Gain and loss of abilities in type II SMA: a 12-month natural history study

Giorgia Coratti[1,2], Simona Lucibello[1,2], Maria C Pera[1,2], Jacqueline Montes[3,4], Amy Pasternak [5], Jessica Exposito Escudero [6], Elena Mazzone [2], Anna Mayhew [7], Allan M Glanzman [8], Sally Dunaway Young [9], Rachel Salazar[3], Tina Duong[9], Robert Muni Lofra[7], Roberto de Sanctis[2], Sara Carnicella[2], Evelin Milev[10], Marion Main[10], Matthew Civitello[11], Marika Pane[2], Mariacristina Scoto[10], Laura Antonaci[1,2], Annalia Frongia[1,2], Julita Medina[6], Sonia Messina[2], Maria Sframeli [12], Gloria Ferrantini[1,2] , Gianluca Vita [12], Adele D'Amico[13], Marleen van den Hauwe[14], Emilio Albamonte[15], Chiara Marini-Bettolo[7], Nathalie Goemans[14], Basil T Darras [5], Enrico Bertini [13], Valeria A Sansone[15], Francesca Salmin[15], John Day [9], Andres Nascimento Osorio[6], Darryl C De Vivo [3], Francesco Muntoni[10,16]*, Richard Finkel [11]*, Eugenio Mercuri[1,2]*

[1]*Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy*

[2]*Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*

[3]*Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, USA*

[4]*Departments of Rehabilitation and Regenerative Medicine and Neurology, Columbia University Irving Medical Center, New York, USA*

[5]*Departments of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA*

[6]*Neuromuscular Unit, Neuropaediatrics Department, Institut de Recerca Hospital Universitari Sant Joan de Deu, Barcelona, Spain.*

[7]*The John Walton Muscular Dystrophy Research Centre,Newcastle University, Integrated Laboratory Medicine Directorate, Institute of Genetic Medicine, Newcastle Upon Tyne NHS Foundation Trust, Newcastle Upon Tyne, UK*

[8]*Department of Physical Therapy, The Children's Hospital of Philadelphia, Philadelphia*

[9]*Department of Neurology, Stanford University, Stanford, California, USA.*

[10]*Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital, London*

[11]*Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, USA*

[21]*Department of Clinical and Experimental Medicine and Centro Clinico Nemo Sud, University of Messina, Messina, Italy*

[32]*Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy*

[14]*Department of Child Neurology, University Hospitals Leuven, Leuven, Belgium*

[15]*Neurorehabilitation Unit, University of Milan, The NEMO Clinical Center in Milan, Italy*

[16] *NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom*

Corresponding author:

Eugenio Mercuri

Pediatric Neurology, Catholic University

Largo Gemelli 8, 00168 Rome, Italy

Tel.: +390630155340; fax: +390630154363

E-mail: eugeniomaria.mercuri@unicatt.it

Declaration of interest:

GC, RDS, JM, EM, AM, AMG, SDY, RS, MP, SM, ADA, EA, BTD, EB, VAS, JD, FM, DCDV, RF reports personal fees BIOGEN S.R.L.

GC, MC, JM, EM, AM, AMG, SDY, MS, BTD, EB, JD, FM, DCDV, RF, EM reports personal fees ROCHE

GC report personal fees GENESIS PHARMA and Biologix

GC, RDS, EM, AM, AMG, RS, MP, SM, BTD, EB, VAS, JD, FM, DCDV, RF, EM reports personal fees AVEXIS

AP, SDY, RS reports personal fees SMA FOUNDATION

EM, SDY reports personal fees SCHOLAR ROCK

MS report personal fees SMA REACH UK

ADA, JD, RF reports personal fees NOVARTIS

SL, JEE, SC, EM, LA, AF, MVDH, FS, CMB, MC, RML, MM, MS, GV, TD, NG, ANO, JM, GF have nothing to disclose.

Abstract

The advent of clinical trials in spinal muscular atrophy (SMA) has highlighted the need to define patterns of progression using functional scales. It has recently been suggested that the analysis of abilities gained or lost applied to functional scales better reflects meaningful changes. We defined as “gain” a positive change between scores from 0 to either 1 or 2 and as “loss” a negative change from either 2 or 1 to 0.

