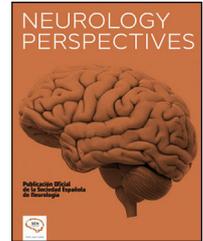




NEUROLOGY PERSPECTIVES

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ORIGINAL ARTICLE

Physical fatigue and perceived fatigability in adolescents and adults with spinal muscular atrophy: A pilot study



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KEYWORDS

Spinal muscular atrophy;
Fatigue;
Fatigability;
Physical fatigue;
Perceived fatigability

Abstract

Introduction: Fatigability is a frequent phenomenon in spinal muscular atrophy (SMA). However, there is a lack of scales designed for and validated in SMA patients to determine the frequency and impact on daily life of physical fatigue and perceived fatigability in these patients.

Material and methods: This is an observational cross-sectional study in a cohort of patients older than 14 years with genetically confirmed SMA. We used a new questionnaire (*PROfuture*) designed to assess physical fatigue and perceived fatigability, and classified patients with SMA according to their functional status as non-sitters, sitters, and walkers.

Results: Fifty-one patients completed the questionnaire. More than half of them reported symptoms of physical fatigue, although the frequency and type of symptoms varied between functional groups. Non-sitters reported a greater impact of physical fatigue on daily activities, while walkers more frequently presented fatigue associated with overexertion. Regarding perceived fatigability, non-sitters reported it most frequently when performing activities that involve the upper limbs and axial muscles, followed by sitters. Walkers presented high perceived fatigability in the lower limbs, but lower severity in the upper limbs.

Conclusion: Physical fatigue and perceived fatigability in patients with SMA are very frequent and affect activities of daily living. Therefore, their assessment should be included in the routine

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follow-up of these patients. A holistic approach to the fatigue–fatigability phenomenon in SMA is essential to understanding its pathophysiology and achieving an adequate therapeutic management.

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PALABRAS CLAVE

Atrofia muscular espinal;
fatiga;
fatigabilidad;
fatiga física;
fatigabilidad percibida

Estudio piloto de la fatiga física y la fatigabilidad percibida en el paciente adolescente y adulto con atrofia muscular espinal

Resumen

Introducción: La fatigabilidad es un fenómeno frecuente en la atrofia muscular espinal (AME). Sin embargo, no disponemos de escalas validadas y diseñadas para AME que nos permitan medir la frecuencia y repercusión en la vida diaria de la fatiga física y la fatigabilidad percibida en estos pacientes.

Material y métodos: Estudio transversal observacional en una cohorte de pacientes mayores de 14 años con AME con confirmación genética utilizando un nuevo cuestionario (*PROfuture*) para determinar la fatiga física y la fatigabilidad percibida. Los pacientes se clasificaron según su funcionalidad en *non-sitters*, *sitters* y *walkers*.

Resultados: 51 pacientes completaron el cuestionario. Más de la mitad presentaban algún síntoma de fatiga física, aunque la frecuencia y tipo de síntomas variaron según el grupo funcional. Los *non-sitter* son los que refieren un mayor impacto de la fatiga física en las actividades diarias (37–75%), mientras que los *walkers* presentan una mayor sensación de cansancio asociado a esfuerzos. Respecto a la fatigabilidad percibida, los *non-sitter* registran una mayor frecuencia en actividades que implican a miembros superiores (74–100%) y musculatura axial (67–78%), seguidos de los *sitters* (22–95%). Los *walkers* presentan elevada fatigabilidad percibida en miembros inferiores (67–87%), pero escasa en los superiores (17%).

Conclusión: La fatiga física y la fatigabilidad percibida por los pacientes con AME son síntomas muy frecuentes y afectan a actividades básicas de la vida diaria, por lo que deberían evaluarse en el seguimiento rutinario de los pacientes. Una aproximación holística al fenómeno fatiga-fatigabilidad en la AME es esencial para entender su fisiopatología y realizar un adecuado abordaje terapéutico.

