symptom in itself. This contribution reviews the main aspects of fatigue in MS, its pathophysiology and management.

Definition

Fatigue is an overwhelming sense of tiredness, lack of energy or feeling of exhaustion. It may exist independently of both depressed mood and weakness. Fatigue is frequently present even at rest. Patients have the feeling that the effort required to perform actions is disproportionately high [27]. As a consequence patients tend to reduce their physical activity, even if beneficial effects of rest are usually modest. Fatigue is usually greater in the second part of the day and is worsened by stress. This

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condition must be distinguished from fatigability. Fatigability is a generalised sense of exhaustion, not present at rest, affecting the patient after a few minutes of physical activity and which disappears after a short rest. Both fatigue and fatigability affect MS patients, and they are sometimes present in the same patient. The pathophysiology of the two disturbances probably differs, as fatigability affects predominantly the lower limbs and is invariably associated with clinical or subclinical involvement of the motor pathways.

Fatigue is a common symptom of MS patients, reported by about one-third of patients [19, 28, 44], and for many fatigue is the most disabling symptom [18]. However, this high prevalence is affected by the frequent occurrence in MS patients of motor problems, painful syndromes and mood abnormalities [39]. Fatigue may occur at any stage of MS, even if it is more frequent and severe in patients with primary- or secondary-progressive disease than in those with relapsing-remitting disease [1, 29]. Fatigue occasionally signals the onset of MS and may precede by weeks or months the first attack. Fatigue may be a transient phenomenon, frequently associated with or preceding clinical relapses [23, 35], or chronic, being present at all times. It is unclear whether transitory and chronic fatigue are different types of fatigue, or whether they share a common pathophysiology. While there are no clear correlations between disability and fatigue in MS, fatigue nevertheless has a tremendous impact on the activities of daily life, interfering with work, family life and social activities.

Many factors may affect fatigue in MS. Heat worsens fatigue, while cool relieves the condition. The effect of increased body temperature is explained by the instability of the nervous conduction in partially demyelinated fibres: the increased body temperature induces a conduction block at Ranvier's nodes with a reduced density of sodium channels, with a consequent deterioration in neurological functions. Depression affects about 20 % of MS patients, and if present it may worsen fatigue [39]. Pain affects about 40 % of MS patients and is correlated with fatigue in a number of chronic disorders. We can therefore expect a similar negative impact in MS. The relationship between sleep disorders and fatigue is controversial. Most MS patients with fatigue also complain of sleep abnormalities, but polygraphic studies show that median sleep latency is normal, and that fatigue is not associated with nocturnal hypoxia or breathing associated sleep fragmentations [4]. Some of the objective, physiological measures of fatigue are described below.

There are reasonable doubts that these instrumental tests really measure the phenomenon described by patients. Fatigue is a subjective experience, and this is the reason self-report instruments are probably more appropriate for quantifying the phenomenon although they have obvious limitations. Multidimensional scales (Table 1) allow different characteristics of fatigue to be evaluated. The most frequently used include the Multidimensional Assessment of Fatigue, developed for patients with rheumatoid arthritis and recently used in MS patients [17], the Fatigue Assessment Instrument, which identifies both severity and situation-specific factors [43] and the Fatigue Impact Scale, with 40 items including cognitive, psychosocial and physical dimensions [18]. The Fatigue Severity Scale is the most commonly used unidimensional scale, and measures the impact of fatigue in daily living [29]. It is very easy to be administered and has also been used in clinical trials [11, 30]. The longitudinal use of these scales has not been fully validated; particularly some of the intrinsic characteristics of these scale, such as proportionality and responsiveness, have not been defined.

Tab. 1 Principal fatigue scales (modified from [26])

Name of scale	Dimensions	No of items
Multidimensional		
Fatigue Impact Scale (FIS)	Cognitive, psychosocial, physical	21
Multidimensional Assessment of Fatigue (MAF)	Severity, timing, distress, interference	16
Multidimensional Fatigue Inventory (MFI)	General activity, mental, physical, motivation	24
Fatigue scale (FS)	Physical, mental	14
Unidimensional		
Fatigue Severity Scale (FSS)	Severity on daily living	9
Functional Assessment of Multiple Sclerosis (FAMS)	Tiredness-thinking subscale	9
Rand Index of Vitality (RIV)	Vitality	4

Bigland-Ritchie et al. [3] define fatigue physiologically as "the inability of a muscle or group of muscles to sustain the required or expected force". This may occur because of a loss of force-generating capacity within the muscle itself (peripheral fatigue), or because of an inability to sustain the central drive to spinal motoneurons (central fatigue). The phenomenon of fatigue can be studied with variable tools. Fatigue can be quantified neurophysiologically by the curve that express the change in the force over time, both to a maximal voluntary contraction or to maximal repetitive electrical stimulation. During maximal voluntary contraction, as the amount of force declines, the frequency of motor unit potentials on electromyography (EMG) decreases [15], and the changes can be seen objectively by the spectral EMG analysis. Finally, metabolic changes in the muscle during activation (voluntary or stimulated) can be studied using magnetic resonance spectroscopy.

