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Change in muscle strength over time in spinal muscular atrophy types II and III. A long-term follow-up study

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Abstract

Whether muscle strength deteriorates with time in spinal muscular atrophy (SMA) types II and III is still debated. We present a long-term follow-up study on muscle strength in 30 patients with SMA types II and III. Median follow-up time was 17 years. Median number of assessments was four. All patients were assessed by Manual Muscle Testing (MMT), Brooke upper limb scale and EK scale. There was a difference in muscle strength of the upper limbs from first to last assessment in SMA II ($p < 0.0001$) and SMA III patients ($p < 0.02$). In SMA II patients, the rate of yearly decline in strength (% MRC score) was 0.22 units ($p < 0.03$). The decline was independent of the grade of muscle strength at entry. In SMA II patients the decline in muscle strength was reflected in a loss upper limb function as measured by Brooke upper limb scale ($p < 0.0001$) and motor function as measured by EK scale ($p < 0.0001$), a loss of great importance to the patients' need for practical assistance. This study demonstrates loss of muscle strength over time in SMA II and III patients. Because of the very slow deterioration, it takes years to detect this change, which has to be taken into account in future treatment trials.

Keywords: Spinal muscular atrophy; Natural history; Muscle strength

1. Introduction

Spinal muscular atrophy (SMA) is caused by mutations in the SMN1 gene and is associated with degeneration of the motor neurons in the spinal cord, which leads to muscle atrophy and weakness. The SMN2 copy number is inversely correlated with disease severity, but is an unreliable predictor of phenotype in individual patients [1]. Therefore, the classification of SMA in types I, II, and III is still based on clinical findings, time of onset and maximal achieved motor function [2].

In SMA II, the child achieves the ability to sit independently, but never learns to stand or walk independently. In SMA III, the child achieves the ability to stand and walk independently, but often loses this ability later in life. The phenotypic spectrum of SMA represents a continuum, and therefore there is a wide range of functional abilities within each SMA subtype, and some borderline type I/II and type II/III do exist.

The natural history of SMA II and III has not been studied systematically. There is a general agreement that patients lose functional abilities over time [3,4], and that loss of function is related primarily to maximum function achieved [4], but although electrophysiological studies have indicated an age-related loss of innervations in SMA [5], opinions differ on whether muscle strength also deteriorates. This diversity is likely explained by the various outcome measures and observation periods used to study the course of the disease, in patients that cover a wide field of disability from hardly any measurable muscle strength to nearly normal muscle strength.

Manual muscle strength recorded on the MRC scale [6] has been used as an outcome measure in several studies of SMA. In a cross sectional study of 54 SMA II patients, it

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was shown that younger SMA II patients had more muscle strength compared to older patients, suggesting that muscle strength deteriorates over time [7]. In the same study, it was also shown that Manual Muscle Testing (MMT) of the upper limbs could differentiate more precisely among individuals than a whole-body muscle test. A prospective study of muscle strength in SMA II and SMA III patients over a period of up to 10 years, showed that the average MMT score declined in patients with SMA II, and that the rate of decline in upper and lower extremity strength was not significantly different [8]. Another prospective study in patients with SMA II/III found deterioration in MRC % score over a five-year period [9]. In a 10-year prospective study of SMA III patients (onset >3 years of age), the MRC grade declined in all of the muscles measured [10]. In contrast, no significant decline in MRC % score was found in a study of SMA II and III patients with a mean follow-up time of 3.2 and 5 years, respectively [11].

Quantitative muscle tests have been used as outcome measure in other studies of SMA II and III patients. In a cross sectional study, young ambulant patients performed better than adults in the timed tests, and had stronger knee extensors as measured by handheld dynamometry (HHD), indicating a relationship between motor function, muscle strength and age [12]. In a prospective study over a period of 1–6 years, no change in muscle strength, measured with a fixed dynamometer, was found, although loss of motor function was observed [13]. In an observational study over a period of 12 months, no changes were found in motor function and muscle strength as measured by HHD [14]. Overall, these studies on muscle strength and function over time in SMA II and III patients seem to suggest that the period of time for follow-up is important, if any change in muscle strength must be observed.

