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Physical characteristics and applicability of standard assessment methods in a total population of spinal muscular atrophy type II patients

U. Werlauff *, B.F. Steffensen, S. Bertelsen, I. Fløytrup, B. Kristensen, B. Werge

The National Rehabilitation Centre for Neuromuscular Diseases, Kongsvang Allé 23, DK 8000 Aarhus C, Denmark

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ABSTRACT

The aims of this study were to evaluate muscle strength, functional abilities, contractures and Forced Vital Capacity in a population of 54 spinal muscular atrophy (SMA) type II patients between the ages of 5 and 70, and to evaluate the applicability of conventional assessment methods.

The patients were evaluated by means of functional scales, muscles tests, joint motion measurement and Forced Vital Capacity test.

There was a significant score difference in functional tests and muscle tests as well as in the sum of contractures between younger individuals (⩽20 years) and older individuals (⩾21 years).

The functional scales were not sensitive enough to differentiate among the most impaired persons. A reduced Manual Muscle Test score of the upper limbs was found to differentiate more precisely among individuals than a total score derived from testing 38 muscle groups.

There is a need for clinical tools that can evaluate patients with SMA type II of all ages and with severely reduced functional abilities.

1. Introduction

Spinal muscular atrophy (SMA) is an inherited neuromuscular disease characterized by degeneration of the spinal cord motor neurons, which is caused by a mutation in the SMN1 gene. Incidence is approximately 1:10.000 [1–3].

The Danish National Rehabilitation Centre for Neuromuscular Diseases registers nearly 100% of the calculated prevalence of all persons with SMA type II (SMA II) in Denmark.

The clinical spectrum of SMA ranges from severe hypotonia and weakness to mild weakness, and the disease is classified into three types according to age of onset and achievement of motor milestones [4]. Studies have demonstrated a relation between disease severity and the number of SMN2 copies, although the number of SMN2 copies cannot provide a prognosis for each individual [5,6].

SMA II is characterized by onset at around age six months. A child with SMA II will achieve the ability to sit independently but will not be able to stand or walk unaided. Within these motor abilities, there is extensive variability of clinical severity from child to child [7]. The distribution of muscle weakness is well described. Proximal muscle groups are significantly weaker than distal muscle groups, and lower extremities weaker than upper extremities. [8,9]. Extensive muscular weakness in the trunk affects the spine and thus, most persons with SMA II develop scoliosis during childhood [10,11]. Another consequence is inability to cough sufficiently to clear secretions. Although the diaphragm is often relatively well preserved, [12] Forced Vital Capacity (FVC) is diminished and decreases over time [13–15]. FVC is often increased in supine compared to sitting position [16].

While lower limb contractures are common, fewer are seen in the upper limbs [9,10,17,18]. Incidences of limited maximal mouth opening (MMO) have been reported [19–21].

Several studies have indicated that when measured by means of Manual Muscle Test, muscle strength is weak but stable [15,17], and that muscle strength measured by quantitative muscle test does not change over time [22]. Other studies have indicated a gradual loss of functional abilities over time [23] as well as a decline in FVC [9,15,24].

In order to examine change over time in persons with SMA II, it is important to have sensitive, reliable and clinically meaningful outcome measures [25,26]. There is, however, a problem in finding assessment methods that are able to evaluate persons with very weak muscles as well as persons with comparatively more muscle strength [27]. Several clinical tools have been used to study physical impairment in persons with SMA II, but muscle strength and functional abilities are mainly tested in children and youths and often in a mixed population of persons with SMA II and -III.

Since longevity of the SMA II population has increased, it is necessary that clinical evaluation tools can be used to assess the effect

* Corresponding author. Address: The National Rehabilitation Centre for Neuromuscular Diseases, Research Unit, Kongsvang Allé 23, DK 8000 Aarhus C, Denmark. Tel.: +45 89482222; fax: +45 89482238.
E-mail address: ulwe@rcfm.dk (U. Werlauff).

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of rehabilitation on patients of all ages and with extremely limited muscle strength and functional abilities.

In the absence of longitudinal studies evaluating patients with severely reduced muscle strength a cross-sectional study of a population with various degrees of functional abilities could enhance existing knowledge of the natural history of SMA II.

2. Purpose

The aim of this study was firstly to study muscle strength, functional ability, contractures and Forced Vital Capacity in a total population of SMA II patients from five years of age in Denmark and secondly to evaluate the applicability of standard assessment methods and their ability to detect variations in muscle strength and functional ability among these individuals.

