Review

Fatigue as a common signature of inflammatory myopathies: clinical aspects and care

G. Ricci, L. Fontanelli, F. Torri, E. Schirinzi, G. Siciliano

Clinical Neurology, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Giulia Ricci, MD, PhD
Lorenzo Fontanelli, MD
Francesca Torri, MD
Erika Schirinzi, MD
Gabriele Siciliano, MD, PhD

Please address correspondence to:
Gabriele Siciliano,
U.O. di Neurologia,
Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: gabriele.siciliano@unipi.it

Received on January 30, 2022; accepted in revised form on February 4, 2022.

Clin Exp Rheumatol 2022; 40: 425-432.

Key words: fatigue, idiopathic inflammatory myopathies, treatment

Competing interests: none declared.

ABSTRACT

Fatigue is a common symptom in idiopathic inflammatory myopathies (IIMs), which greatly affects activities of daily life. Fatigue is a complex phenomenon that covers a range of dimensions from biological to behavioural, the pathophysiology of which is still poorly understood. The aim of this review is to describe the different determinants of fatigue in IIMs, discuss their clinical implications and how to evaluate and manage the condition, which are all relevant issues for the treating physicians in their everyday practice.

Introduction and topic context

Myositides, also known as idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare, chronic, autoimmune diseases characterised by muscle weakness and various grades of chronic inflammation in skeletal muscles, together with multiple organ involvement (*e.g.* skin, lung, heart, joints) (1-3). Albeit some controversies exist over the classification of IIMs and no consensus has yet been published (4), they are commonly categorised, on the basis of nature and localisation of symptoms and clinical signs as well laboratory and biopsy findings, into dermatomyositis (DM), of which a juvenile form (jDM) also exists, polymyositis (PM), overlap myositis (OM), inclusion body myositis (IBM) and immune-mediated necrotising myopathy (IMNM) (5). Cardinal clinical manifestations of IIMs, as in general for all types of myopathies independently of their origin, are muscle weakness, fatigue and sometimes pain. Fatigue, in particular, is one of the main causes of significantly decreased quality of life (QoL). In a cohort of 95 patients with DM and PM, 89% of subjects reported fatigue and about a third considered fatigue the symptom that most impacted their QoL (6), interfering especially with those activities of daily life (ADL) that require sustained shoulder abduction (7).

Despite the high frequency of this complaint in myositis, several aspects on this clinical characteristic are rather poorly defined and need to be better profiled. The definition of fatigue is not easy and several, also conceptual, aspects need to be considered before transferring it to a clinical ground. This is the reason why, although referring to one of the more if not the most, important clinical characteristics of these diseases, which affects skeletal muscle function in the different everyday life activities, fatigue is often not properly considered by the clinician. In addition, considering its complex physiopathology and the high number of factors that are involved in its determination, reports from the scientific literature about its frequency and clinical aspects are often vague and also contradictory. An example of this is how to consider interrelationships between fatigue, in the proper meaning of the term, and psychiatric disturbances that often coexist and in turn can influence this complaint. As reported by Campbell *et al*., fatigue in DM and PM is common and is associated with depression (8). Taking these considerations into account, the aim of this review is to analyse several aspects of fatigue in IMMs. To do so, we will firstly define the concept of fatigue and how fatigue is relevant in the wider field of neuromuscular disorders. Then we will describe the proposed mechanisms of fatigue in IIMs and the available clinical tools to measure it, concluding with a chapter on its management treatment, which is still a particularly challenging area. This review also looks at the possibilities a specialist has to

properly consider this undervalued, yet so common, symptom in patients with IIMs in everyday clinical practice.

Fatigue: definition and general concepts

Although a definition of fatigue has not been universally adopted, partly because of its semantic overlap with other terms such as tiredness, muscle weakness or sleepiness, in clinical use it can be defined as a process consisting of difficulty in sustaining over time prolonged or repeated motor voluntary tasks (9, 10). As for example for the often shadowed contours of the concept, Campbell *et al*. (11) argued as perceived fatigue, in this sense a subjective impression, in patients with IIMs was unrelated to contractile endurance, a more physical dynamometric dimension of the motor performance, further recognising that fatigue and muscle fatigability are two entangled, yet different, concepts. Although poorly defined, fatigue is one of the most frequent symptoms in clinical practice, with a stunning prevalence of 5–45% in general population, being chronic in 10% of the cases and neuromuscular diseases are amongst the conditions with the more prevalence of the symptom (12).

In an attempt to summarise this complex topic, there at least three main key factors to consider: the first is a core element that refers to the insufficient capacity to generate torque force due to biochemical and physiologic alterations within the muscles, the effector of body motor machinery; the second regards a more comprehensive failure of the motor system including central pathways activated during the efforts, somehow also subjected to sensory pathway feedback modulation that leads to reduced work and endurance (*i.e*. tolerance to prolonged exercise) motorneuron output; the third involves a behavioural condition which includes subjective aspects of feeling of tiredness and mental discomfort. This composite of meanings is reflected by how patients usually refer to it when complaining of fatigue (*e.g*. "to be exhausted", "to have no ambition", "to be tired all the time", "to be burned out") (13).

Fatigue is also a physiological phenomenon and, as such, it has a protective and conservative role (14) as it prompts the body to rest after demanding physical exertion that, if excessive, can prove dangerous for individual homeostasis. Physiological fatigue is in general acute, as a reaction to a sustained activity, and it is alleviated by a period of refreshment. On the contrary, pathological fatigue usually begins gradually (15), is not alleviated by sleep and rest (16) and is disproportionate to the intensity of the activity (10, 17).

However, in most cases the underlying mechanisms of fatigue remain poorly understood (18). Depending on the origin of the symptoms, fatigue can be classified in central, where the central nervous system (CNS) reduces neural drive to the skeletal muscle, and peripheral, due to alterations in recruitment of motoneurons, the conduction of action potentials along peripheral nerve fibres or neuromuscular transmission at plaque level – all referred to by the term "neurogenic fatigue" – or impaired muscle function, in this case more appropriately speaking of "muscle fatigue" (19, 20) (Fig. 1).