MS patients frequently complain of marked difficulty in mental performance. A recent psychometric study suggests that mental fatigue does in fact really occur. Elkin and colleagues [16] subjected a group of patients to a battery of cognitive tests and found a striking decline on measures of memory and conceptual thinking across the testing session, whereas the control group

continued to improve with practice. It would be interesting to determine whether these changes are associated with a subjective complaint of fatigue.

Pathogenesis

The ability to produce and maintain a given level of exercise requires an increase in heart and respiratory rate and a 20-fold increase in blood flow to the muscle; the muscles must have a normal metabolic activity and normal elastic properties. There is some evidence that peripheral abnormalities contribute to produce fatigue in MS. MS patients complaining of fatigue show significantly less maximal voluntary force during exercise than normal controls and patients affected by chronic fatigue syndrome [14, 34]. Miller et al. [34] found lower muscle force during repetitive peripheral nerve stimulation in MS patients complaining of fatigue. Lenman et al. [31] assessed fatigue of the tibialis anterior muscle by repetitive electrical stimulation and found lower muscle tension and longer half-relaxation time during repetitive activity in MS patients than in controls. They explained the observed changes as due to a transformation of fatigue-resistant fibres into fatigable ones. Magnetic resonance spectroscopy confirms the existence of peripheral components of the fatigue in MS; intramuscular phosphocreatine resynthesis following exercise is slowed in MS patients, probably as a consequence of disuse and deconditioning [25].

Although peripheral mechanisms may have some role in the pathogenesis of fatigue in MS, there are clear indications that a more important role is played by "central" abnormalities [40]. A very simple explanation is that impaired conduction along central motor pathways due to demyelination and secondary axonal degeneration causes a reduced recruitment of spinal motor units or the inability to drive the motoneuron pool at sufficient rates to generate full tetanic force [36]. The observation that in MS patients with fatigue, there is a greater decrease in force over time is in the presence of pyramidal signs [14] supports the the involvement of corticospinal tracts. However, objective fatigue is not associated with a decrease in central motor conduction [10, 38, 40] (Table 2). Brasil-Neto et al. [5, 6] have reported transient decreases in motor evoked potential amplitude after exercise and a post-exercise decrease from the first to the fourth amplitude during repetitive transcranial magnetic stimulation. Galardi et al. [20] performed repetitive transcranial magnetic stimulation in a group of patients complaining fatigue and in a control group and found that the amplitude of the motor evoked potential was significantly lower in MS patients, but the decrease during and after exercise was the same in patients with and those without fatigue. The results of this study again indicate that a progressive conduction failure of large-diameter, fast-conducting pyramidal fibres activated by repetitive transcranial magnetic stimulation does not occur and thus cannot explain the phenomenon of fatigue in MS.

Tab. 2 Central motor conduction times in patients with and without fatigue (from [26])

	With fatigue		Without fatigue	
	Median	Range	Median	Range
Right arm	6.4	5.3–19.4	6.6	5.5–7.9
Left arm	6.7	5.3–12.3	6.8	5.5–7.7
Right leg	16	12.1–31.7	15	11.2–16.3
Left leg	16.6	11.1–26	14.8	13–21.4

All results non-significant

There is the possibility that central fatigue develops in cortical pathways rostral to the pyramidal tract. Sandroni et al. [38] found that reaction times accompanying the performance of auditory memory tasks are significantly greater when MS patients are fatigued than when they are at rest. Interestingly, neither P300 latency nor central motor conduction is significantly increased by fatigue, suggesting that fatigue affects neural processes acting before activation of the primary motor cortex. Impairment of volitional drive to the descending motor pathways has also been suggested to explain the "normal" central fatigue [22] and chronic fatigue syndromes [32]. Possible mechanisms for the withdrawal of volitional drive include the involvement by demyelinating lesions [22] of pathways directing the motor cortex or of the facilitatory afferent pathways. Feedback from both muscular and cutaneous afferents affects motor drive, either at the spinal or the supraspinal level. Colombo et al. [10] found that the lesion load in T2-weighted magnetic resonance imaging of the brain is significantly higher in MS patients complaining of fatigue than in MS patients not complaining of fatigue, with the two groups matched for age, sex, duration of disease, disability and pyramidal functional system score (Table 3). Moreover, the T2-weighted lesion load was correlated significantly

Tab. 3 Lesion loads on brain magnetic resonance imaging in patients with and without fatigue (from [26])

	With fatigue		Without fatigue	
	Median	Range	Median	Range
Frontal lobe	6	0–21	1	0–30
Parietal lobe	2*	0–24	0	0–3
Temporal lobe	0	0–4	0	0–2
Internal capsule	0*	0–7	0	0–2
Basal ganglia	0	0–4	0	0–02
Periventricular	20	3–46	14	4–53
Trigone	4*	0–10	1	0–8
Total	32	5–82	22	6–60

*$P < 0.05$

with the fatigue severity scale score. Roelcke et al. [37] carried out a study using positron-emission tomography with fluorodeoxyglucose and found a significant reduction in metabolic activity, bilaterally in lateral and medial prefrontal cortex, in the premotor cortex and putamen and in the right supplementary motor area. These very interesting results clearly indicate that frontal cortex and basal ganglia play a role in MS fatigue.

