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Proposal of a new clinical protocol for evaluating fatigability in adult SMA patients

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Objective. Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disease affecting the lower motor neuron, carrying a significant burden on patients' general motor skills and quality of life, characterized by a great variability in phenotypic expression. As new therapeutic options make their appearance on the scene, sensitive clinical tools and outcome measures are needed, especially in adult patients undergoing treatment, in which the expected clinical response is a mild improvement or stabilization of disease progression.
Methods. Here, we describe a new functional motor scale specifically designed for evaluating the endurance dimension for the upper and lower limbs in adult SMA patients.
Results. The scale was first tested in eight control healthy subjects and then validated in ten adult SMA patients, proving intra- and inter-observer reliability. We also set up an evaluation protocol by using wearable devices including surface EMG and accelerometer.
Conclusions. The endurance evaluation should integrate the standard clinical monitoring in the management and follow-up of SMA adult patients.

Key words: adult spinal muscular atrophy, physical endurance, clinical protocol, outcome measure

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Introduction

5q-Spinal muscular atrophy (5q-SMA) is a rare neuromuscular disease affecting one on 10.000 live births, due to the loss of function of SMN1 gene, thus leading to lower motor neurons degeneration [1]. In type 1 SMA (SMA1), the severe and most common form (60%), most individuals carry two SMN2 copies and die within the first 2 years of life. For type 2 and 3 SMA patients, the correlation between phenotype and SMN2 copy number is debated [2]. SMA 3a patients typically experience symptoms onset before the age of 3, while patients that develop weakness between the ages of 3 and 30 years old are classified as 3b [3]. Once an intractable condition, SMA has in recent times witnessed the advent of effective pharmacological treatment, namely nusinersen and risdiplam, targeting the splicing process of SMN2, and gene therapy with onasemnogene abeparvovec. Furthermore, several other treatments are currently in development, targeting SMN1-independent factors, such as sarcomere calcium sensitivity and contraction, autophagy, and synaptic neuromuscular transmission [4].
In this dynamic scenario, assessment of treatment efficacy is mandatory and is currently evaluated with standardized motor scales (HINE, HMFSE, RULM, CHOP, 6MWT) to capture

significant changes. While in the pediatric population significant results are more evident from clinical practice with commonly used disease specific standardized scales [5], in adult, SMA 2-3, treated patients, a smaller improvement or stabilization of disease progression are more commonly expected and observed; on the other hand, patients often subjectively report amelioration of fatigability, experienced as the inability to perform prolonged repetitive tasks in daily life activities, such as eating, working and performing physiotherapy exercises. SMA is characterized by structural and physiological abnormalities of the neuromuscular junction as shown by post-mortem studies and the presence of pathological decrement upon repetitive nerve stimulation supporting the hypothesis that neuromuscular junction dysfunction is associated with fatigability [6]. Fatigability and reduced endurance are common in neuromuscular disorders [6] and particularly in SMA, potentially disabling symptoms in terms of patient's independence, adherence to physiotherapy, working and social interactions.

While fatigue is a complex symptom made up of central, peripheral, and psychological components and is often inquired in the clinical setting via patient-reported questionnaires, fatigability and motor endurance can be defined as the capability of sustaining a repeated motor task; hence, while their presence may be partially overlapping, distinction of these features is crucial as well as their correct assessment during patients' examination and follow-up.

Here, we propose a new clinical protocol, called ENDUSMA, specifically designed for adult SMA patients assessing the muscle endurance dimension for the upper and lower limbs.

Materials and methods

The protocol was developed by a team including three neurologists (GS, GR and AG) and a physiotherapist (RC) with clinical experience in SMA and other neuromuscular disorders. A set of endurance tests was developed using the four methodological steps recommended by the "Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)" [7], which include identification and definition of the construct (i.e. outcome or domain) to be measured and the target population (e.g. age, gender, characteristics of the disease); search for all existing Outcome Measure Instruments (OMIs) from systematic reviews, literature searches, and other sources; quality assessment of the identified OMIs and final selection. The constructs subject of the study were endurance and motor fatigability, to be measured in adult SMA 3 patients, so the evaluating team focused on simple, already existing repetitive tasks which could mirror daily life gestures and activities.

