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

Maria Carmela Pera¹,²¶, Giorgia Coratti¹,²¶, Elena S. Mazzone³¶, Jacqueline Montes³,⁴,
Mariacristina Scoto⁵, Roberto De Sanctis¹,², Marion Main⁵, Anna Mayhew⁶, Robert Muni Lofra⁶,
Sally Dunaway Young³,⁴, Allan M. Glanzman⁷, Tina Duong⁸, Amy Pasternak⁹,¹⁰, Danielle Ramsey⁵,
Basil Darras⁹, John W. Day⁸, Richard S. Finkel¹¹, Darryl C. De Vivo⁴, Maria Pia Sormani¹²,
Francesca Bovis¹², Volker Straub⁶, Francesco Muntoni⁵,¹³, Marika Pane¹,²&, Eugenio
Mercuri¹,²&, for the iSMAC Consortium Group.

*All first authors

¹Both senior authors

¹Paediatric Neurology Unit, Catholic University, and ²Centro Nemo, Fondazione Gemelli, Rome,
Italy

³Departments of Rehabilitation and Regenerative Medicine, Columbia University Medical
Center, New York, USA

⁴Departments of Neurology, Columbia University Medical Center, New York, USA

⁵Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital,
London

⁶John Walton Muscular Dystrophy Research Centre, Newcastle University, UK

⁷Department of Physical Therapy, The Children’s Hospital of Philadelphia, Philadelphia

⁸Department of Neurology, Stanford University, Stanfod, California, USA

⁹Department of Neurology, Boston Children’s Hospital, Harvard Medical School, Boston, MA,
USA

¹⁰Department of Physical Therapy and Occupational Therapy, Boston Children’s Hospital,
Boston, MA, USA
Corresponding author:

Eugenio Mercuri

Pediatric Neurology, Catholic University

Largo Gemelli 8, 00168 Rome, Italy

Tel.: +390630155340; fax: +390630154363

E-mail: eugeniomaria.mercuri@unicatt.it
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 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.

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.
The interaction between the three SMA groups and age was significant (p=0.011). There was a significant association with the four age levels (<4 y; 5 y - 9 y; 10 y -14 y; >15 y) in ambulant type 3 patients (p=0.002), while there was no association with age in type 2 and non-ambulant type 3 patients (p=0.12 and p=0.14, respectively).

12 month changes

The changes ranged between -7 and 9 (mean -0.41; SD 2.93). Table 1 shows details of the changes subdivided by functional status and age groups.

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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Change (±SD)</th>
<th>% (n)</th>
<th>% (n)</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 (n:12)</td>
<td>-0.2 (±1.0)</td>
<td>0% (0)</td>
<td>100% (12)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>10-14 (n:7)</td>
<td>-1.4 (±2.5)</td>
<td>14% (1)</td>
<td>86% (6)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>&gt;15 (n:7)</td>
<td>-1.4 (±2.7)</td>
<td>29% (2)</td>
<td>71% (5)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

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).

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).

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).

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 ±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 ± 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.
Acknowledgments

The SMA Foundation, the PNCR Network, the Muscle Study Group, SMA REACH UK, the Italian SMA Network and the patients and families who participated. On behalf of the iSMAC Consortium Group: Chiara Marini Bettolo, Matthew Civitiello, Elizabeth Mirek, Rachel Salazar, Nicola Forcina, Giulia Norcia, Sara Carnicella, Laura Antonaci.

References


