Revised Upper Limb Module for Spinal Muscular Atrophy: 12 month changes

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Abstract

The aim of the study was to use the Revised Upper Limb Module functional scale to assess longitudinal 12 month changes in type 2 and 3 patients affected by spinal muscular atrophy and to identify possible trajectories of progression according to age or functional status.

The study included 114 patients, 60 type 2 and 54 type 3 (32 ambulant and 22 non-ambulant). Their age ranged between 30 months and 49 years. The 12 month changes on the Revised Upper Limb Module ranged between -7 and 9 (mean -0.41; SD 2.93). The mean changes were not significantly different between the three spinal muscular atrophy (SMA) groups (-0.45 in type 2, -0.23 in non-ambulant type 3 and -0.34 in ambulant type 3, p=0.96) and the relationship between 12 month change and age classes was not significantly different among the three types of SMA patients.

Some patterns of changes however occurred more frequently in some age and functional categories. Improvements were mainly seen in children below the age of 5 years. Negative changes >2 points were more common in type 2 compared to type 3. In type 2 the highest rate of deterioration was found between the age of 5 and 14 while in ambulant patients loss of upper limb function occurred more frequently in older individuals.

Our results confirm that the Revised Upper Limb Module explores a wide range of functional abilities and can be used in ambulant and non-ambulant patients of different ages. Although the overall mean 12 month changes were relatively small, age and functional status appear to have some effect on the patterns of changes. This information can be of help at the time of designing clinical trials.

Introduction

There is a growing need for robust clinical measures to assess upper limb motor function in spinal muscular atrophy (SMA), in conjunction with the available gross motor scales which however may lack sensitivity at the extremes of the clinical spectrum[1, 2].

The Revised Upper Limb Module (RULM) was recently designed [3] as a revision of the Upper Limb Module (ULM)[4] originally developed to assess aspects of upper limb function in the weaker end of the SMA spectrum from the age of 30 months onwards.

The RULM includes a number of additional items that expand the spectrum of upper limb activities originally included in the ULM in order to reduce the risk of ceiling effect in stronger children. The revised scale has been shown to measure the same construct as the original ULM and has shown robust psychometric properties[3]. While this reliability, validity and suitability of the scale in a multi-center clinical research setting have been published[3], there is yet no longitudinal data on the RULM.

The aim of the study was to provide longitudinal 12 month natural history data in a large cohort of type 2 and 3 SMA patients using the RULM. More specifically, we wished to establish if the revision of the scale adequately addressed the ceiling effect of the ULM original version. As the study population ranged from weak non-ambulant to stronger ambulant patients, we also aimed to identify if there were different trajectories according to functional status.

Materials and Methods

The study was performed by collecting longitudinal 12 month data within three national SMA networks across USA, Italy and UK. All patients had a genetically confirmed diagnosis of SMA and only those with a diagnosis of type 2 and 3 SMA were included in the study. To reduce selection bias, all patients seen in the neuromuscular clinics who were older than 30 months and who were not participating in any interventional clinical trial were consecutively offered

enrollment. Only patients with two assessments at 12 month interval were selected for this study. Patients in whom one of the two performances was affected by fractures, transient pain episodes, recent respiratory infections, or any other factor that affected temporarily one of the two motor performances, were excluded from the analysis.

RULM

The scale consists of an entry item to establish functional levels and 19 items covering distal to proximal movements [3]. The entry item is a modified version of the Brooke scale, including activities ranging from no functional use of hands (score 0) to full bilateral shoulder abduction (score 6). The entry item does not contribute to the total score but serves as a functional classification of overall upper limb functional ability. Of the remaining 19 items, 18 are scored on a 3 point scoring system and 1 item is scored on a 2 point scoring system. The total score ranges from 0, if all the items cannot be performed, to 37, if all the activities are achieved fully without any compensation. All items were tested without spinal jacket or orthoses.
Patients received the test at two time points at 12± 2 months apart.

Evaluator training sessions

The physical therapist in the participating clinics received the same training programs with establishment of yearly intra and inter-rater reliability, and standardized procedures of scale administration.
Inter and intra observer reliability of the RULM have already been reported[3].

Statistical analysis

The RULM was evaluated longitudinally over a 12 month period of time. Summary statistics (N, mean, median, SD, range) were used.

