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Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials

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Abstract

The aim of the study was to establish 12-month changes in the Hammersmith Functional motor scale in a large cohort of SMA patients, to identify patterns of disease progression and the effect of different variables. 268 patients were included in this multicentric study. Their age ranged between 2.5 and 55.5 years at baseline, 68 were ambulant and 200 non-ambulant. The baseline scores ranged between 0 and 66 (mean 23.91, SD 20.09). The 12-month change was between −14 and +9 (mean −0.56, SD 2.72). Of the 268 patients, 206 (76.86%) had changes between −2 and +2 points. Ambulant and non-ambulant subjects had a different relationship between baseline values and age (p for age X ambulation interaction = 0.007). There was no association with age in ambulant subjects, while there was a significant heterogeneity at different age for non-ambulant patients ($p < 0.001$). The 12-month change (adjusted for baseline) was not associated with age in ambulant patients ($p = 0.34$), but it was significantly different among various age groups in non-ambulant patients. Our results suggest that there are different profiles of progression in ambulant and non-ambulant patients, and that age may play an important role in the progression of non-ambulant patients.

1. Introduction

The advent of clinical trials in spinal muscular atrophy (SMA) has highlighted the need to identify reliable outcome measures and to collect natural history data [1,2]. A few studies have already reported longitudinal data using different functional measures [3–13] such as the Hammersmith Functional Motor

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Scale (HFMS). The HFMS, in its original version for non-ambulant SMA patients or as an expanded version suitable for both ambulant and non-ambulant SMA (HFMSE), is routinely used in several centers across the world and it has also been used for several multicenter natural history studies [6,7,9]. Recent studies in type 2 and 3 SMA patients have suggested that the overall mean of HFMSE 12-month changes were minimal [6] but there was no attempt to identify possible different trajectories of progression in subgroups of patients. This information may be valuable at the time of selecting inclusion and stratification criteria for clinical trials or for the interpretation of the results [14]. Even if the reported data include relatively large cohorts it was felt that larger datasets were needed to perform a more accurate analysis aimed at identifying possible subgroups trajectories.

We retrospectively merged databases from different large multicentric networks in the United States and Europe in order to establish (i) 12-month HFMSE changes in a larger cohort than those previously reported; (ii) possible differences of progression between ambulant and non-ambulant patients; (iii) the possible effect of different variables, such as gender, baseline values or age on the progression of the disorder; and (iv) possible outliers and the reasons for performing differently.

2. Subjects and methods

This retrospective study was performed by collecting data from different existing large multicentric datasets, including one network based in the United States (the Pediatric Neuromuscular Clinical Research Network for SMA) and 5 European centers (three in Italy, one in UK and one in Belgium) that are part of a larger European network.

All patients had a genetically confirmed diagnosis of SMA with a homozygous deletion of exon7 in the *SMN1* gene, and a clinically confirmed diagnosis of type 2 or 3 SMA. To reduce selection bias, all patients seen in the neuromuscular clinics who fulfilled eligibility criteria were consecutively offered enrollment. Only patients with at least two assessments at a 12-month interval were selected for this study. Patients in whom one of the two performances was 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. Similarly, according to recent studies suggesting that the introduction of albuterol may cause a sudden improvement in scores that can persist for the first 12 months [15], we excluded those who had started treatment in the 12 months before the study or who started the treatment between the two assessments.

Clinical information regarding age and weight were noted. Contractures were routinely assessed as part of clinical evaluation but were not prospectively systematically assessed using a standardized protocol. Baseline height, weight and interval changes were identified in most subjects but not in a systematic fashion.

As part of the activities of the two networks, all participants or their guardians provided written informed consent approved by the respective institutional review boards.

2.1. HFMSE

The scale consists of 33 items, investigating the child's ability to perform various activities. Each activity (item) is scored on a 3-point scoring system, with a score of 2 for "performs without modification", 1 for "performs with modification/adaptation" and 0 for "unable to perform". A total score can be achieved by summing the scores for all the individual items. The total score can range from 0, if all the activities are failed, to 66, if all the activities are achieved. All items have to be tested without spinal jacket or orthoses.