At the end of the process, ten timed motor tasks were selected from pre-existing clinical scales, currently used in neuromuscular diseases, evaluating both the upper and the lower limbs. For each item the potential bias during the patient's performance related to compensations, and positioning were accurately defined.

In the first testing phase of the scale, eight control subjects were recruited from the hospital's personnel. Subsequently, the statistical validation process was designed by a medical statistician (LM) and included a first phase in which patients were tested by the same evaluator at baseline and then after two weeks; after that, they were evaluated simultaneously by two distinct operators. Spearman's correlation test was applied to analyze the scale in terms of inter- and intra-observer reliability of the obtained results. The scale was validated directly on patients as the chosen tasks were already used for neuromuscular diseases and each subject served as its own control. The study was conducted according to the Declaration of Helsinki and approved by local Ethics Committee (protocol number 18687).

Results

Definition of ENDUSMA items

The motor tasks include: for lower limb the 10 meters walk/run test [8]; time to climb and descend four stairs; repeated sit to stand in 15 seconds; the Time Up and Go test (sitting start position, record the

Table I. Description of motor tests included in the ENDUSMA scale.

Test	How to perform
10 meters walk/run test	Standing start position, the patient has to run 10 meters as quickly as possible. Total time for completion of the task is recorded
Time to climb and descend four stairs	Record time used by the patient to rise and descend 4 steps, reporting all types of compensation e.g., one-handed support, two-handed support, alternating step / single step
Time to repeated sit to stand 5 times	The patient has to get up and sit 3 times as quickly as possible, note the time
Time Up and Go test (TUG)	Sitting start position, record the time used by the patient to get up, walk 3 meters, turn around and sit on the same chair for 5 times
Endurance of proximal arm	The patient is sitting on a chair, if possible, with no touching between his/her back and the backseat; she/he has to keep the upper limb extended, parallel to the floor, keeping a weight-up to one kg according to the patient capability to lift the weight; the task can also be performed without any weight-lifted; the test ends when the patient fails to keep the limb extended, can no longer lift the weight or reaches 3 minutes
Abduction of upper limbs	Patient is sitting on a chair, she/he has to lower the upper limb as many times as possible, in a minute; the test ends when a minute has passed or when the patient can no longer perform the movement; note the number of repetitions
Repetitive nine-hole peg test (9HPT)	On a start command when a stopwatch is started, the patient picks up the nine pegs one at a time, puts them in the nine holes as quickly as possible, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container; the time to complete the task is recorded; participants will perform five consecutive rounds with the same hand of choice with the Rolyan 9HPT
Digital dexterity	The patient has to touch the thumb with the other fingers of the hand sequentially, back and forth; test ends when a minute has passed or when the patient can no longer perform the task; note the number of repetitions
Handgrip	Patient must perform a maximum contraction for 3 seconds, rest for 1 second and repeat the sequence 3 times. Note the highest score obtained. Patient has to perform "open and close hands" and repeat "handgrip"
Open and close hands	The patient is sitting on a chair with his/her elbows resting on the table, opens and closes one hand as many times as possible in a minute; test ends when a minute has passed or when the patient can no longer perform the task; note the number of repetitions

time used by the patient to get up, walk 3 meters, turn around and sit on the same chair for 5 times) [9]; testing of endurance of proximal arm; abduction of upper limbs; repetitive nine hole peg test [10]; digital dexterity; handgrip [11]; open and close hands.
An overview of the motor tests is provided in Table I. Dominant side is tested in tasks in which the use of one single arm is allowed.
Scoring is based on total time or number repetitions for each test (Tab. I).
Tests evaluating upper limbs must be performed with patients seated on a chair or in their wheelchair facing a table with the forearm placed on the table or on the wheelchair shelf. Before each test, patients are given a description of the tasks, a demonstration of the movement required and advice to maintain correct practice.
The items should be performed starting from the proximal to the distal musculature to follow the distal-proximal involvement of the disease.

