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Longitudinal natural history in young boys with Duchenne muscular dystrophy

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Abstract

The aim of this prospective multicentric study was to document disease progression in young boys affected by Duchenne muscular dystrophy (DMD) between age 3 and 6 years (±3 months) using the North Star Ambulatory Assessment scale. One hundred fifty-three DMD boys (573 assessments) younger than 6 years (mean: 4.68, SD: 0.84) with a genetically proven DMD diagnoses were included. Our results showed North Star Ambulatory Assessment scores progressively increased with age. The largest increase was observed between age 3 and 4 years but further increase was steadily observed until age of 6 years. Using a multiple linear regression analysis, we found that both the use of corticosteroids and the site of mutation significantly contributed to the North Star Ambulatory Assessment changes ($p < 0.001$). At each age point, boys on corticosteroid treatment had higher scores than corticosteroid naïve ones ($p < 0.001$). Similarly, patients with mutations downstream exon 44, had lower baseline scores and lower magnitude of changes compared to those with mutations located at the 5′ end of the gene ($p < 0{,}001$). Very few boys achieved the age appropriate maximum score. These results provide useful information for the assessment and counselling of young DMD boys and for the design of clinical trials in this age group.
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Keywords: North Star Ambulatory Assessment; Duchenne Muscular dystrophy; Outcome measure; Neuromuscular disorders.

1. Introduction

Over the last decades several studies have reported natural history data in Duchenne muscular dystrophy (DMD) [1–6]. Most of the studies using functional scales have focused on boys assessed after the age of 5 years. This is partly due to the

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fact that the mean age at diagnosis is still around 4–5 years [7,8], and partly to the fact that the available tools, such as the North Star Ambulatory Assessment (NSAA) or the Motor Function measure (MFM), were validated for populations over 5 years of age [9–11].

Recently there has been an attempt to use developmental scales to assess very young boys [12–14], or to adapt the existing scales for young patients [15–17]. In a recent study using the NSAA in a cohort of healthy children between 2.9 and 4.8 years, we were able to identify which items were developmentally appropriate at different age points [15,16]. At the age of 3 years (±3months) only 8 items were completed in at least 85% of the typically developing (TD) boys. The number of developmentally appropriate items increased from 8 to 13 at age 3.5 years, while by the age of 4 years all 17 items were appropriate. In that manuscript we suggested that the NSAA could be used before the age of 5 years, but should be focused on the items that could be reliably performed at the different age points. When assessing a cohort of young DMD boys with the NSAA scale [16] we observed a progressive increase in scores between age 3 to 5 years. However, as also reported in other studies using developmental scales [12–14], with few exceptions, scores were always lower than those achieved by their age matched TD peers. In that study, only corticosteroid naïve DMD boys assessed until the age of 5 were reported [16]. It was therefore impossible to establish if the improvement observed between the age of 3 and 5 would continue after the age of 5 years, and what the effect of corticosteroids would be. Indeed, as corticosteroids are typically initiated at around this age, it is also important to establish if and to what extent this therapy produces a further increase in the NSAA scores. A number of ongoing and planned clinical trials specifically target this age group [18].

Therefore it is important to capture the magnitude of the changes in young DMD boys occurring as part of the natural history of the condition, and the additional effect that corticosteroids have on this increase.

The aim of this study was to report the results of the course of disease assessed using the NSAA in a large cohort of DMD children between the age of 3 and 6 years (±3 months) who had been followed for at least one year in order to define possible changes over time. More specifically we wished to establish the range of changes according to age and the possible effect of corticosteroids and site of the DMD mutations. We were also interested to establish 12 month changes in patients assessed at different age points.

2. Materials and methods

The study is a prospective multicentric study involving four tertiary neuromuscular centers in Italy, one in the United Kingdom and one in the United States.

The study was approved by the Ethics committee or the Caldicott Guardian in each center.

As the assessments were performed as part of the clinical routine in all centers, consent to anonymously record the data in a database was obtained by the parents for the underage boys. Data was collected between January 2014 and March 2019. As part of the study, we collected all the assessments from all the patients with a genetically confirmed diagnosis of DMD seen in our clinics between the age of 3 and 6 years (± 3 months) who had been followed for at least a year. Details on the mutations and on corticosteroid treatment were noted.

2.1. NSAA

All patients were assessed using the NSAA, an ordinal scale consisting of 17 items, ranging from standing (item 1) to running (item 17) [10,19].