2.2. Training sessions

Training was performed independently in US and Europe networks. As part of the activity of each network, evaluators used a procedure manual that was common for the two networks, and were trained at in-person meetings. Inter and intra observer reliability of the two networks have already been reported [1,6,7].

2.3. Statistical analysis

The HFMSE was evaluated longitudinally over a 12-month period of time. Summary statistics (N, mean, median, SD, range) were used. Baseline values of the Hammersmith scale were compared between ambulant and non-ambulant subjects using an ANOVA model adjusting for age. The dependence of the baseline values of the Hammersmith scale on age was examined by an ANOVA model testing the heterogeneity among age classes (since the relationship was not linear at a visual inspection) and was compared between ambulant and non-ambulant patients by an interaction test.

A piecewise linear regression was used to assess changes in the slope of baseline values of the Hammersmith scale at different cut points of age.

The 12-month change in the Hammersmith scale values was compared between age classes by an analysis of variance, adjusting for baseline in ambulant and non-ambulant patients. As previous studies have shown that the great majority of changes is within ±2 points, we considered this range of changes [8,9]. The percentage of patients with a change <−2, between −2 and 2, and >2 points was compared across age classes by a Chi-square test (a multinomial model was used to adjust for baseline values).

3. Results

A total of 294 patients fulfilled the inclusion criteria. Twenty had transient issues affecting one of the two assessments (11 transient pain, 9 limited cooperation at one assessment). Another 6 were excluded because they had started albuterol within 6 months or after the first assessment.

The remaining 268 were included in the study for further analysis. One hundred and forty-four of the 268 were males. Their age ranged between 2.5 and 55.5 years at baseline (mean 10.65, SD 8.39). Sixty-eight were ambulant and 200 were non-ambulant at the time of the assessment (196 type 2 and 4 type 3 who lost ambulation).

Table 1
Details of weight and contractures in outliers.

PZ	Age	SMA type	1 year weight gain	Increase in contractures
1	3.6	II	5 kg	No reported change
2	6.3	III A	5 kg	No reported change
3	4.3	III A	7 kg	No reported change
4	20.8	II	5 kg	No reported change
5	7.1	II	7 kg	No reported change
6	9.5	III A	13 kg	No reported change
7	4.33	II	6 kg	10° ankles
8	5.4	II	6 kg	No reported change
9	7.83	II	5 kg	No reported change
10	12.10	III A	5 kg	No reported change
11	10.70	III B	6 kg	No reported change
12	16.83	II	7 kg	No reported change
13	5	II	7 kg	15° knees
14	4.08	II	5 kg	No reported change
15	9.70	III B	6 kg	No reported change
16	6.7	III A	6 kg	No reported change
17	8.25	II	6 kg	No reported change
18	6	III A	1 kg	20° hips
19	10.5	III A	No reported change	15° knees
20	14.7	III A	No reported change	15° hips
21	3.5	II	1 kg	10° ankles
22	7	II	3 kg	15° knees

Fig. 2. Baseline values of the Hammersmith scale according to age in ambulant and non-ambulant children.

The HFMSE scores ranged between 0 and 66 (mean 23.91, SD 20.09) at baseline and between 0 and 66 at 12 months (mean 23.28, SD 20.07). The 12-month change was between −14 and +9 (mean −0.56, SD 2.72) (Table 1).

Of the 268 patients, 206 (76.86%) had changes between −2 and +2 points, 41 (15.30%) had a decrease in scores of more than 2 points and 21 (7.84%) had an increase in scores of more than 2 points on the HFMSE (Fig. 1).