The aim of this study was to describe, over 12 months, which abilities on the Hammersmith Functional Motor Scale Expanded (HFMSE) were more frequently lost or gained in patients with SMA II.

The cohort included 614 12-month assessments from 243 patients (age range: 30 months - 62.51 years; mean 9.94, SD $\pm$7.91).

The peak of abilities gained occurred before the age of 5 years while the highest number of lost abilities was found in the group 5-13 years. A correlation between the HFMSE baseline score and the ordinal number of the items was found for both lost ($p<0.001$) or gained ($p<0.001$) activities. No correlation was found with SMN2 copy number. These findings will have implications for clinical trial design and for the interpretation of real-world data using new therapeutic approaches.

Keywords: spinal muscular atrophy; shift; pattern of disease progression; Hammersmith Functional Motor Scale Expanded; outcome measures; neuromuscular disorders.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive, progressive neurodegenerative disease caused by mutations in the survival motor neuron 1 gene *(SMN1*) and characterized by the degeneration of α-motor neurons in the spinal cord.

Over the last few years there has been increasing attention to longitudinal natural history data as they provide an important key for the interpretation of data obtained in clinical trials or following the commercial availability of new treatments.

A few recent studies have reported patterns or trajectories of progression assessing longitudinal functional data from the Hammersmith Functional Motor Scale, either in the original (1) or in the Expanded version (HFMSE)(2) . In 2016, as part of a large international effort, we reported that while the mean changes on HFMSE over 12 months in type II patients are small , the range of individual changes is much wider(3) and can be partly predicted by stratifying the type II cohort according to age and *SMN2* copy number. More recently we identified the percentage of patients who remained stable ($\pm$ 2 points), improved or declined on the HFMSE in the different age groups (3).

It has recently been suggested that assessing gain or loss of abilities in the individual items using a 'shift' approach may provide an alternative method to assess disease progression, that more closely captures clinically meaningful changes(4, 5).

The aims of this paper are to describe which HFMSE abilities are more frequently lost or gained at different ages and functional levels in patients with type II SMA.

Materials and methods

The retrospective study was performed by prospectively collected data from different national datasets: the international SMA consortium (iSMAc) including centers in US, UK and Italy(6), and from other networks in Spain and Belgium.

All patients with a genetically and clinically confirmed diagnosis of type II SMA were considered for inclusion if they had at least two assessments, with at least one assessment at 12 months from baseline.

Patients in whom one of the two performances was reported by the examiners as not reliable, because affected by transient pain, fractures, recent pneumonia, or other infections, intercurrent surgery, or any other factor that affected temporarily one of the two assessments, were excluded from the analysis. Data from patients participating in clinical trials or open-label studies on investigational drugs were also excluded.

Only anonymous, de-identified data were analysed. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. In accordance with the ethic requirements, all participants or their guardians provided written informed consent approved by the respective institutional review boards.

HFMSE

The Hammersmith Functional Motor Scale (HFMS) was originally developed to assess the gross motor skills of SMA patients(1). It consists of 20 items, from sitting to standing skills. The HFMSE is composed of the HFMS with an add-on module of 13 items, including more difficult activities as rising from the floor, squatting, jumping, ascending/descending the stairs(2). The final version maintained the same scoring system of the HFMS but with a total score of 66.

Each item on the scale has a 3 point scoring system: 0 unable to perform, 1 performed with compensation/modification and 2 performed without compensation/modification. In this paper, we used a different way of analysing the results, assessing the possibility of patients to lose or gain activities over 12 months, irrespective of their ability to fully perform (score 2 in the original scoring system) or to perform with some compensations (score 1). The shifting method defines as "gain" a positive change from 0 to either 1 or 2 and as "loss" a negative change from either 2 or 1 to 0.

Training sessions

All the participating networks shared the same procedure manual. As part of the activity of each network, individual evaluators were trained at in-person meetings across the US and Europe. The clinical evaluators were the same who participated in the reliability studies of many clinical trials (7). As part of the studies both in Europe and the US, evaluators have regular annual in-person refresher training.

Statistical analysis

The HFMSE was evaluated longitudinally over a 12 month period of time. Each patient could contribute with multiple assessments at 12 month intervals with the same criteria used in the associated paper (ref).