In clinical practice, fatigue is variable, sometimes subtle and with a wide range of manifestations, for instance,

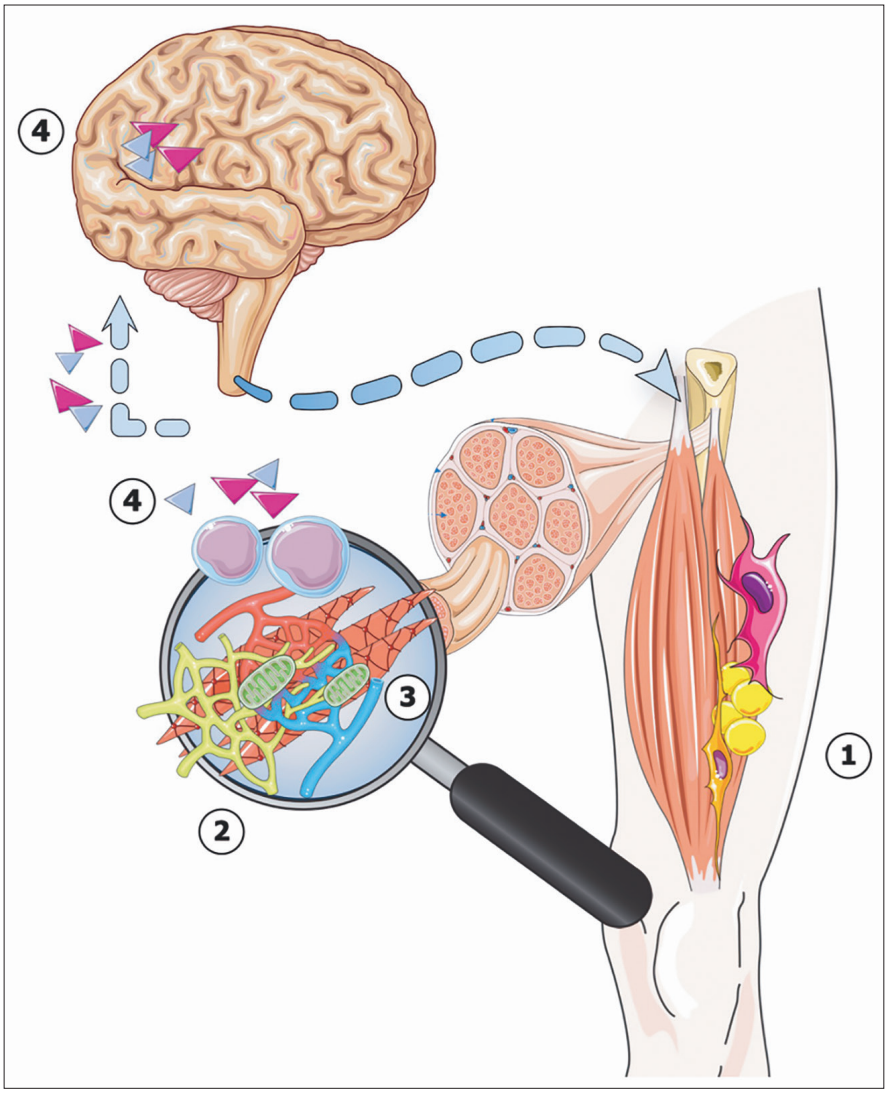

Fig. 1. Different mechanisms underlying fatigue.
The figure illustrates the central and peripheral nervous motor system components that are involved in generating muscle fatigue: points 1-2-3 show structural and ultra-structural muscle remodelling and metabolic impairment in myopathic conditions: (**1**) interstitial fibrosis and fat infiltration; impairment in ATP production due to (**2**) vascularisation alterations or (**3**) primary mitochondrial disfunctions); point **4** indicates the retroactive modulation of the central drive of fatigue through the inflammatory response.

the progressive weakening of the voice during a speech in myasthenia gravis due to impaired neuromuscular junction transmission, or also to the hyperactive manifestations associated to exercise, such as cramps and contractions, due to muscle energy exhaustion in metabolic myopathies, respectively.

Fatigue in inflammatory myopathies: clinical aspects and physiopathology

In IIMs, fatigue typically presents with a progressive inability to sustain prolonged activities with the upper limbs, such as drying hair, using the telephone or driving, preceding or concomitant to muscle weakness. Shorter activities, such as dressing, are usually more tolerated. It is not uncommon that patients cope with fatigue by tailoring their tasks to reduce the duration of exertion, limiting travel and planning rest periods after demanding activities (7).

Central fatigue in IIMs

More generally speaking, different conceptual models have been proposed to clarify whether fatigue can be considered as a symptom or comorbidity in neuroimmunological diseases and intrigued pathways and mechanisms between immune system and CNS are being enlightened in the literature.

With regard to IIMs, a strong link entangles inflammation in muscle with systemic inflammation: for example, in patients with DM a marked upregulation of the type I interferon (IFN) pathway has been demonstrated not only in muscle and skin but also in blood (21, 22). During inflammatory processes in periphery, the brain receives continuous information from the immune system through cytokines and other inflammatory mediators. Cytokines may pass to the brain through choroid plexus and circumventricular organs, where the blood-brain barrier is less tight, or they can be actively transported via molecules on the brain endothelium and influence the synthesis of various neurotransmitters (23).