Scale testing on healthy controls

After selection of the items, the scale was applied to eight healthy controls, age- and sex-matching the patients' cohort. Demographic data and results from application of the scale to controls are reported in Tables II and III.

Statistical validation

The scale was administered to 10 consecutively recruited adult patients with SMA type 3b, 4 male and 6 females, aged 24-64 (mean age 42,1±12,49 years), all carriers of deletions of SMN1 exons, regularly followed at Neurology Unit of University of Pisa, all treated with nusinersen with exception for a naïve patient. Six patients were non ambulatory. Ambulatory patients did not use any walking aid and were able to perform all the tasks. None of our subjects were on NIV/oxygen therapy. Demographic, clinical, and genetic information are shown in Table IV. No significant comorbidities were present in our cohort.
Scores obtained in the testing sessions are listed in Tables V and VI. All the patients understood the administered tasks. Administration of the protocol had a mean duration of 30 minutes. The scale demonstrated internal consistency and test-retest reliability (Spearman's r ranging from 0.7609 to 1 for all tasks).

Wearable devices application

Wearable devices for the assessment of surface EMG and joints positions and angles for upper and lower limbs were tested on two patients, one ambulatory and one non ambulatory, while performing the ENDUSMA scale. The signals acquisition and analysis system, named AUTOMA (Fig. 1), can be used both for the upper and lower limbs. It is composed of one biaxial electro-goniometer SG150 (Biometrics Ltd, Newport, UK) that can be applied to the shoul-

Table II. Demographic data of healthy controls

Control ID	Sex	Age
C1	M	65
C2	F	27
C3	F	34
C4	F	40
C5	M	25
C6	F	50
C7	M	32
C8	F	50

Table III. Results of the scale test in healthy controls.

ENDUSMA Item	Mean	S.D.
Digital dexterity (repetitions)	24,00	5,51
9HPT total timing (minutes)	1,18	0,33
Hand grip pre (Kpa)	68,45	22,46
Hand grip post (Kpa)	60,65	19,31
Open and close hands (repetitions)	100	22,04
Endurance of proximal upper limbs (minutes)	3,00	0,00
Abduction upper limbs (repetitions)	57	8,22
Sit to stand (repetitions)	8	1,68
TUG (minutes)	0,29	0,09
Ten meters walk/run test (seconds)	3,10	0,30

Values are shown as mean and standard deviation

Table IV. Demographic, clinical and genetic data of patients.

Patient ID	Sex	Age	SMA type	Genotype	Examined Side	Ambulatory (yes/no)	HMFSE	RULM
ID1	F	56	3b	Del ex7 SMN1, 3 copies ex7+4 copies ex8 SMN2	Right	No	9	29
ID2	M	38	3b	Del ex7-8 SMN1, 4 copies SMN2	Right	Yes	35	37
ID3	F	39	3b	Del ex7-8 SMN1, 3 copies SMN2	Right	No	40	35
ID4	M	51	3b	Del ex7 SMN1, 3 copies SMN2	Left	No	10	23
ID5	F	32	3b	Del ex7-8 SMN1, 4 copies ex7+3 copies ex8 SMN2	Right	Yes	54	37
ID6	F	31	3b	Del ex7 SMN1, 3 copies SMN2	Right	Yes	38	28
ID7	M	49	3b	Del ex7-8 SMN1, 3 copies SMN2	Right	No	8	22
ID8	M	37	3b	Del ex7 SMN1, 3 copies SMN2	Right	No	16	29
ID9	F	64	3b	Del ex7-8 SMN1, 4 copies SMN2	Right	No	38	37
ID10	F	24	3b	Del ex7-8 SMN1, 4 copies SMN2	Right	Yes	58	37

Table V. Results obtained by the same operator evaluating patients at baseline (T0) and after two weeks (T1).