Statistical analysis was performed with SPSS v26 software. The sample is described in its clinical and demographic features using descriptive statistics techniques. The cohort was subdivided into age groups (<5 years, 5-13 years, 14-18 years and >18 years) using similar criteria adopted in previous papers, based on the slope of progression of the HFMSE (8). Quantitative variables are described using the following measures: minimum, maximum, range, mean and standard deviation. Taking into consideration pairs of HFMSE assessment 12 months apart, each item of the scale is classified as follows:

• Shift up (gained function): item score increases from 0 to 1,2

• No change: item scores remain the same, or had changes between 1 and 2 or vice-versa.

• Shift down (loss of function): item score decreases from 1 or 2 to 0.

Frequency distribution was calculated on each item.

Pearson correlation coefficient was used to assess the association between total HFMSE score at baseline and the ordinal number of the items (i.e. their position on the scale) in which there was a loss or gain over 12 months.The association between the shift of individual items and SMN2 copy number were assessed by chi-square.

Results

The cohort included 614 12-month assessments from 243 patients, 134 males, and 109 females. At baseline 488 assessments were from sitters and 126 from non-sitters. One patient had 1 *SMN2* Copy Number, 17 had 2, 175 had 3, 5 had ≥4, in 45 patients *SMN2* copy number was not available.

Age at baseline ranged between 30 months and 62.51 years (mean 9.94, SD 7.91).

HFMSE scores ranged between 0 and 40 (mean: 10.92, SD: ±9.00) at baseline; and between 0 and 41 (mean: 10.33, SD: ±8.82) at 12 months.

The frequency analysis of the individual HFMSE items showed that at baseline, none of the patients included in the study were able to perform items 23 to 33 (e.g. stand to sit, squat, jump and stairs) .

The results of the shift approach showed a loss of one or more activities in 347/614 (56.51%) 12-month assessments, with a loss of two or more activities in 156/614 (25.41%).

There was a gain of one or more activities in 232/614 (37.79%) with a gain of two or more activities in 101/614 (16.45%).

In patients younger than 5 years there was a loss of one or more activities in 95 of the 172 (55.23%) 12-month assessments in that age range, with 45/172 (26.16%) losing two or more activities.

There was a gain of one or more activities in 113/172 (65.70%), with a gain of two or more activities in 59/172 (34.30%).

In patients between 5 and 13 years, there was a loss of at least one activity in 228 of the 324 (70.37%) 12-month assessments in that age range, with a loss of two or more activities in 107/324 (32.41%). There was a gain of at least one activity in 104/324 (32.10%), with a gain of two or more activities in 35/324 (10.80%).

In patients between 14 and 18 years, there was a loss of at least one activity in 15 of the 60 (25.42%) 12-month assessments, with a loss of two or more activities in 10/60 (6.78%). There was

a gain of at least one activity in only 8/60 (13.56%), with a gain of two or more activities in 3 (5.80%).

In patients aged more than 18 years, there was a loss of at least one activity in 9 of the 58 (15.79%) 12-month assessments (25.42%), with a loss of two or more activities in 2/58 (3.51%). There was a gain of at least one activity in 7/58 (12.28%), with a gain of two or more activities in 4 (7.02%).

Gain and loss of individual HFMSE items over one year

Figure 2 shows the details of the frequency analysis for individual items.

Shifts were observed in the first 24 items. All the subsequent items showed a score of 0 that did not change over 12 months.

The chance of losing any activity ranged between 0.16% to 8.14% (mean: 0.029, SD: ±0.027) with items 21 and 22 (hip flexion, right and left side) being the most frequent activities to be lost (7.65% - 8.14% respectively).

The chance of gaining any activity ranged between 0% and 6.84% (mean: 0.027, SD: ±0.021) with items 10 and 11 (lying to sitting and props on forearms) being the most frequent activities to be gained (6.84% - 6.19% respectively).

Figure 3 shows the details of the frequency analysis for individual items subdivided in age groups. The distribution of the percentage of activities loss or gained was different among different age groups (p<0,001).