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Introduction

Spinal muscular atrophy (SMA) is a genetic neurodegenerative disease caused by a homozygous deletion and/or mutation of the *SMN1* gene, and affects the lower motor neurons almost exclusively.^{1–3} Although weakness and progressive muscular atrophy are the most frequent symptoms of SMA, fatigue and fatigability are also frequent and potentially disabling manifestations.^{4–8} However, these are frequently overlooked in current clinical practice. This is due to the lack of a standardised concept of these phenomena, which has hindered the study and general understanding of symptoms, the development of diagnostic methods, and the implementation of specific therapies.^{9–11}

First, we should distinguish between fatigue and fatigability.^{9,12} Fatigue is defined as perceived mental and physical exhaustion that interferes in daily living activities. This is a subjective symptom and, therefore, may only be

identified using questionnaires assessing its severity and impact on daily life. Fatigue may be further subdivided into several categories, mainly mental and physical fatigue.¹¹ The assessment of physical fatigue is especially relevant in SMA, as it is the type expected to be most strongly associated with the pathophysiology of the disease and thus to respond to specific treatments.^{9,12,13}

Fatigability is the clinical sign that characterises the decrease in physical performance over the duration of a task.^{9,12,14} In SMA, fatigability manifests as a result of the instability of the neuromuscular junction.^{15–17} Therefore, it is assessed using physical tests involving the repetition of tasks using submaximal strength, such as the Six-Minute Walk Test, the Nine-Hole Peg Test, or the Endurance Shuttle Walk Test.^{10,15,17–20} Although these tests enable us to determine the presence of fatigability, they do not reflect its real impact on the activities of daily living. This gives rise to a need to assess perceived fatigability, understood as a variant of the

physical dimension of fatigue that reflects the impact of decreased motor performance on the activities of daily living.^{21,22}

Furthermore, drug regulators recommend using patient-reported outcome measures (PROM) to assess the positive impact of different treatments on patients' lives.²³

There is currently no specific, validated tool for assessing symptoms of physical fatigue and fatigability in patients with SMA. In this study, we aimed to describe the frequency of symptoms of fatigue and perceived fatigability in order to determine their impact on activities of daily living and to conduct a preliminary analysis of a new, ad hoc questionnaire.

Material and methods

Study design

This is a descriptive, cross-sectional study based on patients' responses to the "Fatiga y Fatigabilidad" (Fatigue and Fatigability) scale designed by the FundAME Foundation. The scale is part of the PROfuture questionnaire, which is included in a patient registry (<https://wacean.com/registroame>) developed and promoted by FundAME,^{7,22} which published the questionnaire online and collected users' responses. These data were subsequently provided for analysis and interpretation by the neuromuscular diseases unit of Hospital Universitari i Politècnic La Fe.

Patients

We included the responses of patients with SMA who met the inclusion criteria and completed the questionnaire between 1 May and 30 November 2020.

We included patients with a genetically confirmed diagnosis of the disease (5q13 chromosome alteration consisting of homozygous deletion or mutation of the *SMN1* gene), aged 14 years or older.

Exclusion criteria were not signing the informed consent form or not having completed at least half of the questionnaire.

Four patients were excluded from the study based on these criteria.

Variables

We recorded the following variables: age, age at symptom onset, type of SMA, functional classification, genetic study, number of *SMN2* copies, maximal motor milestone achieved, wheelchair use, surgery for scoliosis, specific treatment for SMA, feeding by percutaneous endoscopic gastrostomy or nasogastric tube, and use of non-invasive mechanical ventilation.

The items included in the scale may be consulted in the supplementary material. Questions refer to the presence of these symptoms over the past 7 days. Questions on physical fatigue address 5 aspects: need to rest during the day, need to select activities, difficulty in maintaining posture, loss of energy over the course of the day, and presence of prolonged tiredness after making a greater effort than usual. In the section on fatigability, participants are asked about the inability to finish a task once started, referring to activities of

daily living that require sustained and repeated use of the upper limbs (taking written notes, sending text messages, combing the hair, brushing the teeth, and eating without help), axial muscles (sitting up straight, holding the head upright), and lower limbs (climbing a flight of stairs, walking at a steady pace, standing up from a chair or bed, getting in or out of a car). Therefore, participants unable to initiate the task did not respond to the corresponding item.

After the preliminary review of the results, we decided to eliminate item no. 8 (*) from the "Perceived fatigability in upper limbs and axial muscles" section, given the low number of responses received.