3. Method and materials

The study was designed as a cross-sectional study. All patients (n = 67) registered with the National Rehabilitation Centre for Neuromuscular Diseases age $\geqslant$5 years in august 2007 with a clinically and genetically confirmed diagnosis of SMA II were invited to participate in the study. The genetic test had confirmed homozygous absence of the SMN1 gene. Estimation of the number of SMN2 copies had been performed according to standard procedures. The clinical diagnosis, age at onset and maximal level of achieved motor milestones were found in medical records. Two of the oldest patients had medical records containing incomplete information pertaining to the ability to stand or walk unaided. To categorize these two patients as SMA II or III information was supplemented by photographs from the patients' own archives along with interviews about their early childhood.

Patients who agreed to participate were asked to fill in a registration form with information on spinal surgery, respiratory problems, respiratory and nutritional aids. Experienced physiotherapists at the National Rehabilitation Centre performed all examinations; interrater reliability among these physiotherapists has been described in earlier studies [28,29].

Since all assessments used in this study were part of standard physical examinations used to set up rehabilitation plans and since these assessments were already known to the patients the local Danish ethics committee declared that approval was not necessary. All patients signed an informed consent.

Assessment of the participants comprised the following measurements:

Anthropometrics

- Height in meters measured as arm span. An assistant supported the patients' arms, and a flexible measuring tape was used to ensure a full length measure of the arms also when elbow flexion contractures were seen.
- Weight recorded in kilos using a scale for lifts. Body mass index (BMI) was calculated as weight/height^2.

Scoliosis and pelvic obliquity

Scoliosis was assessed clinically and sorted into the categories mild, moderate or severe according to the degree of pelvic obliquity. Pelvic obliquity was assessed by means of a spirit level resting on both iliac crests with the person sitting in the wheelchair on a horizontal surface. The degree of pelvic obliquity was indicated by the number of fingers which fit into the space in a vertical line from the lower crest to the horizontal level. The category mild was defined as a pelvic obliquity of a maximum of 1.5 fingers. Category moderate: 1.5–3 fingers and category severe: 3.5 fingers and more.

Functional ability

- The Brooke Upper Limb Scale, an ordinal scale with six levels. Minimum score is 6, maximum score is 1 [30].
- The Hammersmith Functional Motor Scale (HFMS), an ordinal scale with 20 items. Minimum score is 0, maximum score is 40 [31].
- The Egen Klassifikation scale (EK), an ordinal scale with ten items. Minimum score is 30, maximum score is 0 [32].

Muscle strength

The Manual Muscle Test (MMT) recorded as MRC score on an ordinal scale. Minimum score is 0, maximum score is 5 [33]. The MMT score was modified to a 0–10 scale in accordance with the CIDD –protocol [30,34], and muscle strength was calculated as a percentage of normal value [35] (%MRC) = $\frac{\text{Sum of graded scores}}{\text{Number of muscles tested} \times 10}$ of

- total muscle strength (38 muscle groups = neck flexion, neck extension, shoulder flexion, shoulder extension, shoulder abduction, shoulder adduction, elbow flexion, elbow extension, hand dorsal flexion, hand volar flexion, finger flexion, thumb opposition, hip flexion, hip extension, hip abduction, hip adduction, knee flexion, knee extension, foot dorsal flexion, foot plantar flexion),
- upper limbs (20 muscle groups = shoulder flexion, shoulder extension, shoulder abduction, shoulder adduction, elbow flexion, elbow extension, hand dorsal flexion, hand volar flexion, finger flexion, thumb opponens),
- the forearm (12 muscle groups = elbow flexion, elbow extension, hand dorsal flexion, hand volar flexion, finger flexion, thumb opponens) and
- the hand (8 muscle groups = hand dorsal flexion, hand volar flexion, finger flexion, thumb opponens).

Quantitative muscle test was performed as a maximal voluntary isometric contraction with a hand-held dynamometer (Citec™, C.I.T. Technics BV, Groningen, the Netherlands) and expressed in Newton (N). Three muscle groups were tested bilaterally in standardized positions: elbow flexion, elbow extension and grip. Each measure was repeated three times, and the best value was recorded.