To describe the natural history on SMA II and III, there is a need for longitudinal studies and sensitive and reliable outcome measures [15]. The purpose of this study is to contribute to this knowledge.

2. Materials and methods

Data from all patients registered at the Danish National Rehabilitation Center for Neuromuscular Diseases with a clinically and genetically confirmed diagnosis of SMA II or SMA III were reviewed. Patients were included in this follow-up study if they had been assessed by a standardized physical assessment in at least two of our previous or ongoing studies [16,17,9,7] with an interval between first and last assessments of minimum 10 years. At each assessment, patients were as a minimum evaluated by the following tests:

Upper limb function was evaluated by means of Brooke upper limb scale, an ordinal scale with six levels [18]. Level 1 is highest and level 6 is lowest level of upper limb function.

In non-ambulant patients, motor function was evaluated by means of the Egen Klassifikation (EK), an ordinal scale with 10 items [17]. Each item is scored 0–3 and the sum of scores of all items is the EK-sum score. '0' is the highest level of function and '30' the lowest.

Muscle strength was assessed by Manual Muscle Testing (MMT) of the upper limbs (shoulder flexion/abduction, elbow flexion/extension, wrist flexion/extension, and finger flexion). In ambulant SMA III patients, MMT of the lower limbs (hip flexion/extension, knee flexion/extension, foot plantar and dorsiflexion) was also evaluated. MRC score 0–5 was modified to a 0–10 score to make the scale more sensitive [18,19]. MRC score % was calculated for upper limbs, and in SMA III patients also for lower limbs.

Data were collected during a 20-year period, where patients were evaluated by one of four experienced physiotherapist. Two of the physiotherapists were employed during the entire period, two physiotherapists during 18 and 16 years, respectively. Over the years, training sessions in the use of MMT and functional tests were arranged to ensure consistency and agreement among the evaluators. At each training session, patients with NMD were evaluated and results were compared. At the last training session, each evaluator tested two subjects with SMA, and a simple examination of agreement between the scores of the four evaluators were made. There was total agreement regarding Brooke upper limb score and EK sum score and a variance of 4% in MRC % score.

2.1. Statistics

Descriptive statistics (median and range) were used to present data. Because of the limited number of SMA III patients, non-parametric statistics (Wilcoxon signed rank test) was used to test differences between first and last assessments for SMA II and III patients. SAS 9.2 software package (SAS Institute Inc) was used for statistics. Significance level was set at $p < 0.05$.

In the SMA II group, the annual change in muscle strength was determined with linear regression analyses. To account for the repeated measurements for each patient, an approach based on robust estimation of the standard errors was used [20]. This analysis was not performed in the SMA III group due to the limited number of patients.

To assess whether the baseline level of muscle strength at entry had an influence on potential progression, SMA II patients were divided in two groups according to Brooke upper limb function at entry. The cut-off point was set at $\leqslant 3$ on the Brooke scale. Patients with Brooke scores 1, 2 and 3 can lift a glass of water to the mouth as minimum arm function, whereas patients with Brooke scores 4, 5, and 6 can lift hand to mouth as maximum arm function.

3. Result

Twenty-three SMA II patients (14 males/nine females) and seven SMA III patients (two males/five females) met

Table 1
Age, functional ability (Brooke level, EK sum) and muscle strength (MRC %) in upper limbs (u.l.) in patients with SMA II and SMA III. In two SMA II patients, only four muscle groups were tested at entry, consequently these patients were not part of the calculation of MRC %.

SMA II				SMA III			
	Entry median (range)	Last median (range)			Entry median (range)	Last median (range)	
Age	15 (6–53)	33 (22–73)		Age	31 (11–47)	47 (28–62)	
Brooke level $N = 23$	3 (2–6)	5 (3–6)	$p < 0.0001$	Brooke level $N = 7$	1 (1–4)	2 (1–4)	$p = 0.1250$
EK-sum $N = 23$	17 (12–24)	22 (13–25)	$p < 0.0001$	EK-sum $N = 3$	8 (3–15)	16 (12–18)	$p < 0.2500$
MRC % u.l. $N = 21$	29 (9–41)	12 (1–31)	$p < 0.0001$	MRC % u.l $N = 7$	68 (29–77)	49 (21–68)	$p = 0.0156$

the inclusion criteria. Median follow-up was 17 years (12–20). Median number of assessments was 4 (2–6).