Immune factors may also contribute to fatigue. Both human and animal studies have found an association between fatigue and some cytokines, including tumour necrosis factor a and interleukin–1 [2, 9]. Patients treated with interferon-β frequently complain of fatigue, particularly in the first weeks of therapy. However, in a recent short-term longitudinal study in 11 relapsing-remitting MS Mainero et al. [33] used triple-dose delayed scans and observed no correlation between brain magnetic resonance imaging activity and fatigue.

Treatment

Management of fatigue is a complex and difficult task because multiple factors, variably combined in MS patients, may contribute to produce the symptom. The first step is to inform the patient and the family that the symptom is genuine. The recognition of the physical nature of the phenomenon is important, particularly when fatigue is not associated with other major symptoms and signs. The patient's self-esteem is enhanced when informed that the sense of exhaustion is not a mere psychological reaction to the disease but rather is due to nervous tissue damage produced by the disease. Management strategies include medications, exercise and behavioural therapy; in most cases a combined approach is required.

Exercise

Exercise is important to combat deconditioning. The exercise programme must be individualised because overexertion may be detrimental. For the same reason the work load during the day should be carefully distributed, with adequate rest periods. Excessive physical activity is not tolerated because of the easy exhaustion and the negative effects of even a small increase in body temperature. Working or living in warm environments can be intolerable for some patients; air conditioning is very important in hot climates. Positive effects of a graded exercises on fatigue are more relevant in patients with weakness and spasticity. In these MS patients a 1-year multidisciplinary rehabilitation programme has been found to significantly reduce fatigue [24]. In another study 54 patients were randomly assigned to 15 weeks of aerobic exercise or non-exercise. Patients who underwent aerobic exercise had a significant reduction in fatigue and an improvement in quality of life [13].

Behavioural therapy

Behavioural therapy is useful in patients with fatigue and associated mood disorders, as demonstrated by the positive results obtained in patients with chronic fatigue syndrome [7, 12]. We can also expect that MS patients would benefit this therapy, but controlled studies are lacking.

Medication

A number of different medications are used to manage fatigue, sometime with only a poor justification. Most clinical trials have been uncontrolled, involving only a small number of patients and with only a short duration. In clinical setting the response to drugs varied widely from patient to patient.

The drug most widely used is amantadine. This is a synthetic chemical originally introduced to treat infections and later found to be beneficial in Parkinson's disease, probably by promoting the release of dopamine. A Canadian multicentre placebo-controlled trial [8] found that 100 mg amantadine twice daily significantly improves fatigue. Amantadine is relatively safe in long-term use; confusion and urinary retention is seldom and occurs predominantly in the elderly.

Pemoline is a central nervous system stimulant, used in attentional deficit disorders in children. For these central effects it has been used to treat fatigue in MS, without evidence of physical or psychological dependence. A placebo-controlled study [45] failed to demonstrate significant effects of pemoline, although a trend was observed; moreover, poorly tolerated side effects occurred in 25 % of the patients. A placebo-controlled randomised study compared pemoline to amantadine and placebo [30]; again, only a positive trend was found for pemoline, while amantadine showed a benefit over placebo in some fatigue measures. Therefore pemoline mustbe considered a second-line therapy. The range of the doses used varies between 18.75 and 187.5 mg. Nervousness, insomnia and anxiety may occur at the highest doses. Other stimulants, such as methylphenidate and dextroamphetamine, have anecdotally been reported to be effective.

A totally different therapeutic approach is based on restoring nerve conduction in partially demyelinated fibres undergoing conduction block. The potassium channel blocker 4-aminopyridine has shown a clear benefit on fatigue [42]. An open pilot study with 3,4-aminopyridine performed in eight MS patients com-

plaining of fatigue showed a subjective improvement in six, but no changes were observed in nerve conduction [41].

Anti-depressant therapy may prove useful especially in patients with associated fatigue and depression. Fluoxetine and other selective serotonin reuptake inhibitors are preferable to other anti-depressant agents because they produce less sedation and fewer anticholinergic effects.

Patients with fatigue and sleep disorders require specific interventions to correct sleep abnormalities. The use of benzodiazepines for insomnia may provide improvement; however, high doses should be avoided as these can increase fatigue.

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