In detail, it has been proved that proinflammatory cytokines can reduce the production of tetrahydrobiopterin (BH4), which is an essential cofactor in the metabolism of tyrosine and tryptophan. In turn, tyrosine is a precursor of dopamine, noradrenaline, epinephrine, and tryptophan is a precursor of serotonin, important neurotransmitters which produce their effects through a variety of membrane receptors, purposely distributed in different regions of the brain (14). Additionally, tryptophan is degraded to kynurenine in the most part by the liver and, to a lesser extent, extrahepatically by various cells, including microglia (24) by the enzyme indoleamine 2,3-dioxygenase (IDO). Physiologically, the degradation induced by IDO is of little relevance, but IDO is highly inducible by proinflammatory cytokines (23). Indeed, in Dermatomyositis the indoleamine 2,3-dioxygenase 1 (IDO 1) gene is upregulated (25) and in IBM kynurenine is induced (26).

This inflammation-induced alteration in the synthesis of neurotrasmitters may be, in part, responsible for the central component of fatigue. It is unlikely that a single molecule is responsible for the central component of fatigue (27). Previous studies that aimed to find a direct effect of serotonin concentration on fatigue (*i.e.* "the serotonin hypothesis"), yielded contrasting results (28, 29). Interestingly, in different studies, the activation of the kynurenine pathway was linked to reduced motivation (30, 31) It is possible that an imbalance in the concentration of monoamines, in particular a high serotonin-to-dopamine ratio, may be involved in the cause of central fatigue at various levels (28).

In fact, similar inflammatory patterns also participate in the genesis of mood disorders, leading to both structural and functional changes in CNS, especially in the hippocampus regions (32).This entanglement may also explain the frequent co-presentation of fatigue and depression observed in patient with IIMs.

Peripheral fatigue in IIMs

Peripheral fatigue in IIMs basically arises from functional or structural impairment of skeletal muscle. Different pathophysiological mechanisms can be involved in it, depending on the various but often concurrent pathological characteristics of the disease in which primary or secondary myofibre alterations, either structural or metabolic, as well as interstitial connective disarrangement and inflammation and intrinsic vascular involvement have to be considered (Fig. 3).

Alteration of muscle architecture

Alterations of muscle architecture can be found at different, macro and microscopical levels in IIMs. The rearrangement of the muscles reduces the efficiency in generating and propagating force. Fat infiltration, fibrotic replacement and muscle atrophy of varying degrees are common findings in IIMs and may be seen in magnetic resonance (MRI) and ultrasound (US) imaging (33, 34). When muscle fibres diminish, those left are overloaded to sustain the activity undertaken, while at the same time progressively undergoing structural and metabolic alterations that lead to a functional condition of so-called "overworked fatigue" (13).

At histological and histochemical level, in patients with DM and PM, biopsies from vastus lateralis show a lower proportion of type I fibres and a higher proportion of type IIC fibres compared to healthy controls (35). As type I muscle fibres are slow-twitch, mitochondrial rich and less fatigability with respect to type II fibres as they are able to work longer due to their ability to rely on mitochondrial oxidative phosphorylation (36), their loss contributes to increasing the fatigue phenomena.

Moreover, in several pathological conditions, the angle resulting from the force-generating axis of the muscle and its fibres, the so-called "pennation angle" (theta), is altered (37). Since the force generated in a certain direction is directly proportionate to the cosine of the theta angle (cos(thetha)), a greater pennation angle results in a lesser force transmitted to the tendons. Once the transmission of the force lacks its efficacy, more effort is required to maintain the desiderate contraction, leading to an increase in fatigue. Considering also that the pennation angle varies during contraction (38), clear effect on how it affects force production is not simple (37, 39). In patients with systemic lupus erythematosus, a disease charac-

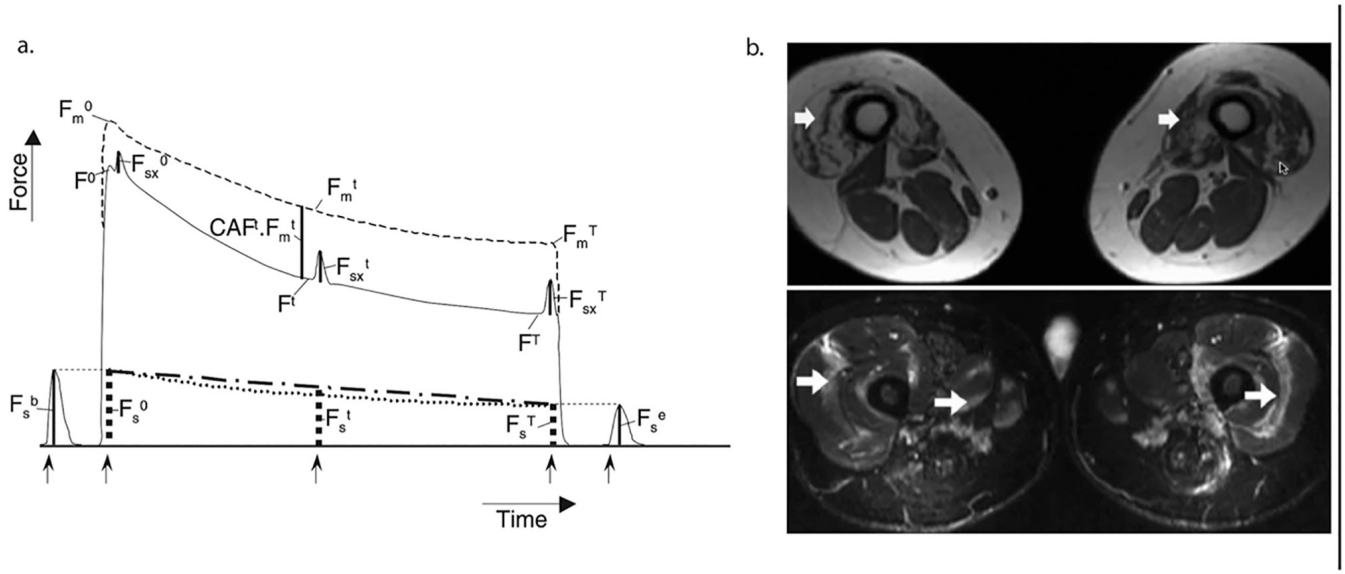

Fig. 2. Defining and measuring muscle fatigue.
a: Force decay during prolonged exercise: Sustained maximal voluntary contraction (MVC) with variable definitions. **F**=force produced voluntarily; **Fm**=maximally possible force; **Fsx**=force added by superimposed electrical stimulation; **Fs**=maximally possible force response on electrical stimulation; **CAF**=central activation failure (From Schillings M.L. *et al*., *J Appl Physiol* 2005; 98: 2292-7, modified).
b: MRI scan of thigh muscles showing correspondent structural (T1 sequences: upper) and inflammatory (STIR sequences: lower) alterations as related to an inflammatory myopathy.