Age, motor function and muscle strength at time of first and last assessment for each of the two SMA types is presented in Table 1.

Before inclusion, three SMA III patients had lost the ability to stand and walk at ages 4, 8 and 9 years. No other SMA III patients lost ambulation during the follow-up period.

Manual Muscle Testing of the upper limbs was assessed in 21 SMA II and all SMA III patients. In two SMA II patients, only four muscle groups were tested at entry. These patients were therefore not part of the calculation of MRC %. There was a difference between MRC % of the upper limbs between first and last assessment in SMA II ($p < 0.0001$) and SMA III ($p < 0.02$) patients. Five SMA III patients were evaluated by MMT in lower limbs. Although there was a nominal decline in MRC % scores over time, no significant difference between first and last assessment was shown ($p = 0.06$).

Decline in muscle strength over time in upper limbs is illustrated in Fig. 1. The slope of the regression line for SMA II patients was −0.22 units per year (CI −0.39 to −0.02) ($p < 0.03$).

MRC % score for patients with superior arm function (Brooke score 2, 3) at entry ($n = 13$) was on average 12% higher (CI 7–17) than patients with inferior arm function (Brooke score 4, 5, 6) at entry ($n = 8$), but no statistical difference between the rate of decline in strength in the two groups was shown (Fig. 2).

4. Discussion

This long-term follow-up study is the first study that has systematically assessed and collated data in patients with SMA II and III over a period of up to 20 years. The study documents a loss of muscle strength of upper limbs over time in both SMA subtypes. In SMA II patients, there was no difference in the rate of decline in muscle strength in stronger versus weaker patients.

The majority of patients with SMA II were diagnosed and referred to our Centre at an early age, but patients were not included in our study until the age of five. SMA III patients have a wider range of onset and physical impairment than SMA II patients, and were referred to our Centre when they were older. This is reflected, not only in the number of patients for each of the two patient groups in our study, but also in the median age at entry, which for SMA III patients was twice that of SMA II patients.

The fact that the number of SMA III patients was small, and that patients could be further classified as SMA IIIa

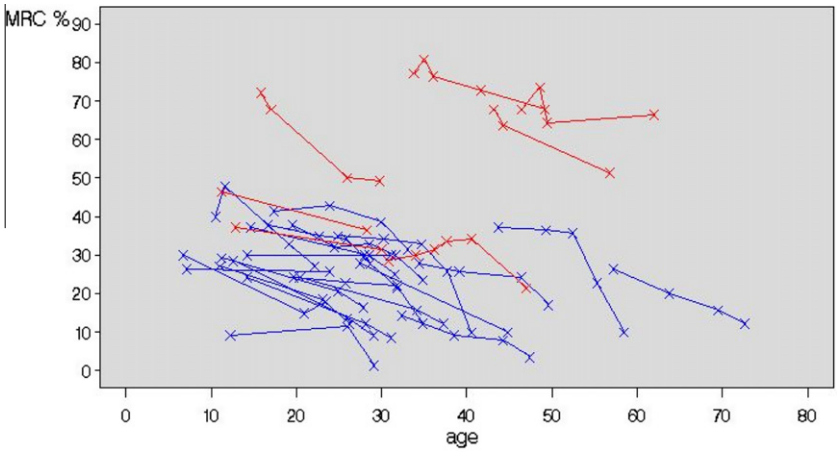

Fig. 1. MRC % in upper limbs in 21 SMA II patients (blue) and 7 SMA III patients (red) as a function of time.