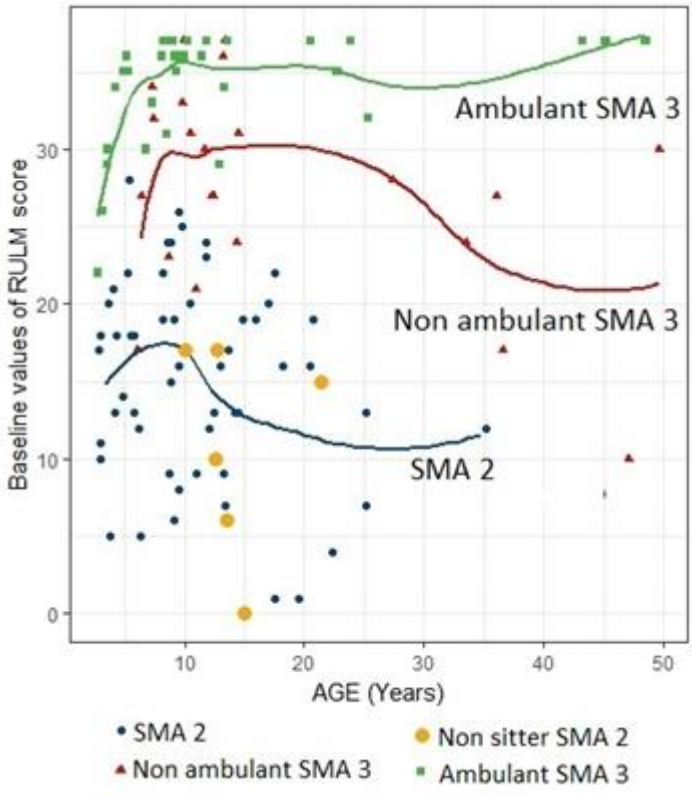
Baseline values of the RULM in ambulant or non-ambulant type 3 patients and in type 2 patients were compared using an Analysis Of Variance (ANOVA) model adjusting for age.
An interaction test between the three different SMA types and age was assessed in order to analyse the dependence of the baseline values of RULM score on age.
The 12 month change in the RULM score was compared between age classes (defined as 30 m-4.11 years; 5 years – 9.11 years; 10 years -14.11 years; ≥15 ys) by an analysis of variance, adjusting for baseline values in the three SMA types (type 2, non-ambulant type 3 and ambulant type 3). The age classes were arbitrarily defined in the protocol on the basis of our previous findings using the HFMSE to define trajectories of progression in SMA patients [4] , showing that different slopes of progression more often occurred around the age of 5 , 10 and 15 years.
The change values were clustered in three groups: patients with stable results (± 2 points), those with loss of more than 2 points and those with improvements of more than 2 points. The cut off of two points was decided on the basis of the experience with the HFMSE and based on patients and carers' questionnaires reporting that any improvement (equal to two points on the scale) was clinically meaningful to patients and their carers [5].
The percentage of patients within each group were compared across age classes by a chi-square test (a multinomial model was used to adjust for baseline values).

Results

One hundred and fourteen patients of age ranging between 2.7 and 49.7 years at baseline (mean 13.3; SD 10.1) were included in the study. Sixty were type 2 and 54 type 3 (32 ambulant and 22 non-ambulant). Of the 60 type 2 patients, six had lost the ability to sit unsupported (non sitters).

At baseline the RULM scores ranged between 0 and 37 (mean 22.6; SD 10.5). At 12 months the scores ranged between and 0 and 37 (mean 22.2; SD 10.7).

Figure 1 shows details of the distribution of scores at baseline according to age and to functional status. The maximum score (37) was found in 13 of the 114 (11.4%) who were, with two exceptions, ambulant patients.



>>>> Fig 1. Baseline distribution of scores according to age and to functional status. Curves represent the resulting fits to a LOESS model.

Baseline values of RULM scores were significantly different between type 2, and type 3 ambulant and non-ambulant patients. The mean value was 14.8 (SD=6.6) in type 2 patients, 27.4 (SD=6.9) in non-ambulant type 3 and 34.2 (SD=3.7) in ambulant type 3 patients ($p<.0001$, adjusting for age). Six of the 60 type 2 patients were non sitters, their scores ranged between 0 and 17 (mean 10.83, SD 6.85) . As the number of the non sitters was small, for statistical purposes they were kept within the type 2 group. Details of the scores of the non sitters are shown in figure 1 and 3.

