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## TITLE

Muscle strength and motor function throughout life in a cross- sectional cohort of 180 patients with SMA types 1c-4

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## ABSTRACT

**Background** Natural history studies in SMA have primarily focused on infants and children. Natural history studies encompassing all age groups and SMA types are important for the interpretation of treatment effects of recently introduced SMN augmenting therapies.

**Methods** We conducted a cross-sectional study to investigate muscle strength, Hammersmith Functional Motor Scale (Expanded) scores and the patterns of muscle weakness in relation to age and SMA type.

**Results** We included 180 patients with SMA types 1-4 in the age range 1-77.5 years and median disease duration of 18 years (range 0-65.8 years). With the exception of the early phases of disease in which children with SMA types 2 and 3 may achieve new motor skills and show a temporary increase in muscle strength, cross sectional data suggest that declining muscle strength and loss of motor skills over time are characteristic for all SMA types. Mean loss of strength is at least 1 point on the MRC and 0.5 point on the HFMS(E) scores per year. Trend lines compatible with deterioration of motor function and muscle strength start in childhood and continue into adulthood. The age at loss of specific motor skills is associated with disease severity. Triceps, deltoid, iliopsoas and quadriceps are the weakest muscles in all patients. Hierarchical cluster analysis did not show a segmental distribution of muscle weakness as was suggested previously.

**Conclusions** Progressive muscle weakness, and loss of motor function are characteristic of all SMA types and all ages.

## INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) shows a striking variability in disease severity despite that virtually all patients have the same genetic defect, i.e. a homozygous deletion of the *SMN1* gene.[1-3] This is primarily explained by variation in the copy number of the backup *SMN2* gene.[3, 4]

Natural history studies that document the rate of progression of motor deficits in specific SMA types and age groups are important for the design of clinical trials to test efficacy of disease-modifying therapies.[5-9] Recent studies have primarily focused on younger patients, in particular infants with SMA type 1 and children and teenagers with types 2 and 3. Natural history studies that capture the full life cycle of SMA and its complete severity spectrum are scarce. (Supplementary material Table S1 for overview)

Information on disease progression later in life is important for gaining insight into care needs of older SMA patients and the interpretation of treatment efficacy of SMN protein augmenting therapies after childhood.

Documenting disease progression in patients with longstanding, severe muscle weakness, or with milder forms of SMA with potentially very slow progression may be challenging.[10, 11] Nevertheless, more detailed insight into disease progression later in life has become highly relevant now that the high-cost antisense oligonucleotide Spinraza (nusinersen) has also been approved for the use in adults with SMA, despite the lack of evidence for efficacy from phase 3 trials in this age group.

Prospective longitudinal studies over extended periods of time are logistically challenging. In order to better understand the disease course of SMA in older children and adults, we analysed data from our prospective nationwide cohort study

on SMA in The Netherlands.[3] Using a cross-sectional approach, we investigated patterns of muscle strength and motor scores in 180 children, adolescents and adult patients, encompassing the full spectrum of clinical phenotypes including older patients with SMA.

## **METHODS**

We performed a cross-sectional study on patients with SMA types 1c-4 in The Netherlands, enrolled between September 2010 and August 2016. We used age at onset and acquired motor milestones to define SMA type (see for details Table S2).

Methods are described in the Supplementary File.

## **RESULTS**

### **Patient characteristics**

We included 180 patients with SMA types 1c-4, of whom 108 (60%) were  $\geq 18$  years old. Patient characteristics are presented in Table 1.

Table 1

### **Decline of motor function and muscle strength**

Muscle sum scores (Figure 1 AB) and HFMSE scores (Figure 1 E) were lower in older patients, irrespective of SMA type ( $p < 0.05$ ).