3.1. Ambulant versus non-ambulant

3.1.1. Baseline values

Baseline values of the HFMSE were significantly different between ambulant and non-ambulant patients (Fig. 1): the mean value was 53.6 (SD = 6.8) in ambulant and 13.8 (SD = 11.0) in non-ambulant subjects (p < 0.001, adjusting for age).
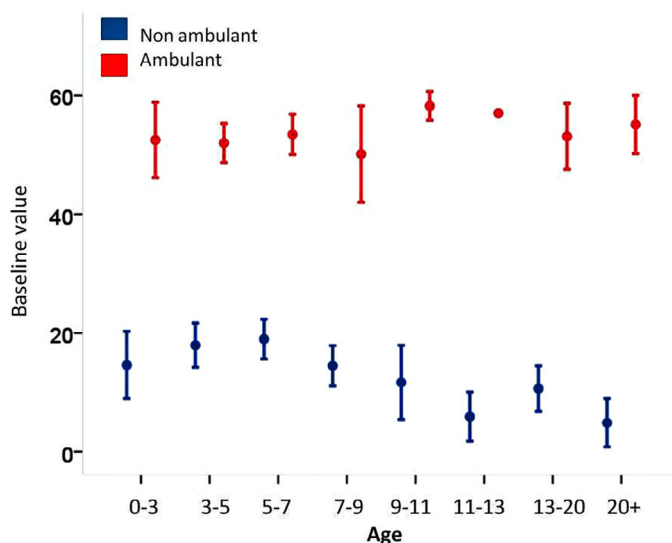
The relationship between baseline values and age was significantly different in ambulant and non-ambulant subjects (p for age X ambulation interaction =0.007): there was no association with age in ambulant subjects (Fig. 2), while there was a significant heterogeneity at different age levels for non-ambulant patients (p for association of baseline values with different age groups <0.001).

Since the relationship clearly was not linear, with an increase at younger age, and a subsequent decrease eventually reaching a plateau, a stepwise regression was applied to test for the presence of cut points of age, where the slope of the dependence of Hammersmith values and age changes. Two relevant cut points were detected: the slope was estimated to be 6.1 (SE = 3.1) points per year up to the age of 4.35 (first cut point, SE = 0.48); followed by a slope of −7.2 points per year between the age of 4.35 and the age of 15.2 (second cut point, SE = 3.4); finally the slope after the age of 15.2 was 0.93 points per year (Fig. 3). The greatest interval change was between 9–11 and
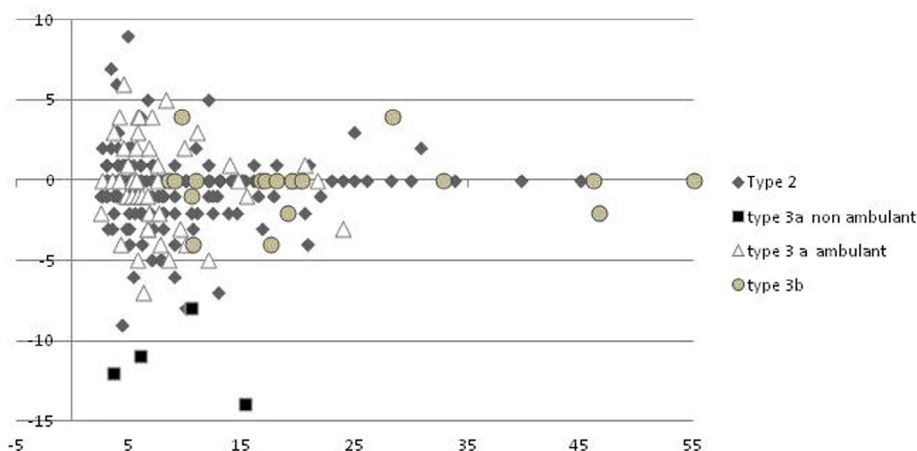

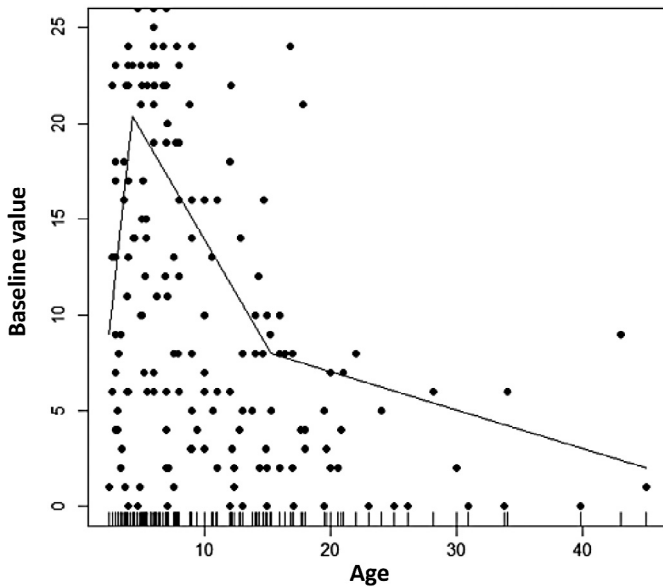Fig. 1. HFMSE 12-month changes: individual details according to age.