Patient ID	Evaluated side (R/L)	10meters T0 (s)	10meters T1 (s)	Climb 4 steps T0 (s)	Climb 4 steps T1 (s)	Descend 4 steps T0 (s)	Descend 4 steps T1 (s)	Sit to stand T0 (times)	Sit to stand T1 (times)	TUG test T0 (s)	TUG test T1 (s)	Endurance of proximal upper arm T0 (s)	Endurance of proximal upper arm T1 (s)	Abduction upper limbs T0 (times)	Abduction upper limbs T1 (times)	9HPT T0 (s)	9HPT T1 (s)	Digital dexterity T0 (repetitions)	Digital dexterity T1 (repetitions)	Handgrip 1 T0 (kPa)	Handgrip 1 T1 (kPa)	Open&Close hands T0 (times)	Open&Close hands T1 (times)	Handgrip 2 T0 (kPa)	Handgrip 2 T1 (kPa)
ID1	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	15	21	23	23	129	123	104	112	12	16	49	63	10	16
ID2	R	7,8	7,6	CNT	CNT	4	5,2	2	1	60	91	32	22	19	18	147	142	184	184	14	22	115	134	14	22
ID3	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	26	35	10	12	106	101	160	176	70	60	94	95	60	50
ID4	L	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	7	6	44	29	169	197	152	112	16	10	60	49	16	10
ID5	R	6,6	6,6	6,4	7,5	[3]	1,9	3	4	55	54	125	85	41	45	114	109	200	216	32	50	95	109	32	50
ID6	R	13,3	12,6	26	25	7,4	6,5	2	1	140	135	55	60	50	55	107	104	184	192	20	25	111	126	20	30
ID7	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	30	30	8	15	78 (not completed, stop after 2° round)	43 (not completed, stop after 1° round)	216	208	8	10	74	84	8	10
ID8	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	19	25	6	6	115	110	168	168	12	20	104	111	12	20
ID9	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	61	48	28	27	120	103	136	136	34	24	102	63	34	24
ID10	R	6,5	8,5	9,2	9	1,8	1,6	4	4	51,3	51	84	78	33	32	88	80	256	240	42	40	125	108	44	40

Table VI. Results obtained by two different operators (O1 and O2) evaluating patients simultaneously.

Patient ID	Evaluated side (R/L)	10meters T0 (s)	10meters T1 (s)	Climb4 steps O1 (s)	Climb4 steps O2 (s)	Descend4 steps O1 (s)	Descend4 steps O2 (s)	Sit to stand O1 (times)	Sit to stand O2 (times)	TUG test O1 (s)	TUG test O2 (s)	Endurance of proximal upper arm O1 (s)	Endurance of proximal upper arm O2 (s)	Abduction upper limbs O1 (times)	Abduction upper limbs O2 (times)	9HPT O1 (s)	9HPT O2 (s)	Digital dexterity O1 (repetitions)	Digital dexterity O2 (repetitions)	Handgrip 1 O1 (kPa)	Handgrip 1 O2 (kPa)	Open&Close hands O1 (times)	Open&Close hands O2 (times)	Handgrip 2 O1(kPa)	Handgrip 2 O2(kPa)
ID1	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	19	19	18	18	101	100	155	155	13	13	85	85	12	12
ID2	R	7,75	7,75	CNT	CNT	3,83	3,85	2	2	65	65	30	30	18	18	145	145	184	184	18	18	112	112	19	19
ID3	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	31	30	69	69	105	105	216	216	30	30	76	75	30	30
ID4	L	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	7	7	44	44	169	170	152	152	16	16	58	58	13	13
ID5	R	6,85	6,85	6,50	6,50	3,2	1,7	4	4	56	56	90	90	45	45	112	112	208	208	35	35	100	100	32	32
ID6	R	13,8	13,8	28	28	7,5	7,4	2	2	141	141	58	58	50	50	109	109	188	188	23	23	116	116	24	24
ID7	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	30	30	10	10	65 (not completed, stop after 2° round)	65 (not completed, stop after 2° round)	200	200	8	8	75	75	6	6
ID8	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	18	18	7	7	112	112	165	165	15	15	110	110	13	13
ID9	R	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	CNT	58	58	28	28	113	113	135	135	32	32	100	100	28	28
ID10	R	6,8	6,8	9,2	9,2	1,6	1,6	4	4	50,2	50,3	78	78	31	31	84	84	250	250	40	40	115	115	42	42