It should be noted that the "Physical fatigue and endurance" section initially had 5 possible answers (never/almost never/sometimes/nearly always/always) and the "Perceived fatigability" section had another 5 options (impossible/very difficult/difficult/somewhat easy/easy). We decided to group answers in 3 categories (never or almost never/sometimes/always or nearly always) in the "Physical fatigue and endurance" section and 4 (impossible/difficult or very difficult/a bit difficult/easy) in the "Perceived fatigability" section, with the aim of facilitating the interpretation of results, as some options were rarely selected.

Statistical analysis

With the data obtained, we performed a descriptive analysis using the mean (standard deviation) and median (percentiles 25 and 75) of quantitative variables, and the frequency (percentage) of qualitative variables.

Some results are represented as graphs to facilitate their interpretation. Graphs were plotted using the Excel software, version 19 (2018). Statistical analysis was performed using the R statistics software (version 4.0.5).

Results

Sample characteristics

The sample included 51 patients with SMA, with a mean age (at the time of completing the questionnaire) of 31.9 years (SD: 13.92). Median age at symptom onset was 15.5 months. By functional classification, our sample included 16 non-sitters (31.37%), 20 sitters (39.22%), and 15 walkers (29.41%). Almost half of the patients (47%) reported following a specific treatment. The demographic and clinical characteristics of the sample are shown in Table 1.

Content validity

After external review by experts from Hospital Universitari i Politècnic La Fe, the questionnaire was considered to present content validity and to be adapted to the functional status of patients with SMA. Furthermore, it refers to relevant activities of daily living, such as hygiene, feeding, and communication. However, one question was excluded from the "Perceived fatigability" section (referring to the fatigability in the upper limbs during games) due to the low response rate. Furthermore, the activities proposed in this section (brushing the teeth, combing the hair, writing, etc)

Table 1 Patients' demographic and clinical characteristics.

	Mean (SD)/n (%) Median (p25-p75)
<i>Total participants</i>	51
<i>Age (years)</i>	31.9 (13.92) 27 (20–42.5)
<i>Mean age at symptom onset (months)</i>	37.92 (54.49) 15.5 (11.25–33)
<i>Functional classification:</i>	
Non-sitter	16 (31.37%)
Sitter	20 (39.22%)
Walker	15 (29.41%)
<i>Type of SMA:</i>	
SMA type 1	1 (1.96%)
SMA type 2	27 (52.94%)
SMA type 3	22 (43.14%)
SMA type 4	1 (1.96%)
<i>SMN2 copies</i>	
2	1 (2.33%)
3	29 (67.44%)
4	13 (30.23%)
<i>Highest motor milestone achieved</i>	
Walking independently	23 (46%)
Standing or walking a few steps with the help of a third party or a device	10 (20%)
Remaining seated independently	15 (30%)
None of the above	2 (4%)
<i>Motor function of the arms and hands</i>	
I can lift my arms above my head	18 (36%)
I can bring my hands to my mouth	23 (46%)
I cannot bring my hands to my mouth but my hands do have useful motor function	6 (12%)
I have no motor function in the hands	3 (6%)
<i>Use of wheelchairs</i>	
No, I do not use one	10 (19.61%)
Yes, sometimes	4 (7.84%)
Yes, permanently	37 (72.55%)
<i>Specific treatment</i>	
Yes	24 (47.06%)
No	27 (52.94%)
<i>Surgery for scoliosis</i>	
Yes	25 (50%)
No	25 (50%)
<i>Genetic study</i>	
Deletion of both copies (in homozygosis) of the <i>SMN1</i> gene	49 (96%)
Deletion of one copy and point mutation of the other copy of the <i>SMN1</i> gene	2 (4%)

may not adequately reflect perceived upper limb fatigability in walkers, as they require little effort. We should also highlight the fact that the third item on physical fatigue, which assesses patients' limitations in maintaining posture throughout the day, includes a question on an issue that is already adequately addressed in the "Perceived fatigability in axial muscles" section; thus, its inclusion in this section is

redundant. Likewise, with a view to facilitating the interpretation of results, we opted to remove some of the options that were selected infrequently, as the variety of options did not lead to better understanding of the SMA phenomenon.

Results in the "Fatigue and fatigability" section, according to functional capacity

Overall, 84% of patients with SMA reported some symptom of physical fatigue, with the need to select activities (52%), and loss of energy over the course of the day being the most frequent (52%). On the other hand, the need to rest was the least frequent (39%).