terised by multi-systemic chronic inflammation and, in 3–11% a myositis, the pennation angle is increased (40). Nonetheless, studies should be made to finely assess the role of these muscle structural modifications in the genesis of fatigue and related weakness in neuromuscular disorders, including IIMs.

Alteration of muscle vascularisation and muscle metabolism

Adenosine triphosphate (ATP) is the molecule that supplies energy for muscle contraction, and it is well known that a reduction of ATP production cause muscle fatigue. ATP is generated anaerobically with a low yield in the first 10–30 seconds of maximal contraction and, with more efficiency, by means of mitochondrial respiratory chain in the presence of oxygen. Several factors, such as hypoxic conditions, intracellular acidosis, and mitochondrial abnormalities, may impair ATP production (41, 42) leading to a switch towards anaerobic metabolism during fatiguing stimulation. The contribution of mitochondrial disfunctions, associated directly with mitochondrial abnormalities or secondary to abnormal oxygen supply, to the pathogenesis and clinical manifestations of IIMs have not been clearly understood yet and few data are available regarding this. In preclinical models of mitochondrial myopathy, no increase rate of fatigue was shown but the ability to generate force was markedly decreased; it is hypothesised that this lack of effect on fatigue is attributed to an increase in mitochondrial mass that compensates for the impairment of the respiratory chain (43).

Biopsies of patients with PM and IBM, but not those of patients with DM (44), show abnormal accumulation of mitochondrial DNA deletions and reduced activity of respiratory chain enzymes complexes (45-48) Rygiel *et al*. performed a histochemical and immunohistochemical analysis on sixteen muscle biopsies from IBM patients and found that fibres at different stages of mitochondrial disfunction were more likely to be atrophic compared to those with normal respiratory chain function, suggesting that a strong correlation between degree of inflammation, mitochondrial disfunction and atrophy exist in IBM (49).

A study of *in vivo* muscle metabolism shows that in DM and PM such oxidative metabolism deficit exists, together with more rapid acidification and a reduction in [H+] recovery during rest (50). On the contrary, unexpectedly, no difference between IBM patients and controls was found relating to *in vivo* mitochondrial metabolism, indicating that mitochondrial oxidative capacity does not seem to be impaired in these patients (51) Considering that in IBM capillary density around muscle fibres is increased (52) and that *in vivo* mitochondrial metabolism is normal, Cea *et al*. concluded that the alterations seen in IIMs are presumably secondary to an impaired oxygen supply and that histological, molecular and biochemical alterations in the mitochondrion observed in biopsies do not have a pivotal role in the pathophysiology of these diseases. In DM the progressive thickness and inflammatory wall infiltration of perimisial vessels may cause muscle hypoperfusion with infarctions or more likely impaired blood supply causing chronic low oxygen delivery to the fibre; in PM, a reduction in number, an abnormal distribution and sometimes a thickened wall of capillaries between muscle fibres may contribute to the same phenomenon (50).

Based on these considerations, no conclusive data are available and further studies are needed to evaluate the role and the burden of ATP impairment due to alteration of oxygen supply secondary to vascular injuries or primary mitochondrial in the determination of fatigue in IIMs.

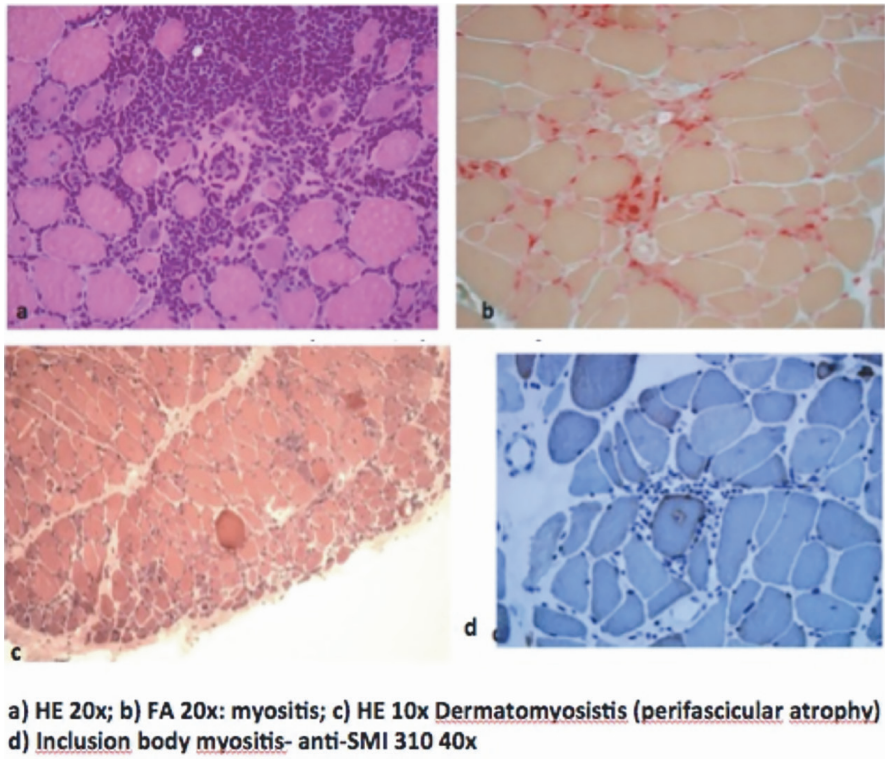

Fig. 3. Muscle biopsy in IIMs showing skeletal muscle alterations at histological level responsible for peripheral fatigue.
HE: haematoxilin-eosin staining; FA: acid phosphatase staining; SMI: intermediate neurofilaments.