Baseline HFMSE level and gain and loss of individual items

There was a correlation between the HFMSE baseline total score and the ordinal number of the items in which there was a loss or gain of activity. This was 0.46 (p<0.001) for loss and 0.25 (p<0.001) for gain (Figure 4).

As items 21 and 22 consistently showed loss of abilities, irrespective of the HFMSE baseline total scores, a second analysis was performed excluding these two items. The correlation was 0.74 ($p < 0.001$) for loss and 0.63 ($p<0.001$) for gain.

Figure 4 shows the distribution of abilities lost (A) and gained (B) according to the baseline HFMSE total scores.

Gain and loss of individual items and SMN2 copy number

There was no association with SMN2 copy number and loss ($p=0.783$) or gained activities ($p=0.991$).

Discussion

Our results confirm the already described pattern of disease progression in SMA II patients at different ages(3, 8). In this paper, we used a new approach, so far not used in SMA, assessing how frequently abilities are lost or gained, irrespective of whether the function was achieved completely or with some compensations. The rationale behind this choice comes from recent papers using a similar approach in DMD (4, 5) and from structured patient and parent surveys(9, 10). While in a clinical setting assessing possible intermediate changes is useful to monitor small changes over time and target appropriate intervention, patients and their families are generally more concerned that an activity is performed, even if with some compensation. They report to be more interested in possible changes in gaining or losing the ability rather than in the changes between the scores of 1 and 2, which captures performing the task with and without compensation.

The shift approach, combining scores of 1 and 2, allowed us to establish not only the frequency but also the distribution of items assessing activities that were more susceptible to be lost or gained over 12 months. The possibility to gain one activity was 31% with an additional 16% gaining 2 or more abilities during the 12-months. In agreement with another study in the same cohort reporting patterns of trajectories using raw HFMSE scores (3), we confirmed that the peak of gaining abilities

occurred before the age of 5 years. The highest number of lost abilities was found in the group between 5 and 13 years, followed by the ones between 14 and 18 years. In patients older than 18 years, who had very low total scores, the chance of losing 2 or more activities was less than 10%. In these older patients, as already reported in previous papers, the HFMSE appear to be less sensitive to detect changes as many of the items assessing gross functional motor testing are affected by a number of variables (scoliosis, severe atrophy, fibrosis, contractures) that are more obvious at this age. Contractures in particular may play a major role in limiting some of the functional aspects in the HFMSE but unfortunately they were not systematically measured with similar methods across the centers.

As the HFMSE was designed as ordinal scales, there is always a concern that some items may be more easily prone to changes than others. Our results showed that the possibility to find changes in the individual HFMSE items was within a narrow range. The items that were more frequently lost were 22 (8.14%) and 21 (7.65%), assessing hip flexion on left and right side. The items that were more easily gained were 10 (6.84%) and 11 (6.19%) assessing sitting to lying and props on forearms respectively.

The changes were not clustered in a number of restricted items but were quite evenly distributed across the spectrum of the abilities that are relevant in a non-ambulant cohort, from item 1 to 22. Interestingly, the items that were lost or gained were always those close to the last item gained on the scale, with a correlation ($p<.001$) between the HFMSE baseline total score and the ordinal number of the items in which there was a loss or gain of activity. This probably reflects the fact that the order of the items on the original Hammersmith scale was based on the frequency distribution of abilities observed in SMA patients (1). Item 1, sitting, was the item gained in the highest percentage of type II patients, while item 20, stepping, was only found in the strongest end of the spectrum of type II.

The shift approach used in this paper may reduce the sensitivity to detect possible intermediate changes (from 1 to 2 or vice-versa) that are often used in clinical settings to monitor possible

changes but, on the other hand, has the advantage of reducing the possible confounding effect of the intermediate scores. As a score of 1 is given even for minor compensations, the risk to observe changes between 2 and 1 in consecutive assessments is relatively high in weak patients. This is likely to reflect the effect of general well being, behaviour, sleep deprivation, constipation or other factors that may interfere with the ability to perform the task with or without compensations.

Two studies applying Rach analysis to the HFMSE and to its revised version that keeps a similar construct of the items(11, 12), suggest the possibility to dichotomize the scoring options to adjust items response categories and ensure scoring options work as intended. While this does not necessarily mean that the current 3 point scoring system is not meaningful for individuals, especially in a clinical setting, it provides evidence that the dichotomization used in the shift approach is statistically sound and justified.