Fig. 1 presents the responses according to functional group. As can be seen, physical fatigue manifests unevenly between functional groups, with non-sitters and walkers being more frequently affected (87%) than sitters (80%). However, the most frequent symptoms vary considerably between groups. Thus, compared to other groups, non-sitters more frequently needed to rest during the day (item 1) and to select activities (item 2) and presented greater difficulty maintaining posture (item 3) and a greater sensation of loss of energy (item 4) at the end of the day.

In sitters, we observed a greater difficulty maintaining posture (item 3) than in walkers, and less need to rest during the day (item 1) than in the remaining groups.

Walkers, in turn, did not show difficulty maintaining posture, and had less need to select activities during the day (item 2). However, they did show an increased need to rest during the day (item 1) and greater reduction in their ability to perform activities throughout the day (item 4), as compared to sitters. Furthermore, walkers were the group most frequently experiencing prolonged tiredness after making a greater effort than usual (item 5).

Results in the "Perceived fatigability in the upper limbs" section, according to functional capacity

Fig. 2 shows the results obtained in the "Perceived fatigability in the upper limbs" section, according to functional capacity.

As expected, we observed a higher frequency of perceived fatigability in the upper limbs in non-sitters (74%–100%), followed by sitters (22%–95%), and lastly, walkers (17%).

In short, taking written notes (item 6), combing the hair (item 8), brushing the teeth (item 9), and eating without help (item 10) are difficult to perform for non-sitters, whereas sending text messages is easier for them. Sitters generally presented mild or moderate difficulties performing basic activities of daily living such as brushing the teeth (item 9), or eating without help (item 10), and greater difficulties when combing the hair (item 8), whereas taking written notes or sending text messages was easier for most of these patients. In the case of walkers, only 17% perceived mild fatigability when performing tasks that involve the use of the upper limbs.