144 The interaction between the three SMA groups and age was significant (p=0.011). There was a
145 significant association with the four age levels (<4 ys; 5 ys - 9 ys; 10 ys -14 ys; >15 ys) in
146 ambulant type 3 patients (p=0.002), while there was no association with age in type 2 and non-
147 ambulant type 3 patients (p=0.12 and p=0.14, respectively).
148
149 *12 month changes*
150 The changes ranged between -7 and 9 (mean -0.41; SD 2.93). Table 1 shows details of the
151 changes subdivided by functional status and age groups.

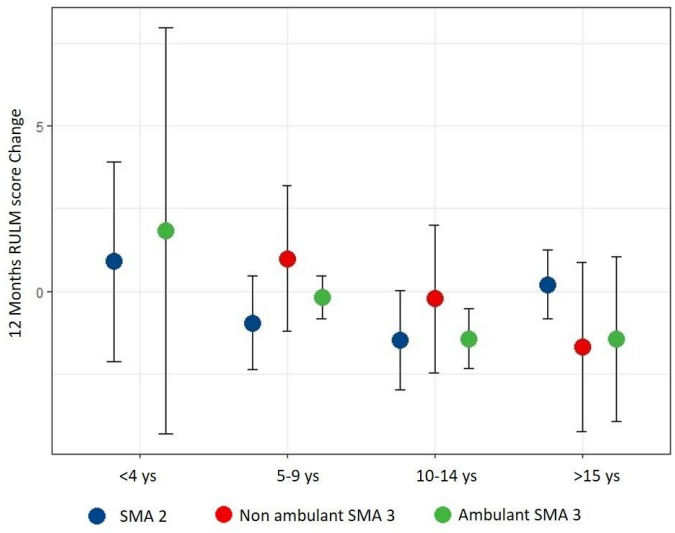
	Mean change (SD)	<-2	±2	>2
All (n:114)	-0.4 (±2.9)	20%(n:23)	67% (n:76)	13% (n:15)
<4 (n:16)	1.2 (±4.7)	31% (n:5)	25% (n:4)	44% (n:7)
5-9 (n:38)	-0.3 (±2.4)	18% (n:7)	71% (n:27)	11% (n:4)
10-14 (n:33)	-1.1 (±2.6)	21% (n:7)	73% (n:24)	6% (n:2)
>15 (n:27)	-0.6 (±2.3)	15% (n:4)	78% (n:21)	7% (n:2)
Type II (n:60)	-0.5 (±3.0)	23%(n:14)	60% (n:36)	17% (n:10)
<4 (n:10)	0.9 (±4.2)	30% (n:3)	30% (n:3)	40% (n:4)
5-9 (n:19)	-0.9 (±2.9)	32% (n:6)	53% (n:10)	16% (n:3)
10-14 (n:17)	-1.5(±2.9)	29% (n:5)	65% (n:11)	6% (n:1)
>15 (n:14)	0.2 (±1.8)	0% (n:0)	86% (n:12)	14% (n:2)
Non ambulant III (n:22)	-0.2 (±2.7)	18%(n:4)	73% (n:16)	9% (n:2)
<4 (n:0)	N/A	0%(n:0)	0% (n:0)	0% (n:0)
5-9 (n:7)	1 (±2.4)	14% (n:1)	71% (n:5)	14% (n:1)
10-14 (n:9)	-0.2(±2.9)	11% (n:1)	78% (n:7)	11% (n:1)
>15 (n:6)	-1.7 (±2.4)	33% (n:2)	67% (n:4)	0% (n:0)
Ambulant (n:32)	-0.3(±3.0)	16%(n:5)	75% (n:24)	9% (n:3)
<4 (n:6)	1.8 (±5.8)	33% (n:2)	17% (n:1)	50% (n:3)

5-9 (n:12)	-0.2 (±1.0)	0% (n:0)	100% (n:12)	0% (n:0)
10-14 (n:7)	-1.4 (±2.5)	14% (n:1)	86% (n:6)	0% (n:0)
>15 (n:7)	-1.4 (±2.7)	29% (n:2)	71% (n:5)	0% (n:0)

>>>>Table 1: 12 month changes by functional status and age groups.

The 12 month change was not significantly different between the three SMA groups (average change =-0.45 in type 2, -0.23 in non-ambulant type 3 and -0.34 in ambulant type 3 patients p=0.91) and the relationship between 12 month change and age classes was not significantly different among the three groups (p for age classes X SMA type interaction=0.36).