Range of motion

- Passive range of motion was measured using a standard goniometer in accordance with the methodology established by the American Academy of Orthopedic Surgeons [36]. Range of motion in the upper limbs (shoulder flexion – elbow extension, supination, pronation – hand flexion, extension, ulnar – and radial deviation – finger extension) was recorded.
- Contractures were calculated as the difference between the recorded range of movement and the normal range of movement [30,36]. Sum of contractures was calculated for each subject.
- Maximal mouth opening (MMO) was measured as the distance in millimetres between upper and lower central incisors. Mean MMO value for persons of more than twenty years of age were calculated and compared to mean value for normal persons of more than twenty years of age. [37].

Respiratory function

- Forced Vital Capacity (FVC) was measured by means of a calibrated spirometer (Medikro Spiro2000) with study subjects in both sitting- and supine position. Each measurement was performed three times. The best value was recorded and compared to the individually calculated reference value and expressed as

FVC%. In order for persons with invasive ventilation to be measured, they had to be able to do without their ventilator for 10 min prior to the measurement. Glossopharyngeal breathing was avoided.

3.1. Statistics

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS 16.0). Descriptive statistics were used to illustrate distribution of data. Correlations were calculated with Spearman rank order correlation coefficient (r_s).

To describe key factors, the total group was divided into four subgroups with intervals (5–20 years, 21–35 years, 36–50 years and 51–70 years).

When calculating influence of age, the three oldest subgroups were collated, hence two groups: ⩽20 years and ⩾21 years were available for statistics. This cut point was chosen to get two groups more equal in size and to improve statistical power.

Differences between these groups were calculated using the Mann–Whitney U test. Differences within groups were calculated by means of the Wilcoxon signed rank test. Significance level was set at $p \leqslant 0.05$.

4. Results

Sixty-seven persons were invited to participate in the study. Four persons declined the invitation and two were excluded because of cognitive impairment. For various reasons, seven persons were not able to participate in the study; mean age for persons ($n = 13$) not participating in the study was 21 (7–53).

Data was obtained from 54 persons. Mean age was 23 (5–70). Information on the participants is illustrated in Table 1.

4.1. Gender

The study population included 21 female and 33 male patients.

In the younger group ⩽20 years ($n = 31$), 21 were male (68%).

In the older group ⩾21 years ($n = 23$), 12 were male (57%).

4.2. Body mass index

In the younger group 3/31 persons had a BMI between 20 and 25. BMI below 20 was seen in 28 persons. None were overweight.

In the older group 4/23 persons had a BMI between 20 and 25. BMI below 20 was seen in 16 persons. Three persons were overweight.

4.3. Number of SMN2 copies

Three persons had two copies of SMN2 (6%), 36 had three copies (67%) and 14 had four copies (27%).

Two of those with two copies were the physically weakest: a 26-year-old woman, invasively ventilated since age 18 (total MRC score at 9% of normal value), and an 18-year-old man, using non-invasive ventilation (NIV) since age 11 (total MRC score at 7% of normal value). The third person with two SMN2 copies was a 6-year-old boy without assisted ventilation (total MRC score at 29% of normal value).

The four oldest participants had four SMN2 copies: a woman aged 70, using NIV since age 61 (total MRC score at 13% of normal value); a 64-year-old man invasively ventilated at age 60 (total MRC score at 12%); a 55-year-old woman, invasively ventilated at age 54 (total MRC score at 18%); and a 47-year-old woman, using NIV since age 36 (total MRC score at 24%).

When influence of SMN2 copies was calculated for all 54 persons, there was a co-relation between number of copies and age ($p = 0.05$) but none between number of copies and functional ability or muscle strength, neither in the younger group nor in the older group.

4.4. Age in relation to functional abilities and muscle strength

When influence of age was calculated, there was an overall co-relation between age and functional abilities and MMT. Correlation coefficients between age and functional abilities and MMT are shown in Table 2.

Table 1
Presentation of the participants. Distribution of data according to age. *Scoliosis were defined as Mild, Moderate, Severe according to the classification in the Section 3.

