Longitudinal changes in respiratory and upper limb function in a paediatric type III spinal muscular atrophy cohort following loss of ambulation

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Abstract

Introduction/Aims

Spinal muscular atrophy (SMA) type III is a relatively mild form of SMA. There is a paucity of studies investigating changes in both respiratory and upper limb function within this population after loss of ambulation. The aim of this study is to investigate the change in percentage of predicted forced vital capacity (FVC% predicted) and the change in the revised upper limb module (RULM) score in these patients across a 24-month period after loss of ambulation. The effect of scoliosis and its surgical correction, disease duration since loss of ambulation, weight and height were also investigated.

Methods

Retrospective analyses were performed on 24 non-ambulant SMA III patients on data collected at two UK centres.

Results

The FVC% predicted score showed a significant progressive deterioration of 17% over the 24-month period. Respiratory deterioration was significantly correlated with age, weight, disease duration since loss of ambulation and spinal correctional surgery. Longitudinal data on RULM was available in 16 patients; a significant deterioration was observed with a mean decrease in score of 3 over 24 months. Age was negatively correlated withRULM score, as was height and time since loss of ambulation. A significant positive correlation between FVC% predicted and RULM was demonstrated.

Discussion

This study highlights that SMA type III patients demonstrate progressive deterioration in their respiratory and upper limb function after loss of ambulation. Combining data from these assessments could provide insight into clinical progression, inform clinical trials and help to manage disease progression expectation for patients.

Key words: **Spinal Muscular Atrophy, Respiratory function, Outcome measure, Physical therapy**

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by an absence of the survival motor neuron 1 gene *(SMN1)* and a deficiency of SMN protein [1 - 5]. SMA is associated with proximal muscle weakness which can lead to secondary complications including scoliosis, joint contractures and respiratory decline [1, 5]. Type III SMA children are ambulant but lose motor function over time and many become wheelchair dependant [5, 6]. Information on individual patient outcomes is limited; while some studies indicate a relatively stable clinical course, others describe the condition as a slowly progressive disorder associated with a decline of strength [1, 5, 7 - 10]. These inconsistent descriptions are likely to complicate the evaluation of treatment-related clinical data and may in part be due to the limited scope of motor performance measures used in this group. Earlier manuscripts suggest that SMA III individuals are less likely to develop scoliosis and have little respiratory muscle weakness compared to type II, however newer evidence shows respiratory complications in type III patients [1, 6, 11]. Non-ambulant paediatric SMA III patients commonly develop contractures and scoliosis and this requires spinal fusion when the scoliosis deformity is sufficiently severe [6].

At the time of this manuscript's submission the disease modifying drug nusinersen was not available for SMA type III patients who had lost ambulation for more than 12 months, as per the UK managed access agreement approval in 2019 [4]. Nusinersen is specifically designed to increase the amount of functional SMN protein by altering splicing of *SMN2* pre-mRNA [12 - 14]. A recent study reported the benefit of nusinersen treatment over a three-year period for 17 type III patients with an improvement in 6-minute walk test time and a maintenance of skills in the Hammersmith motor function scale [12]. However, this study did not specify ambulation status and longitudinal data on upper limb function was not reported for the type III patients. Due to the lack of evidence proving sufficient benefit for the non-ambulant SMA type III at the time of the managed access agreement, this sub-population is currently outside the label of prescription in the UK.

Here we present a study assessing two key variables in a cohort of SMA type III non-ambulant patients: Pulmonary function test and the Revised Upper Limb Module (RULM). The aim of this retrospective, longitudinal, multicenter natural history study is to assess whether SMA type III non-ambulant patients

continue to significantly deteriorate in their pulmonary function and/or their upper limb strength following loss of ambulation.

2. Methods

2.1 *Identifying patient cohort*

Patients with a confirmed genetic and clinical diagnosis of SMA type III were included in this retrospective study across two research centers in the UK: Great Ormond Street Hospital in London and John Walton Muscular Dystrophy Research Centre in Newcastle. The study had local ethical approval and all patients were consented to SMA REACH (11DN15).

Inclusion criteria is as follows, ages between 4 and 18 years old, Nusinersen naïve and non-ambulatory as per the WHO definition [12].

