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ORIGINAL ARTICLE

# Fatigue in Spinal Muscular Atrophy: a fundamental open issue

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**Hereditary proximal 5q Spinal Muscular Atrophy (SMA) is a severe neuromuscular disorder with onset mainly in infancy or childhood. The underlying pathogenic mechanism is the loss of alpha motor neurons in the anterior horns of spine, due to deficiency of the survival motor neuron (SMN) protein as a consequence of the deletion of the SMN1 gene. Clinically, SMA is characterized by progressive loss of muscle strength and motor function ranging from the extremely severe, the neonatal onset type 1, to the mild type 4 arising in the adult life. All the clinical variants share the same molecular defect, the difference being driven mainly by the copy number of SMN2 gene, a centromeric gene nearly identical to SMN1 with a unique C to T transition in Exon 7 that results in exclusion of Exon 7 during post-transcriptional processing. In all the types of SMA the clinical picture is characterized by hypotonia, weakness and areflexia. Clinical severity can vary a lot between the four main recognized types of SMA. As for the most of patients affected by different neuromuscular disorders, also in SMA fatigability is a major complaint as it is frequently reported in common daily activities and negatively impacts on the overall quality of life. The increasing awareness of fatigability as an important dimension of impairment in Neuromuscular Disorders and particularly in SMA, is making it both a relevant subject of study and identifies it as a fundamental therapeutic target. In this review, we aimed to overview the current literature articles concerning this problem, in order to highlight what is known and what deserves further research.**

**Key words:** SMA1, SMA2, SMA3, neuromuscular fatigue, skeletal muscle, SMN1 gene

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## Introduction

Neuromuscular disorders (NMD) encompass inherited and acquired diseases affecting, at any level, the motor unit: i.e. the second motor neuron in the anterior horns of the medulla, the nerves and roots, the neuromuscular junction (NMJ) and the skeletal muscle fibers.
Among the NMD, the hereditary proximal 5q Spinal Muscular Atrophy (SMA) is a severe disease mainly with infantile or childhood onset. SMA is due to the loss of alpha motor neurons in the anterior horns of the spine, caused by the lack of the survival motor neuron (SMN) protein as a consequence of the deletion of the SMN1 gene [1]. Clinically, SMA is associated with progressive weakness and motor impairment, ranging from the utterly severe form, the neonatal onset type 1, to the mild type 4 form with the onset in the adult life. All the clinical variants of the disease share the same molecular defect and the difference is mainly driven by the number of SMN2 gene copies. This is a centromeric gene nearly identical to SMN1 with a unique C to T transition in Exon 7 that results in the exclusion of Exon 7 during post-transcriptional processing. This defect leads to the production of nonfunctional SMN protein. Each SMN2 copy builds up only 10-15% of the functional SMN protein. So, in the absence of SMN protein due to the loss of SMN1 gene, SMN2 copies inversely relate to the clinical severity of the disease [2].

**Table I**. Different types of SMA.

| Type of SMA | Age of Onset | Symptoms |
|---|---|---|
| Type 1 (Werdnig-Hoffman disease) | 0-6 months | Severe muscle weakness, difficulty breathing, unable to sit or stand, may not survive beyond a few years |
| Type 2 | 6-18 months | Muscle weakness, difficulty standing or walking, may need support to sit up |
| Type 3 (Kugelberg-Welander disease) | Childhood, adolescence | Muscle weakness, able to walk but may have difficulty with balance and strength |
| Type 4 | Adulthood | Mild muscle weakness and tremors, usually able to walk and live a normal life |

In all the forms, SMA is characterized by hypotonia, weakness and areflexia. Without treatment, the most severe variant (type 1) invariably leads to early death from respiratory failure. The intermediate form (type 2) is characterized by stalled gross motor development but, generally, the ability to sit without support is maintained. The milder form with an onset after the 1st year of life (type 3) causes loss of ambulation later in life, whereas the mildest adult-onset form (type 4) causes relatively slight impairments in the adulthood [3-5]. The old and most used classification (types 1-4) (Tab. I) has been recently revised on the basis of the most recent natural history study and of the identification of prognostic factors, such as the age at onset: i.e. in type 3 SMA, an onset before 3 years of age is related with loss of ambulation usually in adolescence. Instead, an onset after 3 years of age is usually related with prolonged ambulation (Tab. I). Furtherly, as to the clinical management, a "functional" classification, subdividing the patients in non-sitters, sitters and walkers seems to be more useful in order to plan rehabilitation programs and to focus on the patient's clinical needs.