Figure 1 ABCDE

We used linear regression to estimate the rate of decline in muscle strength over time and divided patients into age cohorts to estimate age-specific decline in muscle strength and motor function, stratifying both analyses for SMA type (Figure 1 A). The estimated average decline in MRC sum scores was 1 point per year (Figure 1 A). HFMSE scores declined by an estimated 0.5 points per year (Figure 1 E). There were clear differences in trend line slopes between SMA types and between age cohorts with the same SMA type ( $p < 0.05$ ; Figure 1 B-D). In general, muscle deterioration started in the lower limbs (Figure 1 D), followed by progressive decline of strength in upper limbs (Figure 1 C). Patterns of deterioration differed slightly among SMA types. In SMA type 2a we observed a steady decrease in muscle strength and motor function, whereas in SMA types 2b and 3 there was a relatively stable phase of muscle strength followed by a more pronounced decline in roughly the third decade in SMA type 2b and type 3a and after the age of 40 in SMA type 3b (Figure 1 BCD).

SMA type was associated with the age at which patients lost specific motor skills (Table S3). The age at which patients lost the ability to sit without support differed between SMA types 2a, 2b and 3a (mean age 8.7, 16.5 and 19 years, respectively;  $p < 0.01$ ). Similarly, patients with SMA type 2b lost the ability to stand or walk with aids at a significantly younger age than those with type 3a (mean age 5.5 and 15 years, respectively;  $p = 0.03$ ). Loss of the ability to walk without support in SMA type 3 generally occurred in the second decade in patients with onset before 3 years (mean 11.5 years; range 2.5-35), the fourth decade in those with onset between 3-12 years (mean 32 years; range 6.5-59) and after the fifth decade in case of onset after 12 years (mean 59 years; range 33-66). Two patients with SMA type 4 needed walking

aids 15 years after disease onset, although they could still walk short distances unaided (Supplementary material; Table S3).

MRC sum score and HFMS(E) score differed significantly between SMA types ( $p < 0.01$ ). HFMS(E) score correlated strongly with the MRC sum score, lower limb score and upper limb score (Spearman rho's correlation coefficient = 0.91;  $p < 0.001$ ), although these correlations were not linear and the correlation between functional changes by HFMS(E) and muscle strength by MRC scores was present only at the higher end of both scores. We observed a ceiling effect of the HFMS in SMA type 3 and a floor effect of the HFMS(E) for SMA types 1c and 2 (Figure 2 AB).

Figure 2 AB

Stratification by *SMN2* copy number was not informative, mainly because of the under-representation of patients with 2 and 4 *SMN2* copies in our cohort.

### **Patterns of muscle weakness**

Triceps, deltoid, iliopsoas and quadriceps were the weakest muscle groups in all patients. Strength of flexors and extensors of the hand and fingers, biceps and hamstrings was relatively preserved in the majority of patients. Twenty-one out of 180 patients (12%) had biceps weakness MRC  $< 3$  and 33 out of 180 (18%) patients had a severely impaired hand function.

Hierarchical clustering of strength in individual muscles identified proximal and distal muscles as principal components (Figure 3). Weakness was not segmentally distributed (e.g. more pronounced in C5 or L1-3) as suggested previously [10].

Patterns of weakness were similar in all SMA types.

Figure 3

## Discussion

The natural history of SMA has primarily been studied in infants and children. Recent studies have shown age-dependent differences in disease progression.[12, 13] In contrast, natural history in older patients with genetically confirmed SMA has not been studied in detail due to the rareness of the disease in combination with the slow rate of progression of weakness and motor impairment.[10, 14] The cross-sectional data from this cohort of 180 genetically confirmed patients, including children, adolescents and adults with SMA types 1c-4 in all disease stages of SMA throughout life, are a proxy for longitudinal natural history data. Progressive muscle weakness, motor function impairment and disability are characteristic of all SMA types and are not restricted to children or more severe phenotypes. The data indicate that the patterns of gradual progressive loss of motor function are comparable, but that time at onset of a more pronounced decline may differ between SMA types, but cannot be predicted by SMN2 copy number.