Patients with recent surgery (less than 6 months) or in whom one of the performances were temporarily affected by another factor were excluded.

Respiratory function and upper limb strength, amongst other routine measurements, were measured on average every 6 months. Height and weight were measured at each visit and if patients were unable to stand, standardized arm span measurements were used instead to estimate the height, according to SMA REACH UK protocols.

Information regarding timing of spinal surgery and onset of scoliosis were evaluated along with key patient demographics. Contractures, Cobb angles and use of knee ankle foot orthoses were recorded at clinical visits but excluded from this study's analysis due to the incomplete datasets; all are summarized in **Supplementary Table 1.** All recruited patients who had undergone spinal surgery had a fixed spinal fusion. No patients were lost to follow-up and none started on nusinersen throughout the course of the study. Data collection occurred between 2002 and 2019.

2.2 Respiratory function

Respiratory assessments were performed by a lung function technician or physiotherapist who had received appropriate training and certification for clinical trials on Vyaire's SES Software. The global lung initiative equations were used to collect the percentage predicted equations.

Patients were required to blow into the spirometer at maximal effort; three reliable efforts were recorded with the maximum result used for analysis according to international guidelines [16].

2.3 *Revised upper limb module for SMA*

The RULM is an established scale to evaluate upper extremity function in SMA; it was assessed as per standard protocol [17]. Patients were allowed two attempts per item; the total score can range from 0 – 37. All items were tested without any orthosis. Only the dominant arm was tested for each patient and the same arm was used for each patient throughout the study. The RULM assessment was carried out by trained physiotherapists as part of the SMA REACH network. Total RULM score was used for analysis [17].

2.4 *Data analysis and statistics*

Analysis was carried out on data that contained 24-month follow-up results. A 24-month follow-up period was used due to previous studies investigating changes in motor function scales over a 12-month period rarely finding significant results due to the slow progression of the disease [1, 18]. Results are presented as median change over 24 months. As the outcomes are measured on different scales they have been calculated separately. All analyses were performed using SPSS Statistics version 25 (IBM, Armonk, NY). Wilcoxon signed rank test was used and the limit of statistical significance was set to 0.05. Pearson correlations were calculated for height, weight, gender, age, disease duration since loss of ambulation, scoliosis and spinal surgery for FVC% predicted and RULM. Disease duration since loss of ambulation was used as a separate variable by grouping it into 6 monthly sections e.g. 0-0.5 years, etc. Summary statistics of mean (standard deviation), median and range were used.

3. Results

3.1 *Patients*

A total of 24 patients were included (9 male and 15 female), with a median age at baseline of 10.5 years (4.2 – 15.3). Ten had a scoliosis prior to the study while an additional four developed scoliosis during the study. One patient previously had spinal surgery and six had spinal surgery during the 24 months. None of the patients was treated with nocturnal ventilation. Not all the Cobb angles were known for these patients; those that are can be found in **Supplementary Table 1.**

3.2 Forced vital capacity

The median FVC% predicted score was 96% (range 66%-131%) at baseline and 80.5% (range 39% - 129%) at 24 months (**Figure 1a)** with an average statistically significant decrease of 17% (SD 14.3%) ($p<0.05$). The large range of +9 to -51% is due to one patient increasing whilst the remaining patients deteriorated.

The age of the patient was negatively correlated with their FVC% predicted score (**Figure 1a**). This was explored by splitting the cohort into categories of ≤ 13 and >13, these results were not significant. The disease duration since loss of ambulation also correlated with respiratory function (**Figure 1b**). The median disease duration was 0.5 to 1 year since loss of ambulation. Patients who had surgery within the 24-month study period deteriorated significantly more in the FVC% predicted score compared to individuals without scoliosis or surgery (0.432, $p = 0.040$). Those who had surgery deteriorated by an average of 27%, those with scoliosis by 15% and those with neither scoliosis nor surgery by 12%. Patients who had or developed scoliosis within the 24-month study period, but who did not undergo spinal surgery, did not show a significantly different rate of deterioration than those without scoliosis. The weight of the patients was not significantly correlated with FVC% predicted score nor was the change in FVC% predicted versus change in weight over 24-months and there was no significant difference between male and female FVC% predicted rates of change.