In NMD fatigue is a fundamental clinical feature. According to recent conceptualization based on experimental results [6], fatigue may be defined in terms of fatigability, to allow the normalization of the level of fatigue reported by an individual relative to the demands of the task that produces [7]. Thus, when a person reports the level of fatigue during an activity, the value at a specific time point will depend on the rates of change in its two attributes: performance and perceived fatigability. Perceived fatigability refers to the performer's sensations, modulated by fluctuations in body homeostasis and changes in the subject's psychological state [8]. This condition can be assessed when a person is either at rest or performing a physical task. Conversely, performance fatigability during ongoing activities comes from the rates of change in the central and peripheral factors used to regulate the performance pace [8].

In SMA, perceived fatigability and performance fatigability can parallel in common daily activities, such as driving power-wheelchair for a long time, eating – either as to lifting cutlery repeatedly either as to chewing food [9], and negatively impact on the overall quality of life. The increasing awareness of fatigue as an important clinical constraint in NMD and, particularly, in SMA, identifies it as relevant research topic and a fundamental therapeutic target [10-13].

## Fatigue in SMA

In SMA, fatigue has always been considered a fact, regardless of whether it arises from central, peripheral, or both causes. In 2021 Bartels et al. [14] exploring the relationship between fatigue and muscle strength in individuals with SMA, found that fatigue was significantly associated, yet not equivalent to, with reduced muscle strength, suggesting that fatigue may be a consequence of muscle weakness. The study also found that fatigue was associated with lower physical activity levels and poorer quality of life. Additionally, the study found that muscle strength was a significant predictor of fatigue, further supporting the idea that muscle weakness may contribute to fatigue [14]. These findings suggest that interventions aimed at improving muscle strength may also lead to improvements of the patient's fatigue and overall quality of life.

Attempts have been made to measure both perceived fatigue, possibly related to disease severity and concomitant emotional concerns, and motor fatigability. Unfortunately, questionnaires, such as Fatigue Severity Scale 15 and PROMIS [16], failed to demonstrate fatigue in SMA, as they both highlighted more perceived fatigue in Congenital Myopathies than in SMA, notwithstanding a total fatigue score higher than in the general population. Considering that a discrepancy exists between clinical observations and results from questionnaires, authors of both these papers concluded that these items probably unfit to properly highlight fatigue in this condition.

Furthermore, Wan et al. [17], reviewing different aspects in adult SMA, found that the general perception of fatigue is not related to the clinical and functional severity but to anxiety and depression, although these conditions are very rare in this population of patients.

On the other hand, electrophysiological and clinical tools have been successfully used to measure fatigability in motor function shedding some light onto the hypothetic pathogenic mechanisms of fatigue and seem capable to discriminate subgroups of patients [18-20]. Fatigue in SMA consists in progressively reduced motor responses in daily tasks, such as walking, using upper limbs and, in the most severe forms, even chewing. In particular, chewing fatigue was found both in ambulant and not ambulant patients, appears 30% faster than in their respective controls [12,21,22] and worsen in a time frame of 2-5 years in type 3 patients [23]. In ambulant SMA the 6 Minutes Walk Test (6MWT), instead, was studied with the attempt to quantify fatigue [24]. The electromyography (EMG) technique has been used to study the correlation between force of bite and masticatory muscular activation, clearly showing that SMA patients require increasingly muscle activity to achieve a given amount of force and that, if patients are asked to generate the same amount of force as controls, the time of task inevitably shorten [12]. However, it should be considered that this finding could be not related to the severity of the NMD [21].