Each item can be scored on a 3-point scale using simple criteria: 2- Normal achieves goal without any assistance; 1- Modified method but achieves goal independent of physical assistance from another person; 0- Unable to achieve independently.

A total score can be achieved by summing the scores for all the individual items. The score can range from 0, if all the activities are failed, to 34, if all the activities are achieved.

Details of the training for the physiotherapists involved in the study and of the inter-observer reliability for NSAA among the centers have already been reported [16].

2.2. Statistical analysis

Data were analyzed in different ways. First, we reported NSAA data in all the patients assessed between 3 and 6 years. Data were plotted against the reference normative data, i.e. the maximum score achieved in TD children for each age point and analyzed taking into account the type of mutation and the possible steroid treatment. Descriptive analysis was used to describe the cohort. Variables were described by mean and standard deviation. Multiple linear regression model was performed to predict the influence of age, treatment with steroid and site of mutation on NSAA score. Pearson Correlation test was used in order to define the relationship between the variables. Version 23 of the SPSS software (SPSS, Inc.) was used for all statistical analyses, setting the significance at $p < 0.05$. For DMD boys who had at least one year follow up, data were also analyzed, looking at 12-month changes at different age points. As we aimed to establish 12-month changes in young boys at different ages, each patient contributed with multiple 12-month segments starting from different age points (e.g. 3 years, 3.5 years etc.).

3. Results

Five hundred seventy-three assessments from 153 DMD boys younger than six years of age (mean: 4.68, SD: 0.84) and with a genetically proven DMD diagnosis were included.

Table 1 and Fig. 1 describe NSAA scores by age group and steroid treatment.

Of the 26 DMD boys assessed at 3 years, only 3 (11.53%) achieved the mean age appropriate target score of 16. Of

Table 1
Describes NSAA baseline scores for each age group and steroid treatment.

		3 (n:26)	3,5 (n:53)	4 (n:100)	4,5 (n:113)	5 (n:107)	5,5 (n:96)	6 (n:78)
	MEAN	11,08	13,79	18,04	20,27	22,48	23,20	24,08
Whole cohort	**SD**	3,21	4,14	4,69	6,05	5,36	6,07	5,00
(n:573)	**MAX**	20,00	23,00	30,00	33,00	33,00	34,00	34,00
	MIN	6,00	4,00	6,00	7,00	11,00	7,00	15,00
		3 (n:25)	3,5 (n:50)	4 (n:94)	4,5 (n:89)	5 (n:76)	5,5 (n:48)	6 (n:37)
	MEAN	11,16	13,64	17,96	19,71	22,05	21,69	23,84
Naive	**SD**	3,25	4,17	4,76	5,92	5,31	6,28	4,51
(n:419)	**MAX**	20,00	23,00	30,00	33,00	32,00	33,00	30,00
	MIN	6,00	4,00	6,00	7,00	11,00	7,00	16,00
		3 (n:1)	3,5 (n:3)	4 (n:6)	4,5 (n:24)	5 (n:31)	5,5 (n:48)	6 (n:41)
	MEAN	9,00	16,33	19,33	22,17	23,52	24,71	24,29
Steroid treated	**SD**	N/A	3,06	3,44	5,84	5,42	5,51	5,46
(n:154)	**MAX**	9,00	19,00	25,00	33,00	33,00	34,00	34,00
	MIN	9,00	13,00	15,00	13,00	14,00	12,00	15,00