3.3 Upper limb function

Sixteen out of the 24 patients (3 male and 13 female) with a mean age at baseline of 11.5 years (range 6.2-15.7) were assessed with the RULM. Five of the patients already had scoliosis and a further two

developed it during the 24-months. One patient previously had spinal surgery and a further five required spinal surgery during the study.

The median RULM score was 30 at baseline (range 19 - 37), and 27 at 24-months (range 16 - 37) **(Figure 2a)** showing a statistically significant deterioration of 3 points (range -8 to +1) ($p<0.05$). RULM score increased by 1 point in one patient (<9 years at baseline), remained stable for three patients (all >13 years at baseline) and the remaining twelve deteriorated throughout the study period.

The age of the patient was negatively correlated with their RULM score (**Figure 2a)**. This was explored by splitting the ages into groups ≤10 years, 10-15 years and >15, however the results of this were not significant (0.148, $p = 0.584$). The height of the patient was negatively correlated with RULM score (**Figure 2b**). The disease duration since loss of ambulation negatively correlated with the RULM score (**Figure 2c**). There was no significant difference in RULM score for patients with or without scoliosis or between those who did or did not have surgery during the study period. There was no significant difference between male and female RULM score rates of change over the study period and the weight of the patient was not correlated with RULM score.

3.4 Correlation between outcome measures

FVC% predicted positively correlated with RULM score at baseline and at 24 months (**Figure 3)** however the percentage change in RULM score and percentage change in FVC% predicted over the 24-month period did not correlate.

4. Discussion

The data from this study demonstrates that non-ambulant SMA type III patients significantly decline in both FVC% predicted and RULM following loss of ambulation over a 24-month period. The respiratory function decline is in line with previous studies, but these included data mainly from type II patients [5, 19]. Type II patients are considered more severely affected and yet their RULM scores are comparable to type III patients who have also lost ambulation [11, 20]. The average FVC% decrease was a statistically significant 17% in 24-months. According to the most recent standards of care, FVC% predicted below 60% is associated with increased risk of sleep disordered breathing, and 12.5% of our cohort at 24 months were below 60% [21]. The average RULM scores reported for non-ambulant type III patients in this study were comparable to other studies [9, 18]. It has been previously reported that a change in RULM greater than 2 points is deemed clinically significant [18]. As an average reduction of 3 points was observed in this cohort along the 24 months follow up these findings reinforce the significance of the progression observed.

This data suggests that age may play an important part in the profile of progression in non-ambulatory patients. Age was negatively correlated with both outcome measures as shown in **Figures 1a** and **2a**. It should be noted that the average age of the patients within this study is younger than comparable studies due to analysis being conducted specifically on a paediatric population. A previous study found that FVC% predicted decline in type III non-ambulant patients was steeper between 8-13 years [11]. Although we did not find any significant difference in FVC% predicted when splitting into age categories, this was likely due to the small numbers in each group. Another study found that upper limb strength in non-ambulant SMA patients increased before the age of 14 and subsequently decreased [1]. In our study, we did not find a significant difference when considering the age groups, likely due to the small sample size of each group.

Previous studies have shown that females appeared to have worse pulmonary function, with a more pronounced decline, compared to males [5, 10]. However, this was not found to be the case in our cohort; no significant difference was found between genders in their FVC% predicted score or in their RULM score throughout the study.

We demonstrated that weight was not correlated with FVC score, and neither was the percentage change in weight with the percentage change in FVC score over the 24-month period. No significant correlation was found between weight and RULM score in the cohort of patients in our study either. These results were not in line with previous models which found that weight, and an increased BMI, had a detrimental effect on function. However previous studies combined types II and III SMA patients together in their analyses and used the Hammersmith Motor Function Scale Expanded, which considers full body function, as opposed to the RULM, which focuses solely on upper limb function [7].

Height was significantly negatively correlated with RULM score. This is not unexpected as upper limb and trunk growth can affect the way in which patients perform activities with their arms making some of the RULM tasks more difficult to complete.