Among the clinical variants, SMA type 3 patients seem to be the ones who mostly experience fatigue [19]. The reasons why this happens is not entirely clear, as the underlying mechanisms that cause

fatigue in SMA are not well understood. However, it is likely that fatigue in SMA is related to the progressive muscle weakness and atrophy but is also probable that better outcome measures to quantify and track fatigability are available in the relatively milder phenotypes. Furthermore, it should be considered that these outcome measures could be more relevant in capturing perceived and performance fatigability as a problem in milder phenotypes because the activities required, and the questionnaire questions are more likely suitable to patients with a greater level of muscle strength. Indeed, a greater impairment may be linked to a reduced overall functionality that may lead to a lower level of physical activity and, consequently, to lower fatigue.

The correlation between fatigue and SMA type 3 has been demonstrated by using the 6MWT as a functional fatiguing task widely accepted by regulatory agencies as a clinically meaningful endpoint in many NMD [25, 26]. In the 6MWT the gait velocity and the stride length describe fatigue in ambulant SMA, suggesting its validity as an outcome measure. In fact, the change in gait velocity between the beginning and the end of the task, cannot be attributed to muscle weakness as patients with other NMD, such as Duchenne muscular dystrophy (DMD), have a more regular pace and do not show any obvious decrease over subsequent minutes, as observed in SMA [11]. SMA patients manifest around 17% reduction in performance from the first to the sixth minute of the test [11,24,27]. This change has been found in the most (73.3%) but not in all type 3 SMA patients. Considering this subgroup, the signs of fatigue were more common in type 3a SMA (almost 100% without reliance with the total distance covered 6MWT or to age), with onset by 3 years of age expected to lose ambulation later in life, than in 3b (around 50%), with later disease presentation and not expected to lose ambulation.

Using low-rate (3-Hz) repetitive nerve stimulation (LRNS) a decrement (> 10%) response was found in 17 out of 35 (49%) SMA types 2 and 3 patients, unlike in healthy controls or subjects affected by other motor neuron disease [28]. This decrement was considered as a reliable index of excessive fatigability of the upper limbs in the patients [28]. The abnormal response was not specific for the SMA subtype, nor it appeared to be associated with the compound muscle action potential amplitude, the clinical scores, or the disease duration. Importantly, in both neurophysiological [28] and clinical [27] studies, signs of fatigue were not consistent across all the ambulant type 3 patients. A couple of studies have examined the correlation between the outcomes of the 6MWT and the response to LRNS in SMA patients [27,29], showing a strong correlation between the two measures.

Overall, observations during prolonged isometric muscle contractions [12] and 6MWT [24,30] highlight that abnormal performance fatigability represents an additional aspect of the attenuated motor function in SMA [31].

Fatigue has also fundamental implications in the possibility to consider exercise as part of the therapeutical management in patients affected by SMA. In humans, it has been found that the effects of exercise are different from those expected on the basis of the animal studies. In fact, it has been found that, in animal models of SMA, exercise training has a positive effect on survival, muscle weakness and motor behaviors [32-35]. These adaptations to training are driven, at least in part, by the upregulation of the SMN gene expression as well by alternative neuroprotective mechanisms [36]. In humans, available data suggest strength and motor improvements in type 2 or 3 SMA patients underwent to prolonged resistance-type exercise interventions [37].

Nevertheless, Madsen et al. [38], investigating the effects of a six-month endurance cycle training program on the aerobic capacity and functional abilities in SMA 3, found a significant improvement of the oxidative metabolism ($VO_{2max}$) without amelioration of the skeletal muscle function. These findings highlight the complex nature of SMA and the challenges associated with developing effective treatments for this condition. While improving aerobic capacity may be beneficial for individuals with SMA, it may not necessarily lead to improvements in overall physical function, which is influenced by a range of factors beyond aerobic fitness.