Fig. 3. Scatter of baseline values of the Hammersmith scale.

Fig. 4. Average 12-month change of the Hammersmith scale according to age classes and ambulation.

11–13 years. There was no detectable difference in these patterns between males and females.

According to these findings, in order to study the 12-month change, we grouped patients in three different classes based on their age: younger (age < 5 years), intermediate (age ≥ 5 and age < 15 years) and older (age ≥ 15 years).

3.1.2. 12-month changes

The 12-month change was not significantly different between ambulant and non-ambulant patients (average change = −0.56 in ambulant vs −0.57 in non-ambulant patients), but the difference became significant when adjusting for baseline values and age class (adjusted mean = +0.83 for ambulant patients vs −0.84 for non-ambulant patients, p = 0.029).

The 12-month change (adjusted for baseline) was not associated with age in ambulant patients (p = 0.34), while it differed significantly in different age groups in non-ambulant patients: the mean 12-month change was +0.04 (SE = 0.34) in the younger group, −0.96 (SE = 0.24) in the intermediate group and −0.35 (SE = 0.43) in the older group (Fig. 4, p = 0.048). No statistically significant differences were detectable for the sex of the patients.

Separating ambulant children in 2 classes (SMA IIIA and SMA IIIB) did not change the results. A trend for an increase of change with age class was detectable in SMA IIIA children (p = 0.067) while no association with age was revealed in SMA IIIB patients (p = 0.80).

As an additional analysis, patients were classified according to their 12-month change as those having a change ≤−2 points, a change between −1 and +1 point, and ≥+2 points. There was a different distribution of patients with these 3 levels of change according to age class in non-ambulant patients (also after adjusting for baseline levels) (Table S1).

4. Discussion

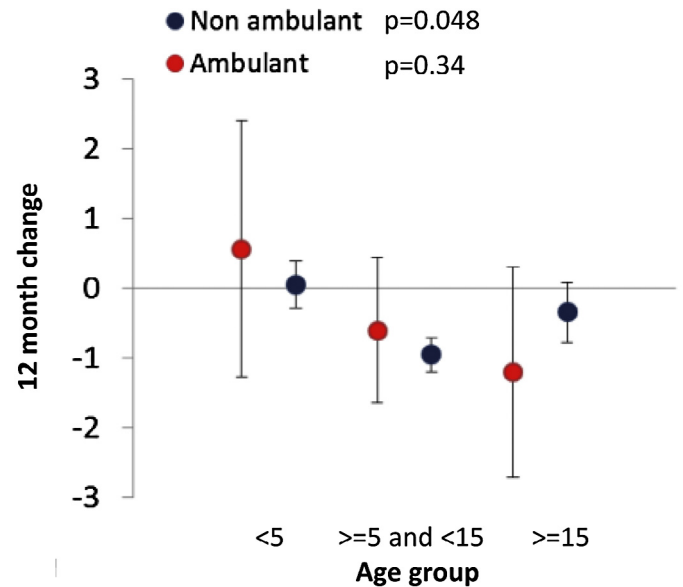Our study provides the largest set of longitudinal data reported so far in patients with SMA types 2 and 3. This was obtained by merging smaller datasets including prospectively collected data from different centers. Combining datasets was possible because all the participating centers used the same functional assessment with similar assessment schedules, and had similar standards of care. Reliability across centers was thought to be appropriate as not only all evaluators within the individual networks received a formal training but evaluators from different networks had the opportunity to share training material and training procedures across networks. There were, however, differences in the methods used for determining contractures or scoliosis and in the additional information collected, such as weight and height, that have limited the possibility to explore the effect of some of these variables on SMA progression.