Interstitial tissue alteration and fibrosis

In normal conditions, the extracellular matrix (ECM) sustains myofibres and blood capillaries, intervening in the physiological remodelling of the muscle (53). The alteration of this scaffold due to quantitative or functional defects of ECM induces progressive fibrotic infiltration of the muscle tissue, contributing in myopathic processes, such as IIMS, to alter tissue elasticity with consequences on vectorial mechanical transmission of strength to the joint levers, as well as increasing muscle susceptibility to injury and decreasing tissue regeneration. Moreover, the activation of various cells of the immune system after skeletal muscle damage is critical in driving the effectiveness of muscle recovery (54). An imbalanced interaction between immune and stromal cells with myogenic cells results in aberrant fibrotic rearrangement of the muscle tissue.

In addition, fibrotic proliferation can strangle terminal intramuscular motor axon branches, which in turn contributes to peripheral fatigue with neurogenic components such as loss of myofibres within the single motor unit domain while the muscle is contracting (53).

Diagnosing and measuring fatigue in IIMs

Despite being a common symptom in myositis, fatigue is not routinely assessed during medical examinations, probably due to a poor awareness of it from both patients and clinicians (7). This is also a reason why there is paucity of validated, IMMs-specific scales to measure fatigue, although different methods and scales have been proposed. They may be in the form of observational functional tests in which an examinator assesses specific patient performances on predetermined tasks, or patient-reported outcome measures (PROMs), consisting of questionnaires exploring different fatigue-related domains.

One of the laboratory tests to measure central and peripheral fatigue evaluates the force (F) obtained from maximal voluntary contraction (MVC) and compares it to the force generated by superimposing twitches with electrical stimulation (F_s). Considering that the force produced by electrical stimulation which usually activates only part of the muscle tissue is representative to the force of the muscle activated as a whole, Schillings *et al*. developed a mathematical model to simultaneously calculate the central and peripheral components of fatigue during sustained MVC (55) (Fig. 2). Alternatively, and when targeting the electrophysiological counterpart of muscle contraction, transcranial magnetic stimulation – recently proved safe in patients with DM (56) – has been proposed to assess central fatigue (57). On the other hand, a decrease in the frequency components of the spectrum of integrated superficial electromyographic (EMG) signal has been classically associated with muscle fatigue (58). Both of them can be compared with the classic decay of evoked EMG signal by repetitive peripheral nerve stimulation, the most historical laboratory model of which is the Desmedt test, very popular to diagnose Myasthenia gravis.

Exercise tests for fatigue can be categorised according to different variables which phenomenologically describe the type of exercise test, maximal *versus* submaximal, continuous *versus* intermittent, ischaemic *versus* non-ischaemic, isometric *versus* isokinetic and so on, and consequently can offer different information about fatigue mechanisms. Peripheral blood biomarkers may be associated to the measure of strength or EMG during the test, of either structural (CK) or metabolic (lactate) muscle significance.

The Childhood Myositis Assessment Scale (CMAS), the Functional Index (FI), Functional Index 2 (FI-2) and 3 (FI-3) scale, the 2- and 6-minute walking distance test (2MWDT, 6MWDT) belong to the category of observational, functional and eventually timed tests. CMAS is the best validated scale specific to IMMs, designed to be used in jDM. FI is a disease-specific index consisting of fourteen functional tests which include evaluating endurance in the extremities, the neck and trunk, the ability to turn in bed and transfer from lying to sitting, grip force and peak exploratory flows (59). It has been criticised for being excessively time-consuming to administer and for its

ceiling and floor effects in patients with mild-to-moderate impairment (60). A shorter version, FI-2, avoids spirometry and evaluates seven different activities constituted by repetitive movements in proximal and distal muscle groups. It is free from ceiling and floor effects, has shown a good content validity and inter-rater reliability in adult DM and PM, and has been used as an endpoint in a few therapeutic trials (61-64). Recently, a third version of the scale (FI-3) has been proposed for DM/PM that further shortens times and maintains high intra- and interrater reliability (64). 6MWDT has been validated for use in adult and juvenile myositis and has been used as primary endpoint in a randomised clinical trial for IBM (65). In patients with IBM, the 2-minute walking distance test (2MWDT) has shown a high correlation to 6MWDT against which it is better tolerated (66). The IBM Weakness Composite Index is IBM specific, but it has not been validated yet (65).

PROMs allow clinicians to standardise the patients' perspective regarding their own symptoms. However, no specific questionnaires exist as yet and generic forms have also been used. The 36-Item Short Form Survey (SF-36) has four items (namely: items 23, 27, 29, 31) that measure fatigue. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and The Fatigue Severity Scale (FSS) are Likert scales consisting of forty and nine items, respectively, regarding fatigue and how fatigue interferes with daily life, and have been used in different studies to assess fatigue in patients with IIMs (6).

Therapeutic challenges of fatigue in IIMs

Fatigue treatment remains challenging, in part due to the mixed, poorly understood, mechanisms.

Different drugs have been proposed to target central or peripheral fatigue but none has been approved yet. Methylphenidate (67) and modafinil (68) act with different mechanisms on various central neurotransmitters (*e.g.* dopamine, norepinephrine, …) and have been studied to treat fatigue in a number of different illnesses, but concerns arise on the risk of addiction, especially in prolonged use, and their use for fatigue is off-label. For peripheral fatigue, carnitine, or branched chain amino-acid supplementation, aiming to restore or enhance intracellular supplies, have shown mixed results in different neuromuscular disorders, but no study has purposedly assessed patients with IIMs. A double-blind, randomised, placebo-controlled trial found that six months of oral creatinine supplements in patients with PM and DM improved functional performance but did not have any effect on fatigue, as measured by Chalder fatigue scores (69).