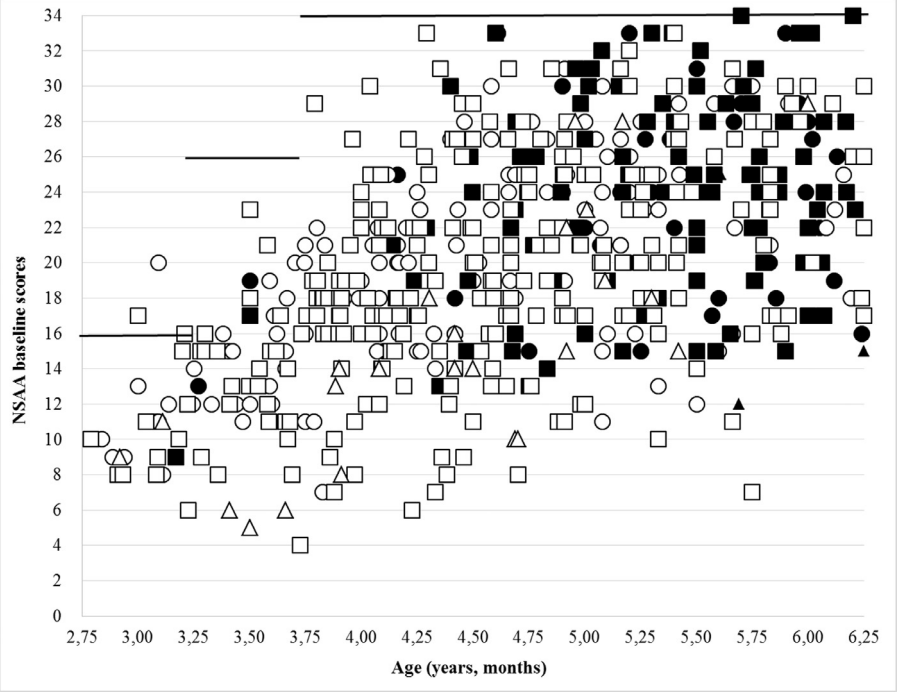

Fig. 1. shows individual NSAA scores by age and corticosteroid treatment. Full lines represent the age appropriate target score. Circles represent patients with a mutation before exon 44, squares represent patients with a mutation between exon 44 and 62, triangles represent patients with a mutation after exon 63. Open symbols represent steroid naïve and full symbols treatment with corticosteroid.

the 53 assessed at 3.5 years, none achieved the mean age appropriate target score of 26. The percentage of patients reaching the mean age appropriate target score of 34 was 0 at 4, 4.5, and 5 years and increased to 1 at 5.5 and 6 years.

Applying the multilinear regression, all independent variables (age, corticosteroid treatment, site of mutation) included in the model gave a statistically significant contribution to the dependent variable (NSAA) with $p < 0{,}001$. Irrespective of age, taking corticosteroids increased NSAA score by 1.55 points. Irrespective of age and pharmacological treatment, having a mutation between exon 44 and 62 reduced NSAA score by 0.64 points compared to those having a mutation before exon 44. Having a mutation after exon 63 reduced NSAA score by 4.67 points compared to those having a mutation before exon 44 and of 4.03 points compared to mutations between exon 44 and 62.

3.1. 12-month changes

Three hundred fifteen assessments at 12 months from baseline were included.

In the 12-month cohort a linear negative correlation ($p < 0.001$) was found between age and NSAA changes at 12 months ($p < 0.001$).

Table 2
Describes NSAA 12 month changes for each age group and steroid treatment.

12 month changes		3 (n:23)	3,5 (n:38)	4 (n:64)	4,5 (n:76)	5 (n:55)	5,5 (n:32)	6 (n:27)
Whole cohort 12 months (n:315)	**MEAN**	7,35	5,84	3,67	2,49	1,45	0,59	−0,74
	SD	3,31	4,50	4,89	4,30	3,44	4,23	4,30
	MAX	13,00	16,00	14,00	16,00	10,00	12,00	8,00
	MIN	0,00	−3,00	−8,00	−5,00	−5,00	−9,00	−8,00
		3 (n:20)	3,5 (n:31)	4 (n:42)	4,5 (n:40)	5 (n:21)	5,5 (n:7)	6 (n:5)
Naive 12 months (n:166)	**MEAN**	7,55	5,65	3,29	1,25	0,52	−2,14	−2,60
	SD	3,41	4,74	5,17	4,11	3,34	3,08	2,51
	MAX	13,00	16,00	14,00	11,00	7,00	2,00	1,00
	MIN	0,00	−3,00	−8,00	−5,00	−5,00	−7,00	−6,00
		3 (n:3)	3,5 (n:7)	4 (n:22)	4,5 (n:36)	5 (n:34)	5,5 (n:25)	6 (n:22)
Steroid treated 12 months (n:149)	**MEAN**	6,00	6,71	4,41	3,86	2,03	1,36	−0,32
	SD	2,65	3,35	4,33	4,15	3,42	4,24	4,55
	MAX	8,00	12,00	12,00	16,00	10,00	12,00	8,00
	MIN	3,00	2,00	−3,00	−3,00	−4,00	−9,00	−8,00

A linear negative correlation ($p < 0.001$) was also found between NSAA score at baseline and NSAA changes at 12 months. The chance of improving >12 points in 12 months seems to be limited to boys with a baseline score ≤15.

Decreases in function (<−2) were found more in those with a baseline score >15.