The 12 month change adjusted for baseline was not associated with age in any of the groups: type 2 patients (p=0.21), ambulant type 3 patients (p=0.22) and non-ambulant type 3 (p=0.79). (Fig. 2)

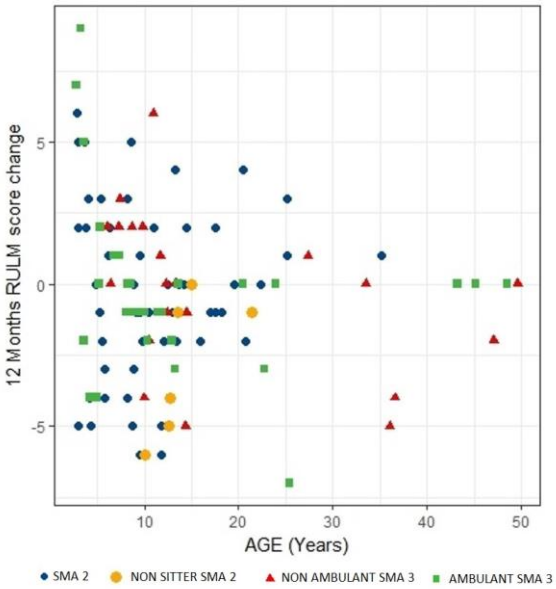


>>>>Fig 2. 12 month RULM score changes according to the ambulatory status and to age classes.

The results were also analyzed according to whether the patients had stable results (± 2 points), or had loss of more than 2 points or an improvement of more than 2 points.

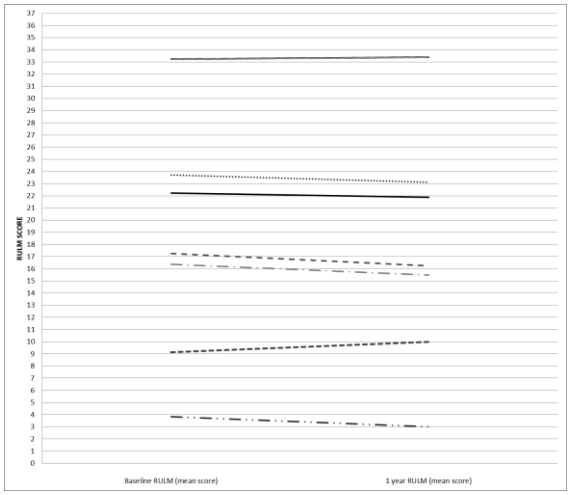
There was a different distribution of patients with these 3 levels of change according to age class in type 2 SMA patients (adjusted for baseline values) (p=0.04) (p=0.63 in non-ambulant

type 3 SMA patients and p=0.11 in ambulant type 3 SMA patients).



>>>>Fig 3. 12 month changes by age.

Figure 4 shows details of the mean changes according to entry level. There was no difference in trajectories among the different subgroups (p=0.48).



>>>>Fig 4. Mean 12 month changes according to entry level. (—··—: Entry level 1; ——: Entry level 2; —·—: Entry level 3; — —: Entry level 4; —: Mean all groups; ·····: Entry level 5; ▭: Entry level 6)

Discussion

Until recently upper limb function has not been systematically assessed in SMA ambulant patients[1] as for ambulant patients upper limb impairment was generally not reported as one

of the major concerns. In these patients the clinical assessment mainly focused on ambulatory performance and range of motion. Our results show that the RULM can capture upper limb function in a broad range of SMA patients, from non sitters to ambulatory patients. Only one of the non sitters had a RULM score of 0, with the others ranging between 6 and 17. At the other end of the spectrum, ceiling effect was reached in 11.4% of the whole cohort and approximately in a third of the ambulant subgroup, these findings suggesting that upper limb function should be assessed also in ambulant patients who may not complain of upper limb weakness or functional impairment.

Baseline values of RULM score were different between type 2, type 3 non-ambulant and ambulant patients. Over 12 months, the mean change in the whole cohort was less than one point even though changes ranged between -7 and +9. The relationship between 12 month change and age classes were not significantly different among the three SMA groups patients. The lack of significance is probably at least partly related to the fact that the youngest group (below the age of 5 years), which mainly included non-ambulant children, had a very heterogeneous pattern of changes.

Nevertheless, we were still able to identify some patterns of changes that occurred more frequently in some age and functional categories, reinforcing our previous observation using the Hammersmith Functional Motor Scale Expanded (HFMSE)[5].