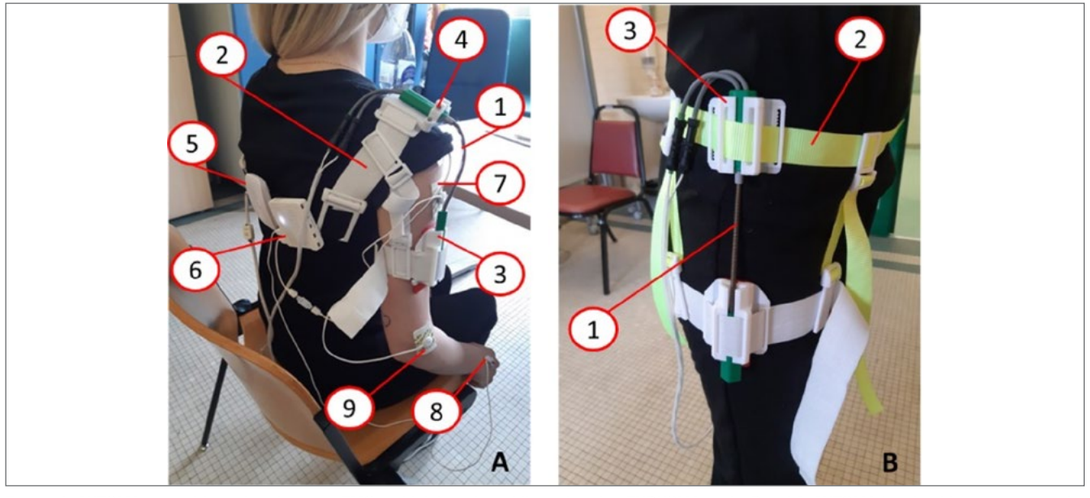

Figure 1. AUTOMA: wearable system to asses EMG and joint angles while performing ENDUSMA scale. Panel A: AUTOMA for shoulder measurements; Panel B: AUTOMA for hip measurement. (1) dual axes electro-goniometer Biometrics SG150 model; (2) Adjustable harness; (3) Goniometer end-block cases; (4) Adjustable hinge joint; (5) Biosignalplux electronic module; (6) BITalino electronic module; (7) EMG electrodes for deltoid activity measurement; (8) Accelerometer; (9) EMG reference electrode.

der or to the hip by means of a harness. Goniometers end-blocks are carried by two cases that can be fixed to the joints over the clothes with adjustable ties. To reduce the high crosstalk between electro-goniometer signals measuring simultaneously the shoulder angle joints, the case for the upper shoulder end-block is endowed with an adjustable hinge. This way the electro-goniometer can be better aligned with the principal axis of movement reducing the angle range on the orthogonal plane. Electro-goniometer signals are acquired at 1000Hz by a 4 channels Bluetooth electronic module (Biosignalplux Explorer Kit - PLUX WIRELESS BIOSIGNALS S.A., Lisbon, Portugal) connected to a laptop and processed with OpenSignals software. For the shoulder, EMG electrodes are placed on the deltoid and are acquired by another Bluetooth module (BITalino - PLUX WIRELESS BIOSIGNALS S.A., Lisbon, Portugal) connected to the same laptop. EMG signals are simultaneously processed with the same software that can synchronize events. EMG and electro-goniometry signals were acquired from the two patients without loss of data and correctly paralleling the motor performance of the subjects during the tasks.