Table 2 and Fig. 2AB describe NSAA 12 month changes for each age group and steroid treatment.

4. Discussion

The advent of new therapies focusing on young DMD boys has highlighted the need for natural history data in this age group. The recent suggestion that the NSAA may be used even before the age of 5 years, taking into account age appropriate reference data [16], has increased the possibility to use the same scale longitudinally from the age of 3 years and to follow the changes over time.

In our previous study, we reported an increase of the NSAA scores in TD boys. At the age of 3 years TD boys are only able to consistently pass 8 of the 17 items with an age appropriate maximum score of 16, that increases to 24 at 3.5 years. Only by the age of 4 years TD boys achieve a full score on the NSAA consistently performing all the 17 activities of the scale.

Our current results, obtained in a larger cohort of DMD boys between the age of 3 and 6 years and observed for a minimum of 1 year, expand previous observations that in DMD boys there is a progressive increase in NSAA scores with increasing age that continues after the age of 5 years. As typically developing children have a ceiling effect on the NSAA after the age of 4 years, the progressive increase in NSAA scores in the DMD boys leads to an apparent reduction of the difference with the typically developing children.

Our results also raise questions if and how several variables may contribute to the functional changes. The interpretation of the results in this age range is a complex task as it is complicated not only by the physiological development but also by the treatment with corticosteroids. According to standards of care recommendations [20] corticosteroid treatment is generally started in this age range and is known to produce a functional improvement [21–23] that contributes to the magnitude of changes observed. Furthermore, as previous studies have suggested that mutations occurring downstream exon 44 involving the Dp140 dystrophin isoform, may be associated with more severe developmental delay [12], we also wanted to assess the impact of different DMD mutations on outcome.

When we analysed the possible effect of these variables over time, we found that both the use of corticosteroids and the site of mutation significantly contributed to the NSAA changes. In agreement with several previous studies [22,23], we found that at each age point, boys on corticosteroid treatment had higher scores than corticosteroid naïve ones. Similarly, the site of mutation also appeared to contribute to the magnitude of changes over time. Patients with mutations downstream to exon 44, predicted to disrupt also the Dp140 brain dystrophin isoform, had lower baseline scores and lower magnitude of changes compared to those with mutations in the first part of the gene. Patients with mutations after exon 63, predicted to disrupt also the Dp71 brain dystrophin isoform had the lowest scores.

It is of interest that there was an inverse relationship between baseline scores and changes with patients who had lower baseline scores tending to improve more than those with higher baseline scores.

This suggests that in this age range the lower baseline scores, rather than identifying the weakest patients, are likely to be found in patients who have achieved less developmental activities that will eventually be achieved at a later stage.

This was also suggested by the analysis of the 12-month changes in boys assessed at different age points. Not surprisingly the largest changes were observed between the age of 3 and 4 years even though in this age group there were only few children who had started corticosteroid treatment. In the DMD boys assessed at 3 years, the 12-month changes