	Group 1 ($n = 31$)	Group 2 ($n = 13$)	Group 3 ($n = 7$)	Group 4 ($n = 3$)	Total ($n = 54$)
Age intervals	5–20	21–35	36–50	51–70	5–70
Mean (years)	13	28	43	63	23
Sex	9 f/22 m	7 f/6 m	3 f/4 m	2 f/1 m	21 f/33 m
BMI (kg/m^2) Mean (range)	15 (9–23)	17 (12–28)	18 (13–27)	21 (13–27)	18
Total MRC score (%/max score) Median (range)	27 (7–41)	19 (9–44)	21 (6–24)	13 (12–18)	24
Upper limb MRC score (%/max score) Median (range)	33 (10–61)	24 (12–54)	27 (9–31)	17 (15–21)	31
Clinical events: (numbers of patients and% of group)					
Lost ability to sit independently	9 (29%)	8 (62%)	5 (71%)	2 (66%)	24 (44%)
Scoliosis					
Mild	12 (39%)	1 (8%)	0	0	13 (24%)
Moderate	14 (45%)	5 (38%)	2 (29%)	0	21 (39%)
Severe	5 (16%)	7 (54%)	5 (71%)	3 (100%)	20 (37%)
Spinal fusion	16 (52%)	10 (77%)	3 (43%)	0	29 (54%)
NIV	10 (32%)	4 (31%)	4 (57%)	1 (33%)	19 (35%)
Tracheostomy	4 (13%)	4 (31%)	1 (14%)	2 (66%)	11 (20%)
Gastrostomy	1			1	2

Table 2
Correlation coefficients between age and Brooke Upper Limb Scale, HFMS, EK scale and MRC score. *Indicates correlation is significant at the 0.01 level.

	Brooke Upper Limb	HMFS	EK scale	MRC total% (38 muscle groups)
Age	.452*	−.435*	.364*	−.663*

4.5. Functional ability

All 54 participants were scored by means of the Brooke Upper Limb Scale. In the younger group ⩽20 years ($n = 31$), median score was 3 (range 1–6). Only one person scored 6, indicating maximum weakness. In the older group (⩾21 years), median score was 5 (range 1–6). Nine persons, corresponding to 39% of the group, scored 6, (which is the highest score and thus indicates maximal weakness).

The difference between scores in the two groups was significant ($p = 0.003$); distribution of the functional scores for the two age groups is illustrated in Fig. 1a.

All participants were scored by means of the HFMS. Because several of the patients did not have an independent sitting balance and could not lift their forearms, almost half of the participants were unable to perform any tasks on the scale.

In the younger group, 9/31 scored 0 – minimum score. Twelve had a score between 1 and 5. Nine persons had scores between 6 and 20, and one person, a 19-year-old boy, scored 25.

In the older group, 15/23 obtained the minimum score – 0 and 7/23 obtained a score between 1 and 5. One person, a 26-year-old woman, scored 30, the highest score among all the participants.

The difference in scores between the two groups was significant ($p = 0.004$); distribution of the functional scores for the two age groups is illustrated in Fig. 1b.

All participants were assessed by means of the EK scale. In the younger group, median EK sum was 15. A 7-year-old boy, the only one who had the ability to stand and transfer in knee–ankle–foot orthoses, obtained the lowest score among the participants (indicating high degree of functional ability): 2. The highest score was 25 (indicating minimal functional ability), scored by a 20-year-old man, invasively ventilated at age 16.

In the older group, median EK sum was 19. Here the lowest score was 3 and was achieved by the previously mentioned 26-year-old woman; a 45-year-old woman, invasively ventilated since age 24, received the highest score: 26.

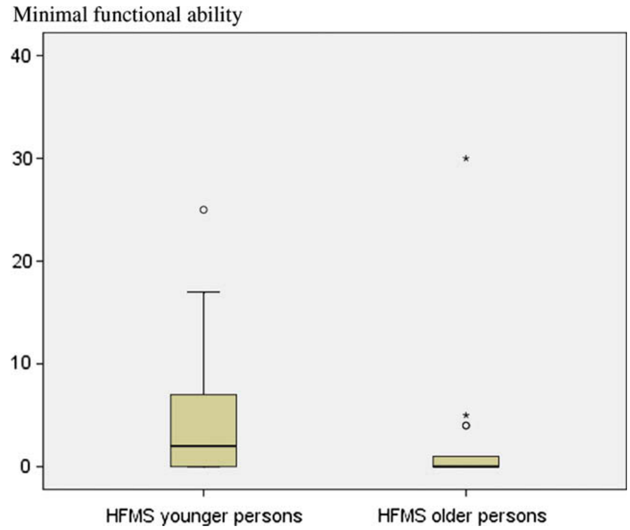

Fig. 1b. Hammersmith Functional Motor Scale for younger persons ⩽20 years ($n = 31$), and older persons ⩾21 years ($n = 23$). Median value for younger persons was 2, and 0 for older persons, resulting in the tiny box ∘ = outliers (value between 1.5 and 3 box lengths from the upper edge of the box) ∗ = extremes (value more than 3 box lengths from the upper edge of the box).