Discussion

Increased endurance in SMA patients treated with nusinersen at the 6MWT was reported in 2019 by Montes et al. [12], with different rates among children, adolescent, and adult patients, hypothetically due to the effect of nusinersen on neuromuscular junction dysfunction observed in mouse models and patients. Kizina et al. evaluated fatigue in SMA type 2-3, treated with nusinersen patients, with the Fatigue Severity Scale (FSS), highlighting a significant burden that transiently responded to treatment [13]; nevertheless, a following study from Dunaway Young et al. explored the association of perceived fatigue and motor fatigability (evaluated with the 6MWT) in children and adults affected by SMA type 2 and 3, failing at finding a correlation between the two [14], thus corroborating the hypothesis of a reciprocal independence among them. A comprehensive clinical and electrophysiological study considering the Endurance Shuttle Test Combined Score (ESTCS), muscle strength scored with MRC, motor function evaluated with the HMFSE, neuromuscular junction function tested through repetitive nerve stimulation and perceived fatigue investigated with the PROMIS SF scale concluded that fatigability in SMA is associated with but not equivalent to muscle strength and function [15].

In our study, we aimed at identifying and assembling a set of motor tasks suitable for an objective evaluation of motor endurance in adult SMA patients. This study was designed to test the consistency, feasibility, and reliability of the scale; hence, it included a small number of patients. The scale includes a set of tests scored as number of repetitions in a certain time or as global time to complete the exercise, thus providing an objective measurement of motor fatigability across the task's duration through a discrete spectrum, not only considering major muscular districts or performances also involving respiration and cardiovascular issues (as the 6MWT), but also distal compartments. Moreover, many of the tests are similar to gestures and tasks that the patient may be required to perform repeatedly during daily life activities (i.e., fine movements of the fingers, postural changes, personal hygiene and dressing). As a consequence of the rarity of the condition, a potential limitation of this first validation phase is the composition of the tested sample, including many non- ambulatory subjects; nonetheless, among the ten identified items, six are dedicated to assessment of proximal and distal sections of upper limbs, thus representing a suitable tool also for evaluation of non-ambulatory patients. We are currently collecting data of a one-year follow-up from an extended cohort of 25 patients to provide further evidence supporting the use of ENDUSMA.
The tested body side and the order in which the tasks were proposed to the patients were defined to obtain the maximum patient's compliance and to achieve completion of the entire scale. The tasks were well understood by the patients. No particular equipment is required. A remaining unsolved issue is the assessment of the most severe patients (i.e. SMA 2 subjects), in which a very limited range of motor capabilities is preserved and cannot be evaluated by functional scales. Overall, future perspectives may involve use of IT technologies including wearable devices, which we are currently testing on a subset of SMA 3 patients, to collect fine, digitalized, and personalized on a case-by-case basis, data on joints' position and function, movement speed and surface EMG. These IT tools will aid the clinician in objectifying any changes in patients' clinical picture allowing evaluation of treatment effectiveness and precocious identification of any worsening.

Conclusions

As diagnosis rate of SMA both in children and adult patients increases and therapeutic options are bound to modify natural history in the future, we believe that assessment of motor endurance, along with strength and perceived fatigue, should be an essential part of the management of SMA, in the perspective of an increasingly chronic, stable clinical picture with a longer life expectancy and growing patients' independency in daily life.

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Conflict of interest

Authors have no conflict of interest to disclose.

Authors' contributions

GS, GR, AG and RC developed the clinical protocol; GR, AG, FT, RC and GV performed the clinical evaluations; AG and FT wrote the paper; LM performed statistical analyses; SR performed the wearable devices-assisted evaluations; GR and GS revised the paper; GC, RL, MC, FM, VV, MM, FF, ST, NG, GR and GS approved it for submission.

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