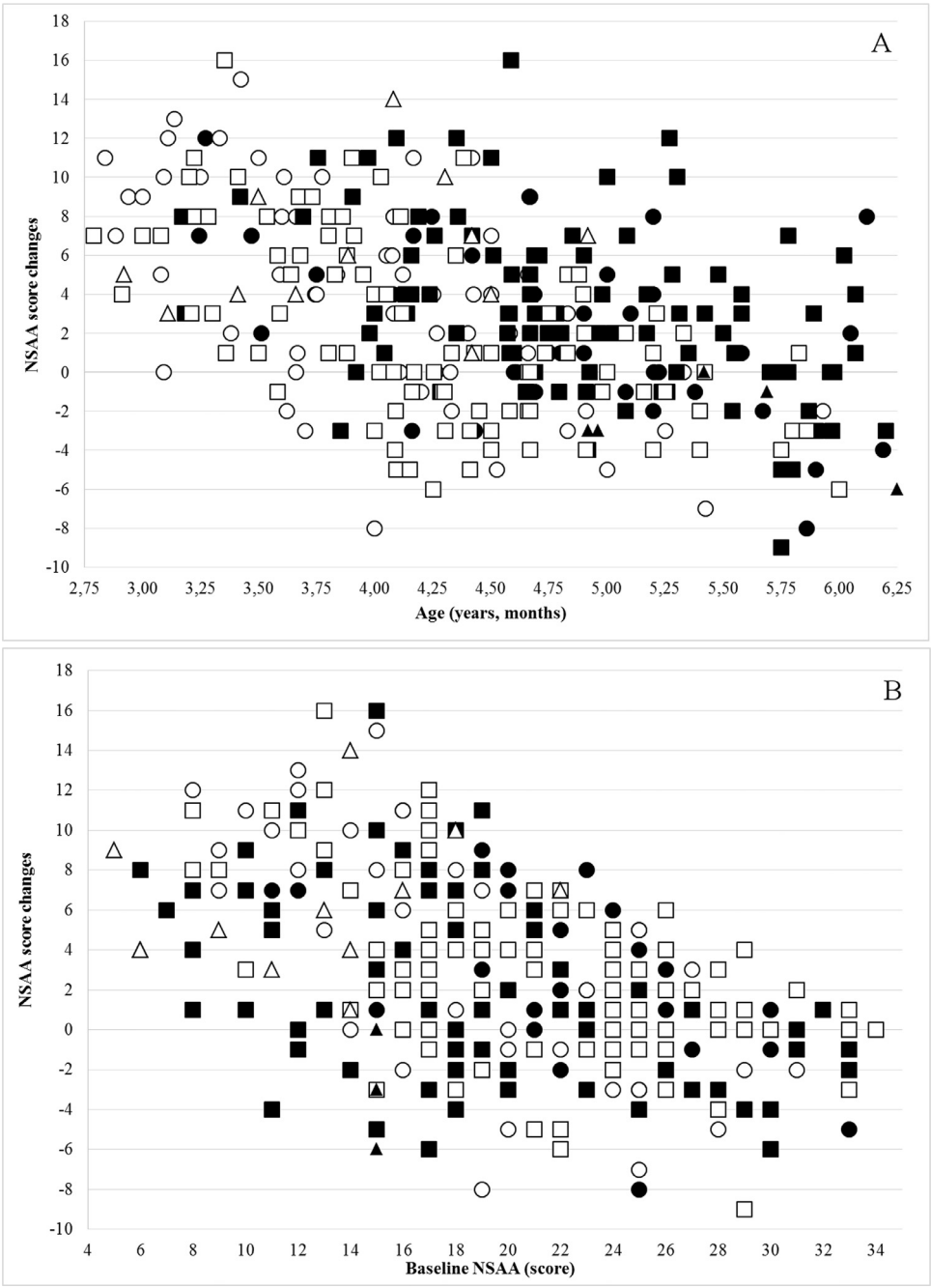

Fig. 2. (A) Shows details of the changes according to age and corticosteroid treatment. (B) shows details of the changes according to NSAA baseline and corticosteroid treatment. Circles represent patients with a mutation before exon 44, squares represent patients with a mutation between exon 44 and 62, triangles represent patients with a mutation after exon 63. Open symbols represent steroid naïve and full symbols treatment with corticosteroid.

showed a mean improvement of 7.35 points. Large 12-month improvements were also found in boys assessed between 3.5 years and 4 0.5 years. In older boys, the magnitudes of 12-month change were lower but still consistent. This suggests that even after the age of 4–5 years, there is additional improvement that persists, to a lesser extent, as observed in other studies [23,24].

These results therefore show that, despite improvements in physical therapy recommendations and the early use of corticosteroids, very few boys achieved or approached the previously reported age appropriate target score. More specifically, we observed that none of the 4-year old-boys achieved a full score of 34, or even a score above 30. The percentage of DMD boys with a score above 30 increased to approximately 4% (5/113) at 4.5 years. Despite a steady improvement of the scores with increasing age, the number who achieved more than 30 was always very low, even at age 6, when a different trend in progression was observed. While some developmental improvement may still occur after age 6 years, this may be counterbalanced by increasing weakness

that becomes more obvious around this age. Not surprisingly, most of those who achieved a NSAA score of 30 were on corticosteroids but this was not always true for individual cases.

These results provide further evidence that the NSAA can be used in boys from the age of 3 years to assess early functional changes, providing information on how the scores change in relation to the increasing age, development, site of mutations and use of corticosteroids. We also expanded previous observations on how the NSAA scores change in relation to age, adding new data obtained after the age of 5 years in relation to the maximum score of NSAA, that is always achieved in typically developing children by the age of 4 years.

These findings will be of help for the interpretation of results of experimental therapies in this age range or at the time of designing new interventional studies, taking into account new concepts of personalised medicine. Further studies looking in more details at other potential variables such as individual mutations, gene modifiers or overall cognitive function may help to further elucidate the variability observed in our cohort.

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