This approach has recently been used in other neuromuscular disorders (4, 5)and may provide a useful additional tool both to assess treatment effect or natural history changes. In a recent study, Mc Donald et al. introduced the concept that the loss of ability in the 17 individual items of the NSAA may provide additional information on treatment effect to the conventional analysis of the changes in the total NSAA raw scores(5). In a posthoc analysis after 48 weeks, patients given ataluren lost 12.2% (203/1,665) of functions compared with 17.8% (294/1,656) of functions lost by patients given a placebo, equating to a 31% reduced risk of loss of function for ataluren-treated patients. This information appeared to be more relevant than the changes in the raw scores. A more recent natural history study also used a similar approach in DMD to better characterize the risk of deterioration or improvement in the different age range categories(4).

These findings suggest that the shift approach could be used, in a research setting, as an additional tool for the analysis and the interpretation of HFMSE data and may prove to be useful at the time real world data are increasingly becoming available in type II patients.

Acknowledgments:

We are thankful to the Italian Telethon, the SMA Reach UK and SMA Foundation four having founded this study.

Funding: This work was supported by the Italian Telethon, the SMA Reach UK and SMA Foundation.

References

1. Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. Eur J Paediatr Neurol. 2003;7(4):155-9.
2. O'Hagen JM, Glanzman AM, McDermott MP, Ryan PA, Flickinger J, Quigley J, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 2007;17(9-10):693-7.
3. 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.
4. Muntoni F, Domingos J, Manzur AY, Mayhew A, Guglieri M, Network UKN, et al. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. PLoS One. 2019;14(9):e0221097.
5. McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10101):1489-98.
6. Mercuri E, Finkel R, Scoto M, Hall S, Eaton S, Rashid A, et al. Development of an academic disease registry for spinal muscular atrophy. Neuromuscul Disord. 2019;29(10):794-9.
7. Glanzman AM, Mazzone ES, Young SD, Gee R, Rose K, Mayhew A, et al. Evaluator Training and Reliability for SMA Global Nusinersen Trials1. J Neuromuscul Dis. 2018;5(2):159-66.
8. Mercuri E, Lucibello S, Pera MC, Carnicella S, Coratti G, de Sanctis R, et al. Long-term progression in type II spinal muscular atrophy: A retrospective observational study. Neurology. 2019;93(13):e1241-e7.
9. Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscul Disord. 2017;27(5):428-38.

10. Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto M, Montes J, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC Neurol. 2017;17(1):39.
11. Cano SJ, Mayhew A, Glanzman AM, Krosschell KJ, Swoboda KJ, Main M, et al. Rasch analysis of clinical outcome measures in spinal muscular atrophy. Muscle Nerve. 2013.
12. Ramsey D, Scoto M, Mayhew A, Main M, Mazzone ES, Montes J, et al. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. PLoS One. 2017;12(2):e0172346.

Figure legend:

Figure 1. Number of items changed over 12 months subdivided by age groups.

Black columns represent % of negative shift (loss) and white columns % of positive shifts (gain). Panel A: <5years (n=172); Panel B: 5-13 years (n=324); Panel C: 14-18 years (n=60); Panel D: >18 years (n=58).

Figure 2. Details of the frequency analysis for individual items in the whole cohort (n=614).

Black columns on the left side represent % of negative shifts (2->0 or 1->0). Black columns on the right side represent % of positive shifts (0->2 or 0->1).

Figure 3. Details of the frequency analysis for individual items subdivided by age. Left side (From 0% to 10%): *Black columns on the left side represent % of negative shifts (2->0 or 1->0). Black columns on the right side represent % of positive shifts (0->2 or 0->1). Panel A: <5years (n=172); Panel B: 5-13 years (n=324); Panel C: 14-18 years (n=60); Panel D: >18 years (n=58).*

Figure 4. Details of the distribution of abilities lost and gained in relation to the baseline HFMSE total score. *Each dot represents HFMSE baseline scores(x-axis) and item lost after 12 months (y-axis). Panel A: loss of abilities; Panel B: gain of ability*