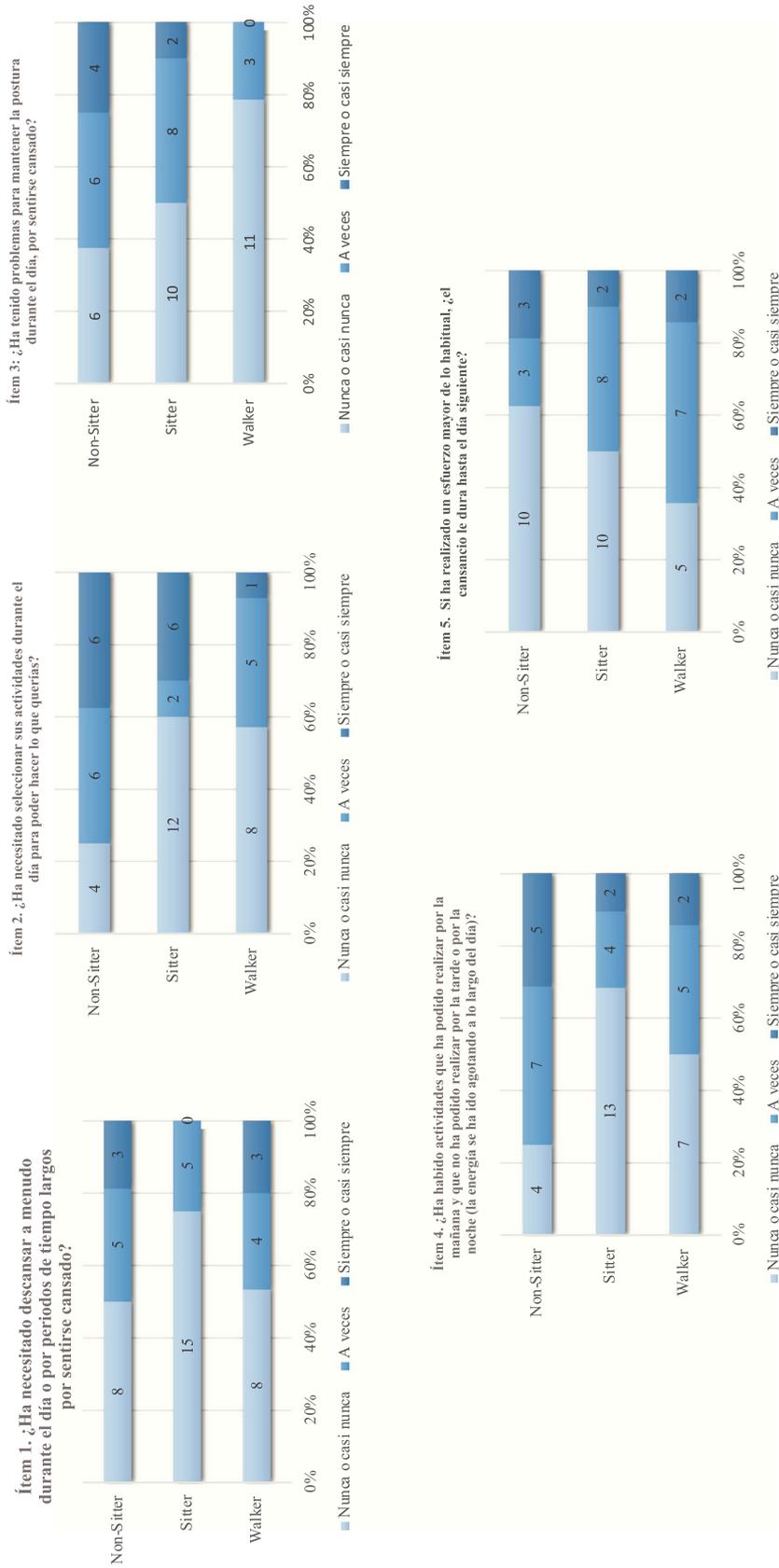


Fig. 1 Results in the “Fatigue and fatigability” section, according to functional subgroup.