Approximately 2/3 of the whole cohort had changes within $\pm$2 points, with type 3 patients remaining more often stable (73%) than type 2 (63%). It is of interest that the magnitude of changes and percentage of stable results in non-ambulant type 3 patients was more similar to the ambulant type 3 than to the type 2 patients. In the past there has been a tendency to cluster type 2 and non-ambulant type 3 patients as they share several common clinical features such as scoliosis, joints affected by contracture and muscle weakness patterns. This does not appear to be the case for upper limb function as even after loss of ambulation, patients with

type 3 SMA have RULM results more similar to those found in ambulant patients. The distribution of patients with these 3 levels of change according to age class was different in type 2 SMA patients (adjusted for baseline values) (p=0.05) but not for the other groups. Improvements were mainly seen in children below the age of 5 years similarly to previous reports of gross motor assessments [5, 6]. These probably reflect development, growth and to some extent improvement in cooperation and understanding. The items that more frequently did not have a full score in young children are tearing the paper, opening container and lifting weights above shoulder height. It is of interest however that only a minority showed an improvement of 5 points or more, as observed in recently reported clinical trials[7]. Negative changes >2 points were observed in 20% of the whole cohort, and were more common in type 2 compared to type 3. Similarly to HFMSE[5], in type 2 the highest rate of deterioration was observed between the age of 5 and 14 years. Although the number of older ambulant patients included in this study was very small, it appears that a loss of upper limb function may occur more frequently at a later age compared to type 2.

As the RULM has an entry item based on the Brooke scale[8] that is able to classify upper limb performance into broad functional levels, we were interested in establishing whether the patterns of changes were related to the entry level, as observed for progressive disorder, such as DMD[9]. However, in SMA there was no difference between the subgroups subdivided according to entry levels as they all were within $\pm$ 1 point. These findings suggest that the functional level at entry does not predict the magnitude of changes at least over a period of 12 months, due to the very modest magnitude of changes observed.

In conclusion, our results confirm that the RULM explores a wider range of functional abilities and can be used in the broader phenotypic spectrum of SMA including ambulant patients. We also demonstrated that although the mean 12 month changes were relatively small, the range of change was broad and that functional level and age can help to identify categories of

patients at higher risk of more substantial changes. Understanding these differences, may help with clinical trial design or interpreting results of an intervention. Further studies using more defined statistical methods and a longer follow up, as recently used in other neuromuscular disorders[10, 11], may help to identify further prognostic elements and define more precise trajectories of progression. Furthermore, studies designed to investigate minimal clinically important difference across ages and abilities will contribute to a better understanding of perceptions of meaningful change during daily activities for patients and families.

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References

1. Finkel R, Bertini E, Muntoni F, Mercuri E, Group ESWS. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord. 2015;25(7):593-602.

2. Finkel RS, Sejersen T, Mercuri E, Group ESWS. 218th ENMC International Workshop:: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. Neuromuscul Disord. 2017;27(6):596-605.

3. Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle & nerve. 2017;55(6):869-74. Epub 2016/10/05.

4. Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Pattern of disease progression in type 2 and 3 SMA: implication for clinical trials. Nueromuscul Disord. 2016;26(2):126-31

5. Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto MC, Montes J, et al. Content validity and clinical meanigfulness of the HMFSE in spinal muscular atrophy. BMC Neurology. 2017; 17(1):39

6. Mazzone E, Bianco F, Martinelli D, Glanzman AM, Messina S, De Sanctis R, et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. Neuromuscul Disord. 2011;21(6):406-12.

7. Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. Neuromuscul Disord. 2016;26(2):126-31.

8. Kaufmann P, McDermott MP, Darras BT, Finkel R, Kang P, Oskoui M, et al. Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. Arch Neurol. 2011;68(6):779-86.

9. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625-35.

10. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy. I. The design of the protocol. Muscle & nerve. 1981;4(3):186-97. Epub 1981/05/01.

11. Mayhew A, Mazzone ES, Eagle M, Duong T, Ash M, Decostre V, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Dev Med Child Neurol. 2013;55(11):1038-45.

12. Mercuri E, Signorovitch JE, Swallow E, Song J, Ward SJ, Group DMDI, et al. Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2016;26(9):576-83.

13. Goemans N, Vanden Hauwe M, Signorovitch J, Swallow E, Song J, Collaborative Trajectory Analysis P. Individualized Prediction of Changes in 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. PloS one. 2016;11(10):e0164684.