The difference between scores in the two groups was significant ($p = 0.04$); distribution of the functional scores for the two age groups is illustrated in Fig. 1c.

4.6. Scoliosis and the impact of spinal fusion on functional ability

All 54 participants had clinically visible scoliosis.

In the younger group (⩽20 years), 16 had spinal fusion. Fifteen persons had none. Six of these had a moderate scoliosis and nine persons had a mild scoliosis.

In the older group (⩾21 years), 13 had spinal fusion. Ten persons had no spinal fusion. Eight of these had a severe scoliosis, one had a moderate scoliosis and one person had a mild scoliosis.

Scores on functional scales (Brooke Upper Limb Scale, HFMS and EK scale) for persons with and without spinal fusion in the younger and the older groups are listed in Table 3.

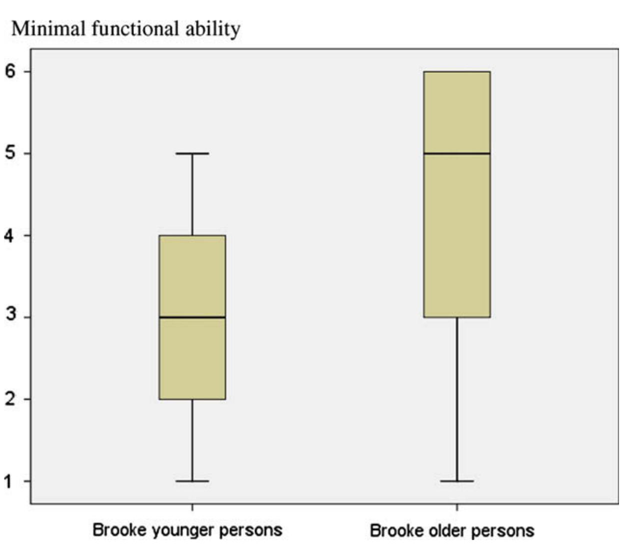

Fig. 1a. Brooke Upper Limb score for younger persons ⩽20 years ($n = 31$), and older persons ⩾21 years ($n = 23$). The boxes represent the inter-quartile range with the median line illustrated.

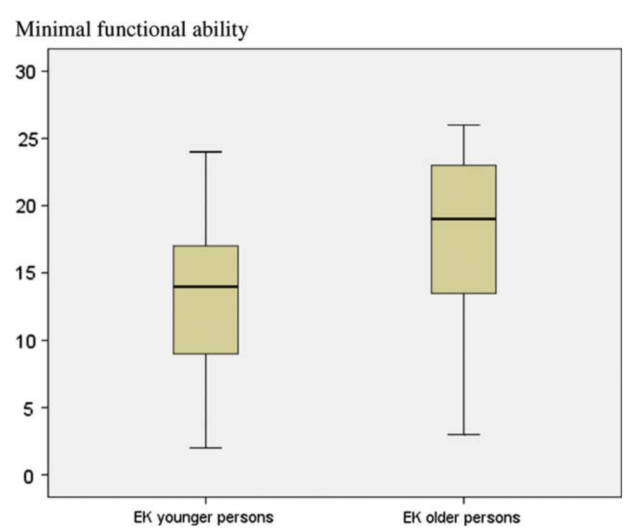

Fig. 1c. Egen Klassifikation (EK) score for younger persons ⩽20 years ($n = 31$), and older persons ⩾21 years ($n = 23$). Median value for younger persons was 15 – and for older persons median value was 19.

Table 3
Median and range score on Brooke Upper Limb Scale, HFMS and EK scale for the younger group (20 years or younger) and for the older group (21 years or more) listed according to spinal fusion and no spinal fusion. Ages are given as means and ranges.