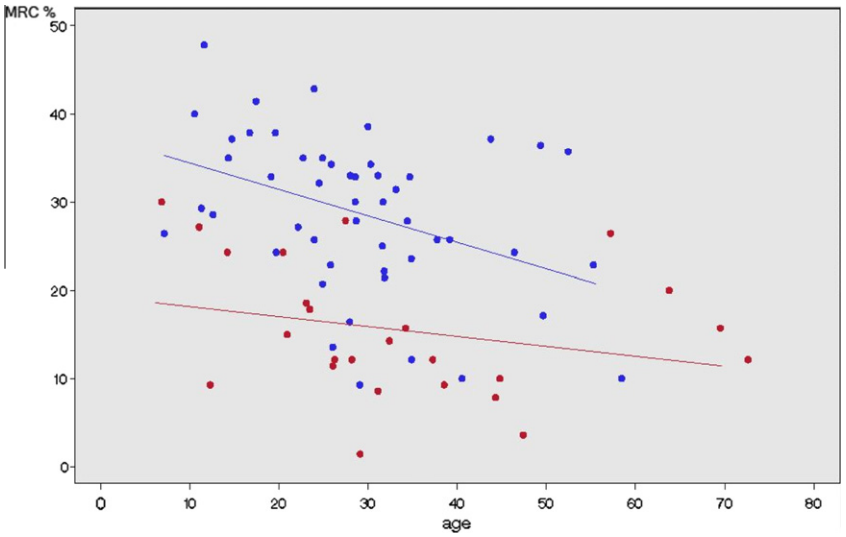

Fig. 2. Linear regression of MRC % score of upper limbs vs. age in 13 SMA II patients with best arm function at entry (blue dots), and eight SMA II patients with inferior arm function at entry (red dots). The definition "best" arm function included patients with upper limb function according to Brooke level 1–3, "inferior" arm function included patients with arm function according to Brooke level 4–6.

($n = 3$ patients) and SMA IIIb ($n = 4$ patients), as described by Zerres [3], made us consider whether we should include this patient group in our study. We still chose to include the SMA III patients, as we believe the long-term follow-up of this small cohort provides important clues to the natural history of SMA.

Muscle strength and motor function was evaluated by the same assessment methods and in the same muscle groups throughout the study period. The assessment methods were dictated by the initial methods used for assessment, and documents that MMT can pick up significant changes in muscle strength over a long observational period, even in a very slowly progressive disease such as SMA. Future studies, using QMT as end point, must show if this type of muscle testing will be able to demonstrate changes in muscle strength in persons with SMA II and III over shorter periods of time than used in this study.

Brooke upper limb scale is an overall classification of arm function based on the ability to overcome gravity in shoulder, elbow and wrist. A decline in Brooke level corresponds to a decline in motor function which has a major impact on daily function to the individual patient. A change in Brooke score from 3 to 5 as found in our study is a change from being able to raise a glass of water to the mouth to not being able to lift forearm against gravity. Put into daily practice this means loss of autonomy as practical assistance is needed for personal hygiene e.g. to comb hair, to shave, to wash face and to eat and drink independently.

The difference in Brooke score from first to last assessment in our group of SMA II patients corresponds to the results from previous studies, i.e. patients loose motor functions over time [3,4,13]. That no difference in Brooke score was shown in the SMA III patients could be due to the small number of patients studied, but also, and perhaps more likely, that the Brooke upper limb scale isn't sufficiently sensitive to pick up a decline in arm function in this stronger patient group. The latter assumption is supported by the fact, that there was a change in MRC % of the upper limb from first to last assessment in the SMA III patients. MRC % score in the lower limbs in our small group of SMA III patients, of whom four patients could be classified as SMA IIIb, tended to decline with time. Deymeer et al. found a decline of approximately one MRC grade for each five-year period in 10 patients with SMA IIIb [10]. Their study was based on full MRC grades of three muscle groups in the upper limb and six muscle groups in the lower limb, but MRC % was not calculated.

Motor function as measured by the EK scale also deteriorated in our study. This is in contrast to a study by Steffensen et al. [9], in which no change in motor function was found in 12 patients with SMA over a period of 5 years. Our findings suggest that more than 5 years is necessary if loss of motor function, as measured by the EK scale, should be shown.

Manual Muscle Testing is used worldwide as a clinical assessment, but was not found to be suitable as an outcome measure in multicenter studies, because of low intra- and inter-reliability when several evaluators are involved [21]. Reliability is improved when testing weak muscles, and when performed by a limited number of experienced evaluators working closely together [22]. In this follow-up study, patients were assessed by the same group of physiotherapists throughout the period of observation. Repeated training sessions among physiotherapists were organized, but no formal test of intra- and inter-rater reliability were held. However, the results from our calculations of variance indicate that the results were reliable.