In our cohort, muscle strength declined by an estimated 1 MRC point and 0.5 HFMS(E) point per year. This is in line with previous observations in adult patients with SMA type 3b.[10] Similar, relatively small declines have also been described in children and young adults with SMA 2 and 3.[10, 15-18] The ceiling and floor effects of the HFMS(E) are a well-known shortcoming of these widely used motor measurements, and might even have caused an underestimation of the extent of decline per year. The effects of cumulative yearly loss of only a few MRC or HFMS(E) points are obviously not trivial and will eventually affect daily functioning,



depending on the patient's functional abilities at baseline. This is, for example, reflected by the loss of commonly acquired motor milestones, i.e. sitting without or standing with support, that occurs at an earlier age in patients with SMA type 2 than type 3. More generally, the progression of muscle weakness after the age of 20 years indicates that SMN deficiency (and possibly its further decline with advancing age[19]) remain relevant in adulthood and that functional deterioration is not only secondary to growth in childhood and adolescence after stalled motor development.[20]

It has previously been shown that disease progression in children is age- and SMA type-specific.[13, 21] Our data suggest that different rates of progression may also be an SMA feature in adulthood. Although our study lacked statistical power, disease progression may be more pronounced during specific periods of life, i.e. roughly the second, third and fifth decades in SMA types 2, 3 and 4, respectively. This would suggest that the impact of SMN augmenting therapies,[7, 8] which have so far not been tested in phase 3 trials in adults, may depend on timing of treatment in relation to age and SMA type.

A second observation is the presence of differences in muscle vulnerability in SMA. Weakness in patients with SMA is generalized but predominates in axial and specific proximal muscle groups, i.e. deltoid, triceps, and quadriceps muscles. This observation has not yet been explained. In mouse models of SMA, median motor neuron pools in the lumbar segments of the spinal cord are more vulnerable than their more laterally located counterparts due to an earlier loss of synaptic connectivity[22] and similar differences in motor neuron vulnerability may exist in humans. We could not corroborate the previous suggestion that some segments of the cervical or lumbar spinal cord are more vulnerable than others.[10] The

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differences in vulnerability of bulbar muscles innervated by the same trigeminal nucleus of the brainstem supports the concept that specific motor neuron pools are most vulnerable to SMN deficiency.[23-25] An alternative, or possibly related, explanation might be that motor unit sizes of muscles determine their vulnerability, i.e. that muscles with on average larger but fewer motor units are weaker than those with smaller motor units.[26]

This study has several limitations. Although we think that a cross-sectional design is the most feasible way to study disease progression in the course of decades, longitudinal follow-up of patients is obviously superior and would allow a more detailed analysis of differences in disease progression. However, such results would require a sustained effort over long period of time and a multicenter approach.

Conclusions on rate and degree of decline in muscle strength can therefore not be more detailed and should be interpreted with care. Secondly, a cross-sectional approach may suffer from recall bias. We did our best to minimize bias, for example by using all available sources that would provide evidence of achieved motor milestones, including family picture books and data from files from general practitioners. Thirdly, the HFMS(E) and MRC scores are widely used to assess muscle strength and function in SMA. However, due ceiling or floor effects and possibility of large inter- and intra-rater differences in HFSME and MRC respectively, both measures are far from perfect but alternative measures or biomarkers reflecting disease progression are not present. Lastly, splitting patients in more than just 3 SMA types (i.e. 1c, 2a, 2b, 3a, 3b, 4) results in subgroups with smaller numbers of patients and this clearly limits statistical power, in particular in patients with late-onset SMA.

The recent introduction of the first high-cost disease course-modifying drug for SMA underlines the need for methodology to monitor treatment efficacy.[7, 8] Our data suggest that timing of treatment in SMA types 2, 3 and 4 may also be crucial in adulthood.[7] Additional tools to predict and determine treatment efficacy particularly in patients with SMA type 3 and 4 and adult patients of all types are urgently needed, if only to justify the burden to patients and high treatment costs.

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### **Disclosures**

R.I. Wadman, M. Stam, C.A. Wijngaarde, B. Bartels, L.A.M. Otto, M.A. Schoenmakers, H.H. Lemmink and I. Cuppen report no conflicts of interest.

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**Author contributions:**

R.I. Wadman: drafting the manuscript for content, including writing for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis.