Supervised physical exercise, both aerobic and anaerobic, is generally safe in patients with neuromuscular diseases, showing some positive effects in terms of muscle strength, muscle loss, maximal oxygen uptake (VO2 max) (70, 71) and, in patients with PM and DM, standardised moderate physical training programme determined an increased muscle fibre area, a change in fibre type composition, increasing the proportion of type I muscle fibres (35). On the contrary, two different studies assessing rehabilitation programmes in a cohort of patients suffering from PM and IBM, respectively, while having positive effect on QoL, perceived pain and peak oxygen uptake (VO2 peak), did not show any significant improvement in fatigue, possibly because of their low statistical power, due to the low number of patients (72, 73). Taking these considerations together, it may be advisable to incentivise patients to take up supervised physical activities, to avoid excessively loading a system burdened with a pathology and, as such, is more prone to be damaged by over-exercise.

Conclusions

For specialists in their everyday clinical practice the most important questions are how to properly investigate and manage fatigue. Fatigue is a common symptom in IIMs and greatly interferes with patients' ADLs and QoL. Its clinical presentation is variable in patients' daily motor activities, such as difficulty in sustaining activities with the upper limbs or walking and is often undervalued by clinicians or not properly considered in a context in which, for instance, also cardiac or respiratory insufficiency can contribute to exercise intolerance. Inflammation may play a role both in the central and peripheral components of fatigue and maybe involved, although indirectly, also in the mood disorders that are often associated with it. Alteration of muscle architecture and metabolism may be determinants of peripheral aspects of fatigue, as well as different inflammatory patterns should influence both central and peripheral fatigue mechanisms which in these cases cannot be easily disjointed. Different scales and methods to measure both central and peripheric fatigue have been proposed but few scales have been validated in IIMs. Treatment is still challenging, the effectiveness of different interventions is very poor and difficult to assess. New pharmacological treatments are needed and supervised physical programmes tailored to patient's performance ability should be considered.

References

1. LUNDBERG IE, DE VISSER M, WERTH VP: Classification of myositis. *Nat Rev Rheumatol* 2018; 14: 269-78.
2. VENCOVSKÝ J, ALEXANDERSON H, LUNDBERG IE: Idiopathic inflammatory myopathies. *Rheum Dis Clin North Am* 2019; 45: 569-81.
3. CARDELLI C, ZANFRAMUNDO G, COMETI L *et al*.: One year in review 2021: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2022; 40: 199-209.
4. FINDLAY AR, GOYAL NA, MOZAFFAR T: An overview of polymyositis and dermatomyositis. *Muscle Nerve* 2015; 51: 638-56.
5. SELVA-O'CALLAGHAN A, PINAL-FERNANDEZ I, TRALLERO-ARAGUÁS E, MILISENDA JC, GRAU-JUNYENT JM, MAMMEN AL: Classification and management of adult inflammatory myopathies. *Lancet Neurol* 2018; 17: 816-28.
6. CAMPBELL RCJ, SCOTT DL, KIELY PD, GORDON P: Fatigue in idiopathic inflammatory myopathy (IIM): prevalence, impact and association with poor quality of life. *Arthritis Rheum* 2011; 63 (Suppl.): S89.
7. OLDROYD A, DIXON W, CHINOY H, HOWELLS K: Patient insights on living with idiopathic inflammatory myopathy and the limitations of disease activity measurement methods - a qualitative study. *BMC Rheumatol* 2020; 4: 1-9.
8. CAMPBELL RC, SCOTT DL, KIELY P, GORDON PA: Fatigue in dermatomyositis and polymyositis is common and associated with depression and poor quality of life. *Rheumatology* 2011; 50: 67-8.
9. CHAUDHURI A, BEHAN PO: Fatigue in neurological disorders. *Lancet* 2004; 363: 978-88.