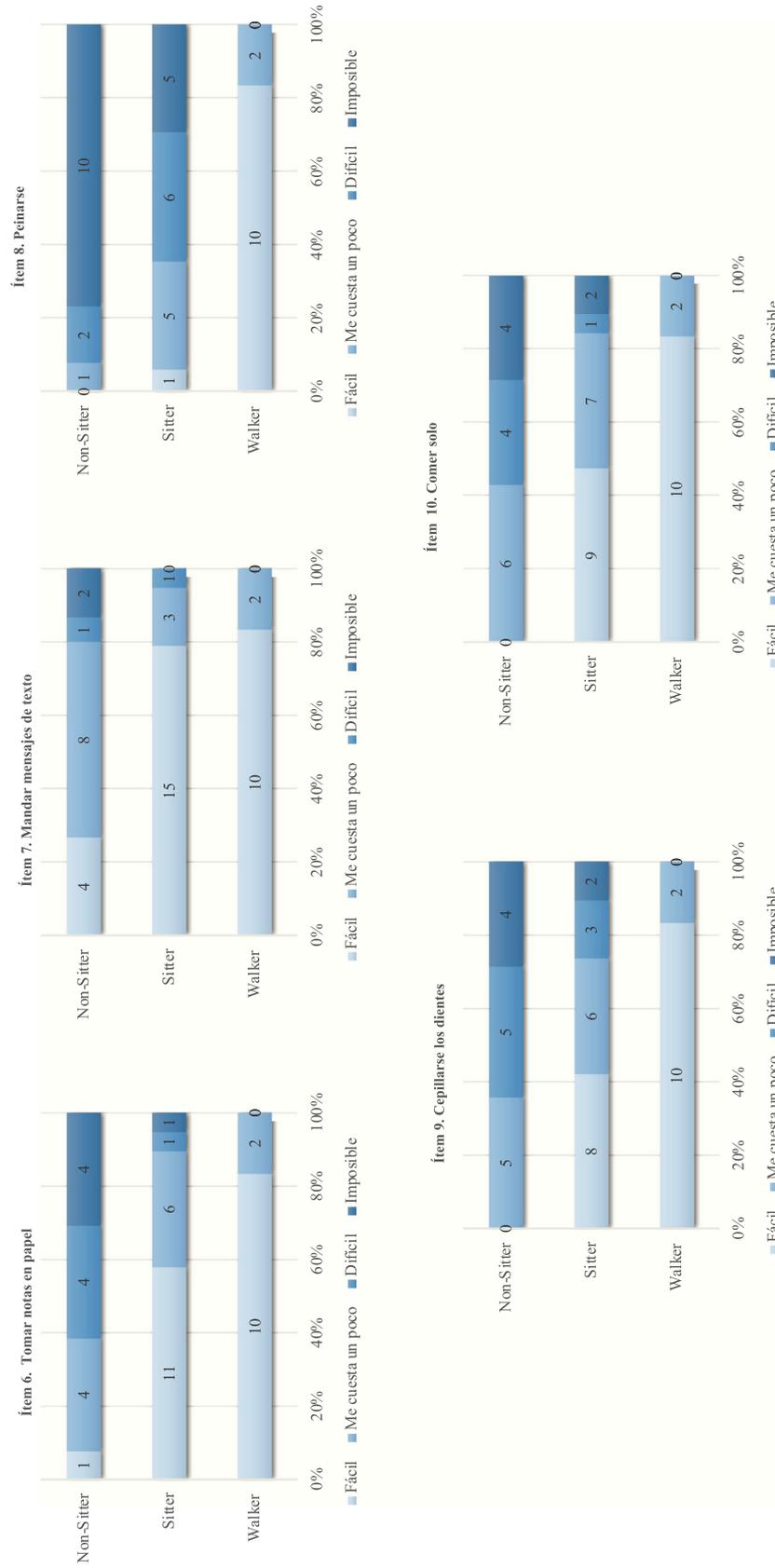


Fig. 2 Results in the "Perceived fatigability in the upper limbs" section according to functional subgroup.

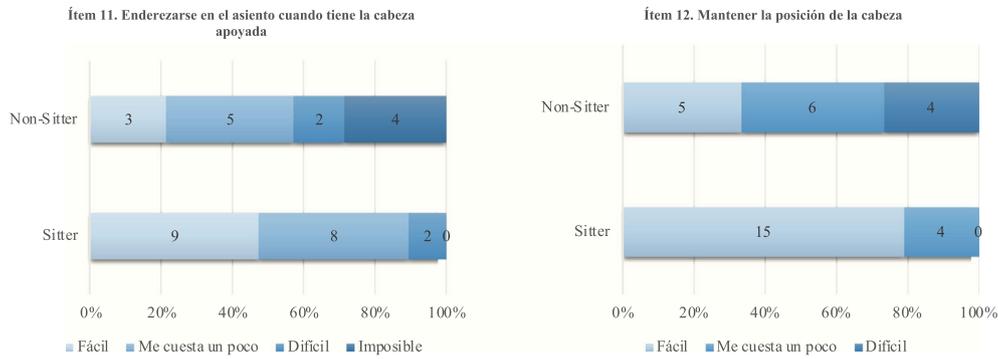


Fig. 3 Results in the “Perceived fatigability in the axial muscles” section in non-sitters and sitters.

Results in the “Perceived fatigability in the axial muscles” section in non-sitters and sitters

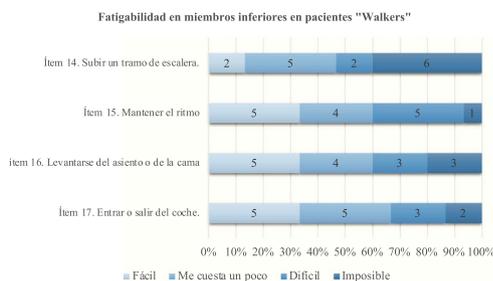
Fig. 3 shows the results of the “Perceived fatigability in the axial muscles” section, which are only available for non-sitters and sitters. It should be noted that these items refer to the ability to perform these actions repeatedly.

Once more, we observed a greater frequency of perceived fatigability in the axial muscles in non-sitters (67%–78%), as compared to sitters (22%–63%). Forty-three percent of non-sitters were unable or found it difficult to sit up straight. Likewise, 27% of them had difficulties holding their head upright. In contrast, only 10% of sitters presented significant limitations sitting upright and none reported having difficulties holding their head upright.

Results in the “Perceived fatigability in the lower limbs” section in walkers

Fig. 4 shows the results obtained in the “Perceived fatigability in the lower limbs” section. Items are exclusively applicable to walkers, as the remaining groups are unable to perform these activities.