Importantly, this exercise paradigm was associated with unexpected worsening of fatigue.

As a whole, available data do not allow to safe conclusions on whether endurance or resistance type exercise is useful or not in SMA [39].

## Pathogenetic mechanisms

Data reported on fatigue in SMA point to the key role of peripheral contributors such as alterations in NMJ and the cell metabolism [9,28,40-43]. In particular, physiological alterations of the synaptic transmission, as well as energy depletion due to the loss of muscle glycogen, followed by lactate accumulation and reduced ATP availability, significantly contribute to its arising. On the other hand, there is no clear understanding of the potential impact of these metabolic changes on the central components of fatigue.

At the NMJ level, the lack of SMN is probably responsible for alterations in the physiological process underlying its development and maturation. Importantly, in neonatal SMN knockout mice a severe neuromuscular phenotype has been reported, whereas a milder phenotype has been observed when SMN depletion was obtained after the NMJ maturation (after P17) or in the adulthood. Together these findings highlight the fundamental role of NMJ in SMA [44,45].

Another role of SMN has been also described at the presynaptic terminals. In fact, it appears to directly interact with the heterogeneous nuclear ribonuclear protein R. This localization identifies the involvement of SMN in RNA particles recruitment and transport into the axons and the axon terminals [46]. Therefore, it can be hypothesized that, although the lack of SMN may be considered the determinant of motor neurons loss in SMA, retrograde signals coming from muscles and NMJs, can be also contributors for its dysfunction [47].

Changes in motor neuron excitability and firing patterns may also play a role in fatigue as suggested in animal models [48,49]. These alterations may add to postsynaptic abnormalities as observed in the NMJs from human muscle samples in type 1, 2 and 3 SMA patients [28,43] and are possibly related to muscular denervation occurring in SMA.

Apart the NMJ, laboratory evidences suggest that SMN deficiency may also impair the muscle mitochondria thus identifying this additional target to be considered for future studies on the pathogenesis of fatigue in SMA [39,50].

## Fatigue response to therapy

Being fatigue a relevant constraint in SMA, it has been proposed as a fundamental endpoint in clinical trials and as an outcome measure to be evaluated in clinical practice.

Since 2017 Nusinersen is used as pharmacological therapy in SMA and more therapies will come in the next future. Nusinersen is an antisense oligonucletotide able to induce SMN2 gene to produce full length SMN protein. Ambulant children and adolescents treated with Nusinersen show ameliorations in the 6MWT, consisting of clinically meaningful increases in walking distance and modest improvement of fatigue.

On the other side, no effects have been demonstrated on ambulation and fatigue following treatment with dalfampridine-ER (4-AP) [51], a chemical voltage- sensitive potassium channels blocking agent that acts on the central and peripheral nervous system [52], prolonging action potentials and thereby increasing neurotransmitter release at the NMJ [53]. This drug has been proved to be effective in increasing five-fold the average EMG twitch and EMG peak to peak in canine motor neuron disease, a condition comparable to the human SMA [54]. Finally, the results from the clinical trial proposed by Stam et al. [55] using pyridostigmine [56,57] are currently available. These authors [56] show a self-reported reduction in fatigability and improved endurance shuttle test (EST) combined score performance in patients presenting SMA type 2 and 4; Habets et al. [57] report that patients with SMA type 2 and 3 using pyridostigmine had fourfold smaller decreases in frequency and twofold smaller increases in amplitudes of the sEMG signals in skeletal muscles recorded during endurance shuttle tests (ESTs). Overall, both experimental observations indicate the role of pyridostigmine as a valuable therapy for reducing fatigability in SMA patients.