10. DITTNER AJ, WESSELY SC, BROWN RG: The assessment of fatigue: A practical guide for clinicians and researchers. *J Psychosom Res* 2004; 56: 157-70.
11. CAMPBELL R, GORDON P, WARD K, REILLY C, SCOTT DL, RAFFERTY GF: Nonvolitional assessment of muscle endurance in idiopathic inflammatory myopathies: There is no relationship between patient-reported fatigue and muscle fatigability. *Muscle and Nerve* 2014; 50: 401-6.
12. FINSTERER J, MAHJOUB SZ: Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Med* 2014; 31: 562-75.
13. ROPPER AH, SAMUELS MA, KLEIN JP, PRASAD S: Adams and Victor's Principles of Neurology. McGraw Hill (11th Ed.), 2019.
14. KARSHIKOFF B, SUNDELIN T, LASSELIN J: Role of inflammation in human fatigue: Relevance of multidimensional assessments and potential neuronal mechanisms. *Front Immunol* 2017; 8: 1-12.
15. PERSSON PB, BONDKE PERSSON A: Fatigue. *Acta Physiol* 2016; 218: 3-4.
16. POULSONT MJ: Not just tired. *J Clin Oncol* 2001; 19: 4180-1.
17. KIRSH KL, PASSIK S, HOLTSCLAW E, DONAGHY K, THEOBALD D: I get tired for no reason: A single item screening for cancer-related fatigue. *J Pain Symptom Manage* 2001; 22: 931-7.
18. KARSHIKOFF B, SUNDELIN T, LASSELIN J: Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. *Front Immunol* 2017; 8: 21.
19. CARROLL TJ, TAYLOR JL, GANDEVIA SC: Recovery of central and peripheral neuromuscular fatigue after exercise. *J Appl Physiol* 2017; 122: 1068-76.
20. ROSSI B, SICILIANO G, MURRI L, MURATORIO A: [Mechanisms of muscular fatigue]. *Riv Neurol* 1991; 61: 23-34.
21. GAO S, LUO H, ZHANG H, ZUO X, WANG L, ZHU H: Using multi-omics methods to understand dermatomyositis/polymyositis. *Autoimmun Rev* 2017; 16: 1044-8.
22. XIE S, LUO H, ZHANG H, ZHU H, ZUO X, LIU S: Discovery of key genes in dermatomyositis based on the gene expression omnibus database. *DNA Cell Biol* 2018; 37: 982-92.
23. DANTZER R, O'CONNOR JC, FREUND GG, JOHNSON RW, KELLEY KW: From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat Rev Neurosci* 2008; 9: 46-56.
24. YADAV MC, BURUDI EME, ALIREZAEI M *et al*.: IFN-gamma-induced IDO and WRS expression in microglia is differentially regulated by IL-4. *Glia* 2007; 55: 1385-96.
25. ALJABBAN J, SYED S, SYED S *et al*.: Investigating genetic drivers of dermatomyositis pathogenesis using meta-analysis. *Heliyon* 2020; 6: e04866.
26. BUZKOVA J, NIKKANEN J, AHOLA S *et al*.: Metabolomes of mitochondrial diseases and inclusion body myositis patients: treatment targets and biomarkers. *EMBO Mol Med* 2018; 10: e9091.
27. MEEUSEN R, WATSON P, HASEGAWA H, ROELANDS B, PIACENTINI MF: Brain neurotransmitters in fatigue and overtraining. *Appl Physiol Nutr Metab* 2007; 32: 857-64.
28. MEEUSEN R, WATSON P, HASEGAWA H, ROELANDS B, PIACENTINI MF: Central fatigue: the serotonin hypothesis and beyond. *Sports Med* 2006; 36: 881-909.
29. LOUBINOUX I, PARIENTE J, RASCOL O, CELSIS P, CHOLLET F: Selective serotonin reuptake inhibitor paroxetine modulates motor behavior through practice. A double-blind, placebo-controlled, multi-dose study in healthy subjects. *Neuropsychologia* 2002; 40: 1815-21.
30. SAVITZ J, DANTZER R, MEIER TB *et al*.: Activation of the kynurenine pathway is associated with striatal volume in major depressive disorder. *Psychoneuroendocrinology* 2015; 62: 54-8.
31. CAPURON L, SCHROECKSNADEL S, FÉART C *et al*.: Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. *Biol Psychiatry* 2011; 70: 175-82.
32. LEE C-H, GIULIANI F: The role of inflammation in depression and fatigue. *Front Immunol* 2019; 10: 1696.
33. KRISTOFOOR E L, JEMIMA A: Muscle ultrasound in inflammatory myopathies: a critical review. *J Rheum Dis Treat* 2019; 5.
34. ALBAYDA J, VAN ALFEN N: Diagnostic value of muscle ultrasound for myopathies and myositis. *Curr Rheumatol Rep* 2020; 22: 82.
35. DASTMALCHI M, ALEXANDERSON H, LOELL I *et al*.: Effect of physical training on the proportion of slow-twitch type I muscle fibers, a novel nonimmune-mediated mechanism for muscle impairment in polymyositis or dermatomyositis. *Arthritis Care Res* 2007; 57: 1303-10.
36. TALBOT J, MAVES L: Skeletal muscle fiber type: using insights from muscle developmental biology to dissect targets for susceptibility and resistance to muscle disease. *Wiley Interdiscip Rev Dev Biol* 2016; 5: 518-34.
37. LIEBER RL, FRIDÉN J: Functional and clinical significance of skeletal muscle architecture. *Muscle Nerve* 2000; 23: 1647-66.
38. FUKUNAGA T, ICHINOSE Y, ITO M, KAWAKAMI Y, FUKASHIRO S: Determination of fascicle length and pennation in a contracting human muscle *in vivo*. *J Appl Physiol* 1997; 82: 354-8.
39. LUERA MJ, ESTRADA CA, HERNANDEZ-SARABIA JA, TROUNG J, MUDDLE TWD, DEFREITAS JM: A preliminary comparison of muscle pennation angle measures to explain variance in maximal force production. *Muscle Physiol Applications* 2018.
40. KAYA A, KARA M, TIFTIK T *et al*.: Ultrasonographic evaluation of the muscle architecture in patients with systemic lupus erythematosus. *Clin Rheumatol* 2013; 32: 1155-60.
41. SAHLIN K, TONKONOGI M, SÖDERLUND K: Energy supply and muscle fatigue in humans. *Acta Physiol Scand* 1998; 162: 261-6.
42. ALLEN DG, LAMB GD, WESTERBLAD H: Skeletal muscle fatigue: cellular mechanisms. *Physiol Rev* 2008; 88: 287-332.
43. WREDENBERG A, WIBOM R, WILHELMSSON H *et al*.: Increased mitochondrial mass in mitochondrial myopathy mice. *Proc Natl Acad Sci USA* 2002; 99: 15066-71.
44. MIRÓ O, CASADEMONT J, GRAU JM, JARRETA D, URBANO-MÁRQUEZ A, CARDELLACH F: Histological and biochemical assessment of mitochondrial function in dermatomyositis. *Br J Rheumatol* 1998; 37: 1047-53.
45. CAMPOS Y, ARENAS J, CABELLO A, GOMEZ-REINO JJ: Respiratory chain enzyme defects in patients with idiopathic inflammatory myopathy. *Ann Rheum Dis* 1995; 54: 491-3.
46. CHARIOT P, RUET E, AUTHIER FJ, LABES D, PORON F, GHERARDI R: Cytochrome c oxidase deficiencies in the muscle of patients with inflammatory myopathies. *Acta Neuropathol* 1996; 91: 530-6.
47. MOSLEMI AR, LINDBERG C, OLDFORS A: Analysis of multiple mitochondrial DNA deletions in inclusion body myositis. *Hum Mutat* 1997; 10: 381-6.
48. SANTORELLI FM, SCIACCO M, TANJI K *et al*.: Multiple mitochondrial DNA deletions in sporadic inclusion body myositis: A study of 56 patients. *Ann Neurol* 1996; 39: 789-95.
49. RYGIEL KA, MILLER J, GRADY JP, ROCHA MC, TAYLOR RW, TURNBULL DM: Mitochondrial and inflammatory changes in sporadic inclusion body myositis. *Neuropathol Appl Neurobiol* 2015; 41: 288-303.
50. CEA G, BENDAHAN D, MANNERS D *et al*.: Reduced oxidative phosphorylation and proton efflux suggest reduced capillary blood supply in skeletal muscle of patients with dermatomyositis and polymyositis: A quantitative 31P-magnetic resonance spectroscopy and MRI study. *Brain* 2002; 125: 1635-45.
51. ARGOV Z, TAIVASSALO T, DE STEFANO N, GENGE A, KARPATI G, ARNOLD DL: Intracellular phosphates in inclusion body myositis--a 31P magnetic resonance spectroscopy study. *Muscle Nerve* 1998; 21: 1523-5.
52. CARRY MR, RINGEL SP, STARCEVICH JM: Distribution of capillaries in normal and diseased human skeletal muscle. *Muscle Nerve* 1986; 9: 445-54.
53. MAHDY MAA: Skeletal muscle fibrosis: an overview. *Cell Tissue Res*. 2019; 375: 575-88.
54. MOYER AL, WAGNER KR: Regeneration versus fibrosis in skeletal muscle. *Curr Opin Rheumatol* 2011; 23: 568-73.
55. SCHILLINGS ML, STEGEMAN DF, ZWARTS MJ: Determining central activation failure and peripheral fatigue in the course of sustained maximal voluntary contractions: a model-based approach. *J Appl Physiol* 2005; 98: 2292-7.
56. MISSÉ RG, DE SOUSA LFA, SANTOS L DE M DOS *et al*.: Safety of transcranial direct current electrical stimulation in dermatomyositis: a case report. *Open J Rheumatol Autoimmune Dis* 2020; 10: 88-93.
57. LIEPERT J, KOTTERBA S, TEGENTHOFF M, MALIN JP: Central fatigue assessed by transcranial magnetic stimulation. *Muscle Nerve* 1996; 19: 1429-34.
58. DOUD JR, WALSH JM: Muscle fatigue and muscle length interaction: effect on the EMG frequency components. *Electromyogr Clin Neurophysiol* 1995; 35: 331-9.
59. JOSEFSON A, ROMANUS E, CARLSSON J: A functional index in myositis. *J Rheumatol* 1996; 23: 1380-4.
60. ALEXANDERSON H, STENSTRÖM CH, JENNER G, LUNDBERG I: The safety of a resis-