	Spinal fusion				No spinal fusion			
	Brooke score (1–6)	HFMS score (0–40)	EK score (0–30)	Age years (mean)	Brooke score (1–6)	HFMS score (0–40)	EK score (0–30)	Age years (mean)
⩽20 years (n = 31)								
Median	3	1	17	17	2	6	13	8
Range	2–6	0–25	3–25	9–20	1–5	0–17	2–20	5–16
⩾21 years (n = 23)								
Median	4	0	16	32	6	0	22	45
Range	3–6	0–5	13–24	23–47	1–6	0–30	3–26	26–70

4.7. Muscle tests

MMT was performed on all participants ($n = 54$). Upper limbs were stronger than lower limbs ($p < 0.001$).

When means and medians for the MRC score of separate muscle groups were calculated, shoulder adductors were the strongest among the shoulder muscles. Elbow flexors were stronger than elbow extensors. Hip adductors were the strongest among the muscles of the hips, and knee extensors were stronger than knee flexors. MRC scores for muscle groups in upper- and lower limbs are listed in Table 4.

When the MRC score expressed in% of normal was reduced from 38 muscles to 20, 12 or 8 muscles respectively, a larger variation in the MRC score among the participants was shown. Total MRC score, upper limb MRC score, forearm MRC score and hand MRC scores expressed in percentage of normal value for each participant is illustrated in Fig. 2.

When scores for total MRC, upper limb and forearm scores were calculated according to age, the younger group had the highest score ($p = 0.001$). The score for the hand was also highest in the younger group, but with slightly lesser significance ($p = 0.003$).

Medians and ranges for MRC scores are listed in Table 5.

Quantitative muscle test was administered to 51/54 patients; due to a malfunction of the dynamometer, three were not tested. Nine were completely unable to overcome the dynamometer's activation threshold. Therefore, elbow flexion was scored in only 42 patients; mean value was 12.8 N.

Elbow extension was scored in 17 persons; mean value was 2.3 N.

Grip was also scored in 17 persons; mean value was 3.2 N.

Once again, the previously mentioned 26-year-old woman plus a 19-year-old man achieved the absolute highest total scores: 219 N and 297 N respectively.

When total dynamometric scores were calculated according to age, younger patients had a higher score ($p = 0.014$).

Scores for dynamometry are listed in Table 6.

4.8. Contractures

None of the participants ($n = 54$) had contractures in their fingers, and only four had a slight contracture in ulnar deviation. Wrist ulnar deviation and hypermobility in fingers were common. Limitations in forearm supination were more common than limitations in pronation. Half of the participants were hypermobile in forearm pronation. Elbow flexor contractures were common, and normal joint motion in both right and left elbow was found in only twelve patients, nine of whom were below twelve years of age. Shoulder flexion was normal for patients under 20, but in those over 20, shoulder flexion was limited and only 4/23 showed normal bilateral shoulder flexion.

When the sum of contractures was calculated according to age, older patients (⩾21 years) had more contractures than younger patients.

Joint upper limb motion for patients (⩽20 years/⩾ 21 years) is illustrated in Fig. 3.

Table 4
Manual Muscle Test scores obtained from bilateral MRC scores in upper and lower limbs according to the CIDD protocol [30]: (0 = 0 MRC score, 1 = 1, 2 = 2, 3 = 3−, 4 = 3, 5 = 3+, 6 = 4−, 7 = 4, 8 = 4+, 9 = 5−, 10 = 5).

		Numbers	Minimum	Maximum	Mean	Median
Neck	flexion	54	0	7	1.9	2
	extension	54	0	8	2.4	2
Shoulder	flexion	54	0	6	1.8	2
	extension	54	0	2	1.6	2
	abduction	54	0	6	1.9	2
	adduction	54	0	8	2.3	2
Elbow	flexion	54	1	7	4.0	4
	extension	54	0	6	1.8	2
Hand	dors flexion	54	1	9	3.8	4
	volar flexion	54	0	7	3.0	4
Finger	flexion	54	0	9	4.2	4
Opponens	pollicis	54	1	9	4.0	4
Hip	flexion	54	0	2	1.4	1
	extension	54	0	3	1.0	1
	abduction	54	0	2	0.8	1
	adduction	54	0	5	2.1	2
Knee	flexion	54	0	4	1.0	1
	extension	54	0	6	2.1	2
Foot	dors.flexion	54	0	6	2.2	2
	plantarflexion	54	0	6	2.2	2