Gene therapy is an emerging treatment approach for SMA that aims to address the underlying genetic cause of the condition. It involves introducing a functional copy of the SMN1 gene into the cells using a viral vector carrying the functional gene. There are currently two FDA-approved gene therapies for SM: onasemnogene abeparvovec (Zolgensma) (https://www.fda.gov/news-events/press-announcements/fda-approves-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-gene-therapy-onaa) and risdiplam (Evrysdi) (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-oral-treatment-spinal-muscular-atrophy). Onasemnogene abeparvovec is a one-time infusion that delivers a functional copy of the SMN1 gene to motor neurons, while risdiplam is an oral medication that increases the production of SMN protein by modifying the way the body processes RNA. Gene therapy for SMA has shown promising results in clinical trials [58-61], with many patients experiencing significant improvements in motor function and quality of life. However, there are still limitations and potential risks associated with the treatments [62,63].

There is limited research on the specific effects of central (intrathecal) versus systemic (oral or IV) SMN-based therapies on fatigability in SMA, but it can be speculated that these treatments may differently affect it. Intrathecal SMN-based therapies, such as Nusinersen, target the spinal cord directly and are designed to increase SMN protein production in motor neurons. While these treatments have been shown to improve motor function and survival in individuals with SMA, their impact on fatigue is less clear. Binz et al. [64] found that the treatment with Nusinersen was associated with a trend towards improvements in fatigue and quality of life in a small population of type 2, 3 and 4 SMA patients. On the other side, systemic SMN-based therapies (risdiplam and onasemnogene abeparvovec), designed to increase SMN protein levels, may have broader systemic effects including functional improvement and beneficial effects on fatigability. Notwithstanding these encouraging results, further research is needed to better understand the specific effects of different SMN-based therapies on fatigue.

Considering non-pharmacological intervention in SMA, physical exercise may be considered. Of importance, while exercise-induced fatigue is a common symptom reported by SMA patients [65], regular exercise may lead to potential benefits. However, to date, the available results need to be confirmed and/or clarified. Montes et al. (2015) report that daily exercise, at a volume recommended for all Americans, including those with disability [66], appears to be safe and feasible in ambulatory SMA 3 children and adults, without deleterious effects on fatigue [67]. Other studies have also suggested that exercise interventions, such as aerobic training, in SMA type 2 patients [68], or resistance training, in animal models [35], may be beneficial. In this regard, further research is needed to understand the optimal exercise regimen. This need seems to be in line with results from the aforementioned Cochrane Review by Barthels et al. (2019) [39] which underpinned that, due to the low quality of evidence, studies adopting protocols that meet international standards for the development of training interventions are still required.

Overall, the current available literature on the topic suggests that high quality experimental trials are needed to unravel whether therapies, including pharmacological and non-pharmacological interventions, are able to really impact on fatigability in clinical subcategories of patients experiencing different levels of performance and perceived impairments.

## Conclusions

Fatigue has been recognized as a main clinical feature in SMA, as reported by patients themselves and as demonstrated by functional and electrophysiological tests. The impact of fatigue in everyday life of patients prompted the scientists to consider it among the fundamental outcome measures in studies regarding the patient's Quality of Life either in the ones aimed at verifying the efficacy of possible new treatments for the disease. Available studies published on fatigue in SMA focus on defining and measuring this condition and correlating it to motor function tests. Questionnaires aimed at measuring perceived fatigue and possible links with emotional aspects of patients should be individuated, due to the low significance of the available studies. Few evidences concern the causes of fatigue and the possible therapies while several works take into account exercise in SMA, both in humans and animal models. Nevertheless, the role of fatigue as a limiting factor of the patients access to exercise programs and *vice versa* to what extent exercise may positively impact on perceived and performance fatigability in SMA should be further elucidated. Moreover, potential dissimilarities between child and adult SMA patients' perception of fatigue, as well as its possible correlation with

peculiar comorbidities, such as scoliosis or respiratory involvement, would be important topics for future experimental studies.

### Conflict of interest

The authors declare no conflict of interest.

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### Author's contributions

OC wrote the first draft of the manuscript; OC, AB, and GD reviewed the research. AB and GD critically revised the manuscript. All authors approved the final version of the manuscript.

### Ethical consideration

The research was conducted ethically, with all study b procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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