Most walkers (67%–87%) reported symptoms of fatigability in repetitive activities involving the lower limbs, unlike their results for activities involving the upper limbs. The most difficult task to complete was climbing a flight of stairs (item 14), which was impossible for 40% of these patients. Furthermore, 40% of walkers found it impossible or difficult to walk at a steady pace (item 15), and to stand up from a



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Fig. 4 Results in the “Perceived fatigability in the lower limbs” section in walkers.

chair or bed (item 16), whereas 33.3% of patients presented limitations or found it impossible to get in or out of a car (item 17).

Discussion

Physical fatigue in patients with SMA

From a clinical viewpoint, SMA is a very heterogeneous disease, and can be highly incapacitating. The development of such disease-modifying treatments as nusinersen, risdiplam, and onasemnogene abeparvovec, as well as such symptomatic treatments as sulbutamol and pyridostigmine,²⁴ represents a paradigm shift in the management of these patients. In this context, the development of specific PROMs for patients with SMA is a fundamental aspect to establishing the effectiveness of these treatments in clinical practice, as reported by several recent publications.^{7,8,22,25} One cause of disability in SMA may be fatigability, a very frequent phenomenon in these patients, which seems to respond to several treatments.^{26–28} Therefore, it is essential to develop PROMs to assess fatigue and perceived fatigability.

Fatigue is a complex phenomenon that involves motor, cognitive, and emotional mechanisms, among others, which ultimately lead to a sensation of exhaustion in patients experiencing it. Although fatigue is a multidimensional phenomenon, the physical dimension is especially relevant in SMA, as it is associated with the pathophysiology of the disease, making it a target for improvement with specific treatments.^{5,29} In contrast, mental fatigue seems to be more strongly associated with sociodemographic factors not directly linked to the disease (such as age, level of schooling, depression, anxiety, sleep, etc) and appears not to respond to disease-modifying treatments.⁵

Several unidimensional and multidimensional scales are currently available to assess fatigue in patients with neurological diseases. The main issue with applying unidimensional scales in SMA is the physical dimension of fatigue, which is the most relevant in neuromuscular diseases, as it may be diluted when combined with cognitive or emotional symptoms that are not directly related with the pathophysiology of the disease.^{22,29} In turn, multidimensional scales individually analyse the different aspects of the symptom. However, interpreting the results is complicated, as these scales are not specifically designed for the disease; as a

result, most patients may be unable to answer some of the items, and fatigue may not be detected.⁵

Although several studies have analysed fatigue in SMA from a multidimensional perspective, all of them present 3 significant limitations: small sample sizes, the use of various unvalidated scales that are not designed for patients with SMA, and the application of heterogeneous methods. It is therefore unsurprising that these studies report very diverse prevalence rates (10%–79%), that they were unable to detect improvements after using disease-modifying drugs, and that demographic or clinical factors related to the presence of fatigue in these patients currently remain unknown.^{5,13,28–31}

The new questionnaire developed by FundAME is intended to meet the increasing need to incorporate a disease-specific PROM assessing these phenomena in patients with SMA in both the clinical and research settings.⁷ This pilot study shows that physical fatigue and perceived fatigability are frequent phenomena in all 3 functional groups (and particularly in non-sitters), although with considerable qualitative and quantitative differences.

The greater prevalence of symptoms (need to rest during the day and to select activities, difficulty maintaining posture, and sensation of loss of energy) among non-sitters suggests that physical fatigue is associated with the motor reserve, which had previously been observed with fatigability.¹⁶ However, walkers presented greater need to rest during the day and a greater decrease in the ability to perform activities throughout the day than sitters; they are also the group most frequently presenting prolonged tiredness after making a greater effort than usual. We should not forget that the activities performed by the patients in each functional group are very diverse. This may explain the fact that sitters presented more difficulties than walkers in maintaining posture, but fewer problems performing activities throughout the day and less tiredness after making a greater effort than usual (probably because sitters perform fewer activities and efforts than walkers). In this case, patients with the greatest functional capacity present more tiredness after a prolonged effort, possibly because they are the group most frequently performing this type of overexertion. Thus, this suggests that physical fatigue is also related to the level of physical activity in their everyday life.

Perceived fatigability in patients with SMA

Unlike fatigue, fatigability is a widely studied phenomenon in SMA. Multiple specific, validated diagnostic methods are currently available to identify the objective decrease in motor performance.^{10,15,19,32,33} However, no validated tool currently exists for detecting perceived fatigability in patients with SMA and its impact on activities of daily living.