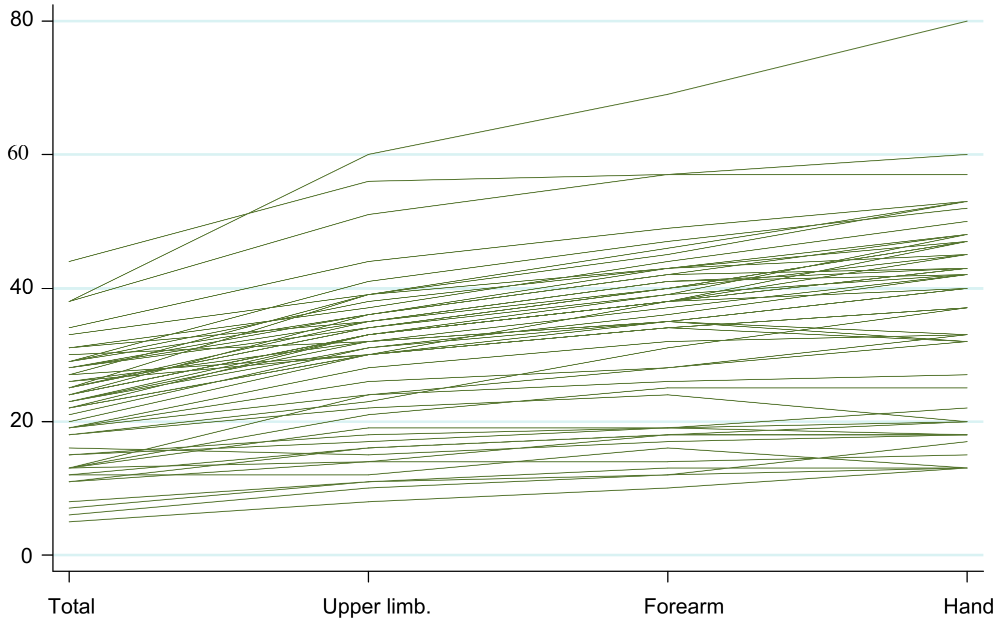

Fig. 2. Total MRC score (38 muscle groups), upper limb MRC score (20 muscle groups), forearm MRC score (12 muscle groups), hand MRC score (8 muscle groups) in percentage of normal value for each participant.

Table 5
MRC score – percentage of normal value – for total muscle strength, and muscles strength in the upper limbs, forearms and hands. The percentages are expressed as medians and ranges for the younger group (20 years or younger), for the older group (21 years or more) and for all persons ($n = 54$).

	MRC total% (38 muscle groups)	MRC upper limb% (20 muscle groups)	MRC forearm% (12 muscle groups)	MRC hand% (8 muscle groups)
⩽20 years ($n = 31$)	27 (7–41)	33 (10–61)	41 (13–72)	44 (18–81)
⩾21 years ($n = 23$)	18 (6–44)	23 (9–54)	29 (12–58)	33 (6–58)
Total ($n = 54$)	24 (6–44)	31 (6–61)	37 (12–72)	40 (6–81)

When the difference between contractures in right and left upper limb was calculated, older patients displayed more asymmetry than younger patients ($p = 0.024$).

Maximal mouth opening (MMO) was measured in 24 persons ⩽20 years and in 19 persons ⩾21 years; 11 were not measured.

Mean value for younger persons was 25 mm (13–40). Mean value of mouth opening in the older group was 20 mm (5–45), corresponding to half of normal value.

4.9. Respiratory function

Nineteen patients (35%) had non-invasive ventilation (NIV). In the younger group, the age for initiation of NIV was 1–10 years (mean 4), and the number of years on NIV was 1–11 years (mean 3). In the older group, the age for start of NIV was 8–60 years (mean 30), and the number of years on NIV was 4–16 years (mean 10).

Eleven patients (20%) were invasively ventilated. In the younger group, tracheostomy had been performed at age 4–13 (mean 9) and the number of years on invasive ventilation was 2–13 years (mean 6). In the older group, tracheostomy had been performed at age 13–59 years (mean 27) and the number of years on invasive ventilation was 1–32 years (mean 12).

The FVC of 42 of the participants was measured in both sitting and supine position; twelve were either not able to participate in this part of the study or could only perform one of the tests due to inability to be without their ventilator long enough for the evaluator to carry out the test and/or inability to coordinate the requisite blowing.

FVC in the sitting position was 9–98% of normal value (mean 42) for the younger group and 11–78% of normal value (mean 34) for the older group.