The results obtained in 268 patients confirm previous findings that ambulant and non-ambulant patients show small mean changes over a 12-month period on the HFMSE. The great majority of patients (over 75%) had changes ±2 points, with less than 10% showing an improvement of more than 2 points, in agreement with previously reported data. We also aimed to establish whether, given a much larger dataset, a number of variables, such as functional level, gender or age could affect the magnitude of changes. We were also interested in establishing if any of these variables could provide some explanation for the patients with changes falling outside ±2 point and, more generally, whether we could identify subgroups of patients showing different trajectories of progression of the disease.

When we analyzed the data subdividing the cohort into ambulant and non-ambulant subgroups, there was a significant difference both at baseline and on the 12-month changes between the two subgroups.

Female patients tended to have better baseline values and smaller changes compared to male patients in both ambulant

and non-ambulant subgroups but the differences were not significant at 12 months.

The relationship between baseline values and age, in contrast, was different (p for age X ambulation interaction =0.007) in the two subgroups as there was a significant heterogeneity at different age levels for non-ambulant patients (p for association of baseline values with different age groups <0.001), but not for the ambulant ones. The profile observed at baseline in the non-ambulant subgroup showed an increase at younger age, with a subsequent decrease between the age of 5 and the age of 15 and a plateau in older patients.

A similar difference was observed also when 12-month changes were analyzed. The 12-month change (adjusted for baseline), again, was not associated with age in ambulant patients (p = 0.34), but was significantly different in different age groups in the non-ambulant ones. Patients between 5 and 15 years had the largest negative 12-month change (−0.96) as opposed to smaller negative changes in the older group (−0.35) and to a small positive mean change (+0.04) in the youngest group. Not surprisingly, when we looked at the outliers, the possibility of improving more than 2 points was highest in the children below 5 years of age. These results are in agreement with findings in previous clinical trials evaluating phenylbutyrate, valproic acid, or salbutamol [15–19] showing that children in this age range were more likely to show motor functional improvement than the older ones. This would also be in keeping with pathological data derived from SMA-like mice suggesting that SMA motoneuron death is a later postnatal phenomenon, preceded by a severe chronic dying-back axonopathy [20].

In contrast, children between 5 and 15 years had the largest negative 12-month change and the highest risk of losing more than 2 points. This is likely to be due to the fact that in the years leading to and throughout puberty, patients are more likely to experience weight gain and increased contractures and scoliosis. In our cohort, a sudden increase in weight or contractures was reported in 22 of the outliers, while these complications were not reported in the rest of the cohort. However, as the study was not prospectively designed to capture these aspects, and weight and height were not always systematically noted at each assessment, we cannot rule out that the annotation of these findings in the outliers was prompted by the magnitude of changes observed and that similar findings may also be occurring in patients with more stable scores. These findings highlight the need to standardize a contracture assessment protocol and systematically collect weight and height and also adverse events using a standardized method.

The possible effect of increased weight and contractures are concordant with previous observations regarding the decremental effect of weight and BMI on functional activities [7,19,21] and are also suggested by the fact that in older patients, in whom contractures and weight are generally more stable, the scores showed less changes. In this subgroup there were several patients who had, in contrast, transient pain episodes that were not included in the analysis. It is of note that altogether there were approximately 10% of the patients in whom one of the two performances was affected by intercurrent factors. This information may be relevant at the time of powering new clinical studies.

5. Conclusions

The overall results confirm that the mean 12-month changes in the whole cohort were very small, but we were also able to demonstrate that the range of individual changes was relatively wide; and that although the majority of patients fell within ±2 points, there were a number of outliers including both patients increasing or decreasing more than two points. Having a larger cohort than those previously reported allowed us to identify different profiles of progression in ambulant and non-ambulant patients. Our data also suggest that age may play a more important role in the progression of non-ambulant patients. These findings will be of help when deciding inclusion and stratification criteria for clinical trials. Further studies collecting more detailed information on the changes in weight and contractures, adverse events, and correlation with SMN2 copy number, that were not available for all the patients included in the present study, will help to better define the effect of these variables on the progression of SMA.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2015.10.006.

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