This pilot study shows that perceived fatigability is a very frequent symptom with a negative impact on the activities of daily living in patients with SMA. Nevertheless, its onset pattern and characteristics are also influenced by functional status, with non-sitters experiencing it most frequently, followed by sitters, and lastly by walkers. This is consistent with findings from previous studies that concluded that fatigability was negatively correlated with motor function.²⁰

Likewise, previous studies (using the Nine-Hole Peg Test) have shown that fatigability of the upper limbs is very frequent in patients with SMA (25% of walkers, 37%–53% of sitters, and 72%–93% of non-sitters).^{15,20} Furthermore, 70%–73% of walkers presented fatigability in the lower limbs, as measured with the Six-Minute Walk Test.^{15,20} The results of our study are consistent with those studies, although we found slightly higher prevalence rates. A possible explanation for this is that some tasks included in the questionnaire (combing the hair, eating, climbing stairs, etc) are more demanding than those assessed with motor tests. In any case, we may infer that the questionnaire on perceived fatigability in the lower limbs reflects the impact caused by the decrease in physical performance, although the instrument is yet to be psychometrically validated.

The analysis of perceived fatigability by functional group reveals that walkers more frequently report symptoms of fatigability in the lower limbs than in the upper limbs. Furthermore, non-sitters present greater perceived fatigability in the upper limbs and axial muscles than sitters. Similarly, a previous study showed a greater neurophysiological decrement in the muscles of the upper limbs in patients with early-onset SMA (types 2 and 3a) than those with late-onset forms of the disease (types 3b and 4).¹⁶ Furthermore, no patient presented a decrement in the bulbar region. This suggests that fatigability, physical fatigue, and perceived fatigability are directly associated with the motor reserve.

Validity of the “Physical fatigue and perceived fatigability” questionnaire

Having analysed the questionnaire and its results, we confirm its content validity, although we propose some small modifications to reduce the number of questions and possible responses. The questions are adapted to the overall functional status of sitters and non-sitters, which is essential to reflect the phenomenon while avoiding the influence of weakness and atrophy as confounding factors.

However, we propose introducing new activities (aimed exclusively at this group of patients), such as carrying shopping bags or cooking, which are better adapted to their functional status. Future studies should conduct a psychometric validation of the questionnaire and seek to create an overall score with reference values.

Towards a comprehensive study of physical fatigue and fatigability

Fatigue and fatigability are different phenomena, but both are closely related, and it is therefore essential to jointly manage both phenomena in SMA.^{10,13,20} Therefore, there is a need for a more detailed study to analyse the association between physical fatigue, fatigability, and motor function, as well as other potentially related factors, such as somnolence, as a recent study has shown an increased rate of sleep disorders in patients with SMA.³⁴ A holistic view of the fatigue–fatigability phenomenon will contribute to scientific advances in our understanding of the pathophysiology of SMA, the interpretation of symptoms in clinical practice, and the therapeutic management of the disease.^{10,35}

Strengths and limitations of the study

This pilot study analyses for the first time the content validity and results of a novel questionnaire specifically designed to quantify physical fatigue and perceived fatigability in patients with SMA, in a large cohort of adult patients. This questionnaire represents a different approach to the assessment of physical fatigue and perceived fatigability and their impact on the activities of daily living. However, future studies must seek to perform a psychometric and construct validation of this scale before it can be used in research or in clinical practice. The scale should also be adapted for and validated in paediatric populations, in whom these symptoms have scarcely been studied.

Conclusions

Our study shows that physical fatigue and perceived fatigability are frequent and disabling symptoms in patients with SMA, as they interfere with basic activities of daily living. Therefore, these symptoms should be included in specific scales for SMA, with the aim of monitoring the overall progression of the disease. Future studies should address the fatigue-fatigability phenomenon from a holistic perspective to clarify its causes and the possible responses to different treatments.

Conflicts of interest

JFVC has received fees as a speaker and lecturer from Biogen and Roche, which have also paid for registrations for congresses.

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Ethical standards

This project has been approved by the Ethics Committee of the Instituto de Investigación Sanitaria La Fe.

Ethical considerations

The authors observed their centre's protocols for the publication of patient data. Patients gave informed consent for the publication of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurop.2022.06.008>.

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