C.A. Wijngaarde: drafting the manuscript for content, including writing for content, analysis or interpretation of data, acquisition of data.

M. Stam: revising the manuscript for content, including writing for content, acquisition of data.

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W.L. van der Pol: revising the manuscript for content, including writing for content, study concept or design, analysis or interpretation of data, statistical analysis, study supervision or coordination, obtaining funding.

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## Figure legends

Figure 1ABCDE. Muscle weakness in relation to age in SMA types 1c-3b.

Muscle strength deteriorates with an estimated mean of -1 MRC sum score point per year. A. Trend lines of MRC sum score representing muscle strength show a linear decline irrespective of age or SMA type. B, C and D. MRC scores of total strength (B), upper limbs (C) and lower limbs (C) respectively, represented per age group. Data suggest differences in the relation of deterioration of muscle weakness with age between SMA types. Analysis was underpowered to statistically confirm different phases of deterioration. E. HFMSE score declines over years in all SMA types. Error bars represent 95% CI.

Figure 2AB. Correlation between HFMS(E) and MRC sum score and their ceiling effects. Same patient cohorts are represented in A (HFMS versus MRC sum score) and B (HFMS versus MRC sum score). Maximum scores are 40 and 66 points in HFMS and HFMS, respectively. Correlation between HFMS or HFMS scores and MRC sum score is not linear, but shows an exponential difference at both ends of the scores. Dotted lines represent 95% confidence intervals.

Figure 3. Pattern of muscle weakness with hierarchical clustering of muscle strength in 180 patients with SMA types 1c-4

Muscle strength in muscles from arms and legs is shown in the heatmap. Colours white through red correspond to MRC scores 1-5. Each patient is represented by one column on the x-axis. Muscle groups are presented at the right y-axis. The left y-axis shows the dendrogram of clusters. Two distinct clusters, i.e. of proximal (blue) and distal (green) muscle groups, were identified. There was no segmental distribution of weakness as suggested previously.

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Table 1. Baseline characteristics							
SMA type		Type 1c (n=18)	Type 2a (n=44)	Type 2b (n=36)	Type 3a (n=40)	Type 3b (n=36)	Type 4 (n=6)
Gender (F:M)		9:9	27:17	23:13	22:18	15:21	4:2
Median age at inclusion in years (range)		10.5 (1.4-49.7)	15.0 (1.8-42.3)	18.2 (2.8-66.8)	30.5 (1.3-65.7)	42 (14-77.5)	50.8 (41-68.8)
Median disease duration at time of inclusion in months (range)		118 (9.6 - 590)	171 (14-492)	206 (54 -790)	347 (18-758)	357 (12-738)	136 (91-291)
Median age at onset in months (range)		6 (1-9)	8 (3.5-24)	12 (6-36)	18 (6-54)	114 (24-294)	456 (366-522)
SMN2 copy number (n)	2	1	1	1	1	1	0
	3	17	40	29	18	6	0
	4	0	2	4	15	24	5
	5	0	0	0	0	2	0
Scoliosis surgery (%)		11 (70)	31 (70)	21 (58)	11 (30)	2 (6)	0 (0)
Median age at time of scoliosis surgery in years (range)		7.9 (4.1-19.5)	7.9 (3.7-15.8)	9.8 (7.3-31.8)	14.1 (10.1-54.5)	15.0 (14-16)	NA
Median HFMS (range)		0 (0-2)	2 (0-25)	5 (0-35)	11 (0-40)	30 (2-40)	38 (36-40)
Median HFMSE (range)		0 (0-4)	2 (0-25)	6 (0-37)	10 (0-57)	32 (2-66)	53 (43-56)

Median MRC sum	62	71	93	105	150	155
score (range) [n]	(34-98) [11]	(39-124)	(63-141)	(52-160)	(70-167)	(120-162)
		[36]	[30]	[30]	[27]	[6]

**Legend Table 1.** NA= not applicable. n= number of patients without missing data on any of the analysed muscles. In case of contractures, the MRC score was scored as 'missing'.