The slope of the line representing the annual decline in MRC % was 0.2 in our group of SMA II patients. Carter et al. found a decline of 0.2 MMT units per decade. Modified to a 0–10 MMT score, this would correspond to an annual decline in MRC % of 0.3. Steffensen found an

annual decline in MRC % of 0.6 [9]. The difference may be explained by the longer follow-up period used in our study. As shown in Fig. 1, some individual variations in muscle strength occurred over the years. This could be due to several factors. Assessments could have taken place at different hours of the day, patients could have been fatigued at one assessment and well rested at the following session, and periods with illness might influence loss of muscle strength, and periods with recovery might partly restore the loss. Such a variation would likely not occur over a shorter period of time. Furthermore, SMA III patients were among the participants in the study by Steffensen et al., and since loss of motor function has been found to be primarily related to maximal function achieved (4), the SMA III patients might have contributed to a more rapid decline in muscle strength.

To study if loss of muscle strength also was related to maximal function, we divided our SMA II patients according to Brooke upper limb function at entry, and found that the patients with highest level of motor function had a higher MRC % score of the upper limbs, as expected, but although patients with higher function seemed to have a steeper decline in muscle strength compared to patients with less function, no significant difference in the slope of the curve between the two groups was found. Loss of function related to maximal function achieved could perhaps be more related to motor function such as walking, standing and sitting independently, and may not be transferable to motor function in upper limbs.

In this study, MMT 0–10 was able to differentiate among individuals with very limited muscle strength in all age groups. At the same time, it is an ordinal scale, which influences the sensitivity across the scale. By transforming the scale to 0–10, a higher sensitivity and variation in scores from 3 to 5 is obtained, but this expanded grading does not exist in the lower end of the scale, and it is therefore not possible to record small changes in muscle strength in very weak muscles. This could potentially influence the evaluation of muscle strength over time as measured by MRC. Thus, we cannot state that muscle strength deteriorates in the same way throughout life in SMA II.

In this follow-up study we did not have the possibility to evaluate muscle strength by means of quantitative measures such as HHD. This method has limited use in a population of patients with very weak muscles, since many of the patients cannot overcome the threshold of the dynamometer [7,13,23]. Furthermore, it has not yet been possible to measure any deterioration in muscle strength in patients with SMA as measured by quantitative measures. The cause of this could be that studies on quantitative muscle strength until now have been performed over a shorter period of time and only specific, measureable muscle groups have been used for evaluation.

Age-related loss of muscle strength (sarcopenia) occurs before the age of 50, and accelerates after that in all healthy humans [24,25]. Studies on age-related loss of muscle strength have primarily been based on quantitative measurements of muscle strength, such as handgrip strength [26] and are therefore not comparable to our findings. However, decline in muscle strength in our population of SMA patients seems to start at an earlier age than in a general population.

In several countries, medical treatment of SMA patients is implemented with the hope of improving or stabilizing muscle strength. It has, however, not yet been possible to show any gain in muscle strength or motor function with any of these interventions [27], although patients in some cases have reported a positive outcome [28]. This could indicate that the outcome measures used are not sufficiently sensitive to detect any potential improvement, and that an improvement doesn't become evident in a short time, but has to be studied over a longer period.

In a very slowly progressive disorder as SMA, it is necessary to have very sensitive instruments to capture the progression and to cover the wide range of motor functions.

Until such scales have been created or existing scales transformed, we have to gather our knowledge on the natural history from the assessment methods that have been used in the past decades, such as the ones reported in this study.

5. Conclusion

Muscle strength in upper limbs deteriorates slowly over time in patients with SMA types II and III. In SMA II patients, the degree of loss of muscle strength seems to be the same irrespective of maximum upper limb function achieved. This was not possible to elucidate in the SMA III patients, because of the small number of SMA III patients included in our study. Because of the very slow deterioration, patients must be monitored for several years in order to show any change in muscle strength.

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