Fatigability as outcome measure in SBMA patients

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Background

Spinal and bulbar muscular atrophy (SBMA) is a genetic disorder caused by a CAG triplet expansion within exon 1 of the androgen receptor (AR) gene, leading to lower motor neuron degeneration and progressive muscle weakness involving both skeletal and bulbar muscles. (1) The resulting fatigability, affecting nearly all patients, represents a major symptom impacting daily life, although it remains poorly quantified to date. In this study, we aimed to derive a fatigability index and to assess whether this measure correlates with the 6-Minute Walk Test (6MWT) and the SBMA Functional Rating Scale (SBMAFRS). We also specifically analyzed the modified-SBMAFRS (m-SBMAFRS), a derived item which incudes the lower limb and trunk subscores, as they have lower variability and larger effect size compared with the other subscales (3). The primary objective was to determine whether the trend of fatigability faithfully reflects the progression of muscle weakness over time, exploring its potential role as a biomarker of disease progression.

Materials and Methods

We retrospectively reviewed the clinical records of 53 SBMA patients previously evaluated at the MND Center of the Clinica Neurologica University Hospital of Padova between January 2014 to May 2025. To be included in the study, patients had to be evaluated at least twice (baseline and annual follow-up visit) and had to perform 6MWT and SBMAFRS. Demographics and main clinical data of each patients were also collected. All patients underwent two follow-up visits approximately one year apart (12,05±3,5 months). We estimated fatigability according to the fatigability index, calculated as follows:

Fatigability (%)= meters $^{1° \text{ minute}}$ - (meters $^{6° \text{ minute}}$ - meters $^{5° \text{ minute}}$)*100

We considered "fatigable" patients with fatigability index > 10%. We also calculated SBMAFRS total score and each subscore (bulbar, superior limbs, inferior limbs, trunk and respiratory); we also considered m-SBMAFRS which is a combined item that includes the trunk subscale and the inferior limbs subscales. Statistical significance between clinical variables and the fatigability index was assessed using Spearman's correlation ($p < 0.05$).

Table 1. Clinical characteristics of SBMA patient.

Item in T0	Value (mean ± SD)
Age (years)	58.6 ±9.3
Age at onset (years)	44.6±9.9
Disease duration (years)	13.44±7.0
Total 6MWT (meters)	366.7±136.3
Total SBMAFRS	45.6±5.7
Bulbar subscore	16.1±1.6
Trunk subscore	13.0±2.4
Upper Limbs subscore	7.0±1.3
Inferior Limbs subscore	5.4±1.7
Respiratory subscore	3.9±0.3
m-SBMAFRS subscore	18.4±3.8

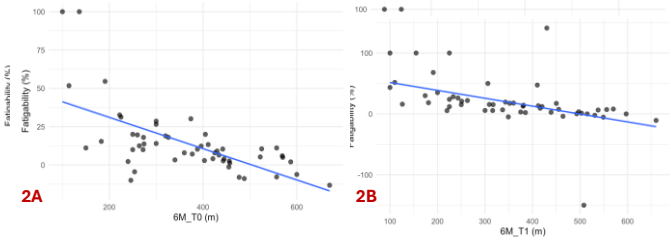
Results

Table 1 reports the main clinical data of SBMA patient at baseline. The mean age at T0 was 58.6 ±9.3, while the mean age at weakness onset was 44.6±9.9 years, with a mean disease duration of 13.44±7.0 years. The mean total 6MWT distance was 366.7±136.3 meters, and the mean total SBMAFRS score was 45.6±5.7; the mean m-SBMAFRS score was 18.4±3.8.

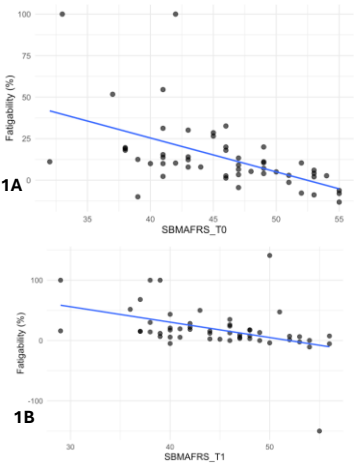
The mean total distance walked during the 6MWT decreased from 366.7 ± 136.3 m (T0) to 352.7 ± 141.7 m (T1), with a significant mean decrease of 4.05% (p=0.0068).

6MWT-derived fatigability was 14.06% in T0, and 18.90% in T1; the percentage of "fatigable" patients increased from 52.83% in T0 to 56.60% in T1. The difference between the two mean fatigability values, however, resulted not statistically relevant (p=0.191). In both T0 and T1 the fatigability index correlates with total SBMAFRS (respectively rho=-0.612 and rho=-0.532, for both p<0.000, see **Graphic 1A and 1B**) and total 6MWT (respectively rho=-0.642 and rho=-0.709, for both p<0.001, as shown in **Graphic 2A and 2B**).

At both T0 and T1, fatigue is strongly and negatively associated with m-SBMAFRS (rho=-0.710, p<0.001 in T0, rho=-0.671, p<0.001 in T1). In T1, fatigue is negatively correlated also with total 6MWT (rho=-0.712, p<0.001).



Graphic 2a and 2b. Correlation between Fatigability Index and 6MWT in T0 and T1, respectively.



Graphic 1a and 1b. Correlation between Fatigability Index and SBMAFRS in T0 and T1, respectively.

Conclusion and Discussion

These findings suggest that increased fatigability in SBMA patients is associated with shorter walking distances and greater motor disability, particularly involving the lower limbs and trunk. The fatigability index thus appears to reflect disease progression in motor function, capturing an aspect—fatigue—that remains difficult to objectively assess but is highly impactful on patients' daily life and activities. Therefore, fatigue-related parameters may represent a promising biomarker to monitor disease progression over time.

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