It has been reported that upper limb strength decreases over time in SMA patients, although longitudinal studies are scarce [1, 9]. While some studies have shown that type III patients continue to deteriorate in their FVC and RULM scores following loss of ambulation, it had not previously been explored whether this deterioration occurs immediately following loss of ambulation or whether the deterioration gradually continues once the patient is non-ambulant. The impact of surgery also has not been explored [10, 11]. One previous study found that ambulatory status at baseline did not significantly affect longer-term respiratory function [10]. We demonstrated that FVC% predicted and RULM scores were both significantly negatively correlated with disease duration since loss of ambulation. Exploring whether disease duration since loss of ambulation affects lung function and upper limb strength has been explored in patients with Duchenne muscular dystrophy [22].

We found that patients who had or developed scoliosis and had spinal correction surgery during the study period deteriorated more in their FVC% predicted; however, this result was only significant for spinal surgery. Another large recent retrospective study also reported a decline in function with scoliosis and surgery in type III patients; however, their result was non-significant [11]. Scoliosis surgery has previously been shown to lead to a subsequent decline in gross motor function as well as pulmonary function [5]. Surgery will only be performed when necessary to preserve long-term lung function, gain postural stability and improve quality of life by stabilising the worsening spine curvature. As this is

beneficial for patient's long-term function it is difficult to assess if an immediate deterioration in function would be a clinically meaningful functional impairment in the long term, also considering that not treating severe scoliosis will in turn lead to restriction of respiratory function [5].

We found that FVC% predicted score correlated with RULM score demonstrating a significant global deterioration in this patient population in both respiratory function and upper limb strength following loss of ambulation and this is in line with a recent large-scale retrospective study [11]. However, we found that there was no significant correlation between the percentage change in RULM score and the percentage change in FVC% predicted score over the 24-months. This is likely due to the two scales measuring different constructs and domains that may deteriorate at different rates.

Limitations of this study include the rarity of the disease, meaning a small sample size especially when trying to look at specific age and functional categories. A highly variable loss of ambulation age and incomplete data sets meant that factors such as Cobb angle, orthotic use and contractures could not be explored.

Nusinersen has been shown to have a positive effect in SMA type I and II patients [12 - 14]. A previous study reported that in type III children nusinersen can stabilize the disease progression [12]. Future research comparing longitudinal data of nusinersen treated type III non-ambulant patients to a matched cohort of nusinersen naïve patients would help to establish whether there is a positive impact in upper limb strength and respiratory function. In the future, research combining correlative data from these assessments, and others such as muscle strength measurements, may provide insight into clinical progression within this patient population and ultimately be used to generate a predictive model. Future research will be needed to explore the minimal clinically significant difference in FVC% predicted for this group of patients. It is particularly valuable with the development of promising new therapies to assess meaningful changes in abilities and scores for patients and caregivers. This information is important as understanding the clinical course will be used to improve clinical trial design, inform future patient guidelines, and assist in interpretation of results of medical interventions. It is important to investigate the changes in this small but specific cohort of patients to accurately depict their natural history following loss of ambulation as it is not currently known what treatments may slow the slope of

deterioration. This study has shown that these patients continue to significantly deteriorate in both their respiratory function and upper limb strength following loss of ambulation. Additional studies aimed at assessing the impact of disease modifying drugs on these outcomes are required.

5. Abbreviations

SMA - Spinal muscular atrophy

SMN- Survival motor neuron

UK – United Kingdom

FVC% predicted – forced vital capacity percentage predicted

RULM – Revised upper limb module

6. References

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7. Figures

Figure 1: FVC percent predicted (a) Age negatively correlated with FVC percent predicted (0.388, p = 0.006) with linear fit line ($R^2 = 0.150$) (b) Disease duration since loss of ambulation negatively correlated with mean FVC percent predicted (0.520, $p<0.01$) with $R^2 = 0.2702$.

Figure 2: RULM scores (a) Age negatively correlated with RULM score (-0.365, p = 0.040) with linear fit line ($R^2 = 0.133$) (b) Height negatively correlated with RULM score (-0.400, p = 0.032) with linear fit line ($R^2 = 0.160$) (c) Disease duration since loss of ambulation negatively correlated with mean RULM score (0.585, $p<0.01$) with $R^2 = 0.3669$.

Figure 3: Positive correlation between RULM score and FVC percentage predicted (0.637, $p<0.005$) with linear fit line ($R^2 = 0.4059$).