tive home exercise program in patients with recent onset active polymyositis or dermatomyositis. *Scand J Rheumatol* 2000; 29: 295-301.
61. ZONG M, DORPH C, DASTMALCHI M *et al*.:Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. *Ann Rheum Dis* 2014; 73: 913-20.
62. TJÄRNLUND A, TANG Q, WICK C *et al*.: Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. *Ann Rheum Dis* 2018; 77: 55-62.
63. RIDER LG, WERTH VP, HUBER AM *et al*.: Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis. *Arthritis Care Res* 2011; 63: 118-57.
64. ERNSTE FC, CHONG C, CROWSON CS, KERMANI TA, NI MHUIRCHEARTAIGH O, ALEXANDERSON H: Functional index-3: a valid and reliable functional outcome assessment measure in patients with dermatomyositis and polymyositis. *J Rheumatol* 2021; 48: 94-100.
65. RIDER LG, AGGARWAL R, MACHADO PM *et al*.: Update on outcome assessment in myositis. *Nat Rev Rheumatol* 2018; 14: 303-18.
66. ALFANO LN, LOWES LP, DVORCHIK I *et al*.: The 2-min walk test is sufficient for evaluating walking abilities in sporadic inclusion body myositis. *Neuromuscul Disord* 2014; 24: 222-6.
67. KERR CW, DRAKE J, MILCH RA *et al*.: Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* 2012; 43: 68-77.
68. MURILLO-RODRÍGUEZ E, BARCIELA VERAS A, BARBOSA ROCHA N, BUDDE H, MACHADO S: An overview of the clinical uses, pharmacology, and safety of modafinil. *ACS Chem Neurosci* 2018; 9: 151-8.
69. CHUNG YL, ALEXANDERSON H, PIPITONE N *et al*.: Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: Six-month, double-blind, randomized, placebo-controlled trial. *Arthritis Care Res* 2007; 57: 694-702.
70. SICILIANO G, SCHIRINZI E, SIMONCINI C, RICCI G: Exercise therapy in muscle diseases: open issues and future perspectives. *Acta Myol* 2019; 38: 233-8.
71. SICILIANO G, CHICO L, LO GERFO A, SIMONCINI C, SCHIRINZI E, RICCI G: Exercise-related oxidative stress as mechanism to fight physical dysfunction in neuromuscular disorders. *Front Physiol* 2020; 11: 451.
72. TIFFREAU V, RANNOU F, KOPCIUCH F *et al*.: Postrehabilitation functional improvements in patients with inflammatory myopathies: the results of a randomized controlled trial. *Arch Phys Med Rehabil* 2017; 98: 227-34.
73. WALLACE A, PIETRUSZ A, DEWAR E *et al*.: Community exercise is feasible for neuromuscular diseases and can improve aerobic capacity. *Neurology* 2019; 92: e1773-85.