When measured in supine position, FVC was 12–85% of normal value (mean 42) for the younger group and 17–81% (mean 41) of normal value for the older group.

Twenty-eight persons had the largest FVC in supine compared to the sitting position. When results of all assessments were compared, there was a significant difference between FVC% in the two positions ($p = 0.01$).

Twenty-five persons had had pneumonia one or more times 12 months prior to testing. Infections seemed to be more frequent

Table 6
Quantitative muscle test by dynamometry (Citec™). Mean and range score for the younger group, the older group and total. Scores are registered in Newton. Number of persons who were not able to overcome the activating threshold from the dynamometer are listed under each test.

	Elbow flexion	Elbow extension	Grip	Total score
⩽20 years ($n = 28$) Persons not able to score	16.3 (0–111) ($n = 3$)	2.8 (0–23) ($n = 7$)	4.0 (0–42) ($n = 7$)	44.6 (0–297)
⩾21 years ($n = 23$) Persons not able to score	9.2 (0–65) ($n = 6$)	1.8 (0–34) ($n = 10$)	2.4 (0–26) ($n = 10$)	29 (0–219)
Total ($n = 51$) Persons not able to score	12.8 (0–111) ($n = 9$)	2.3 (0–34) ($n = 17$)	3.2 (0–42) ($n = 17$)	36.7 (0–297)

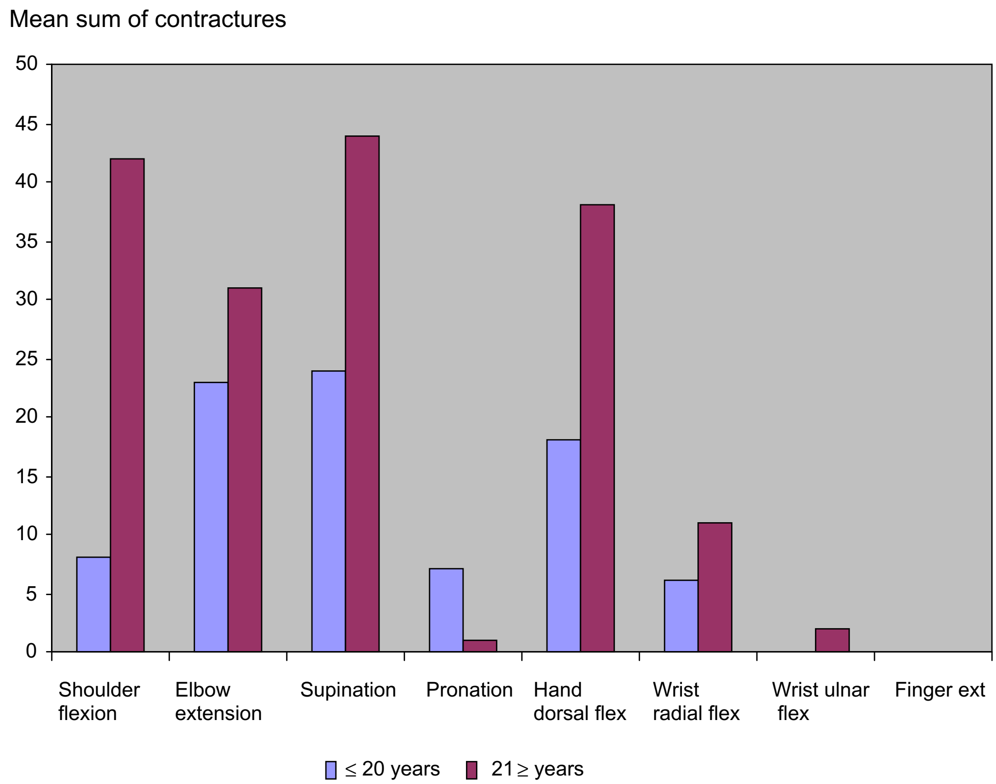

Fig. 3. Mean sum of contractures in upper limbs for persons 20 years or younger and persons more than 21 years of age. Difference between groups is significant for shoulder flexion ($p = 0.001$) and hand dorsal flexion ($p = 0.002$). Notice the reverse situation in pronation due to severe limitation in this movement in three of the young persons.

for persons without respiratory aids than for persons with invasive- or non-invasive ventilation. Fig. 4.

42/54 persons related that they had difficulty in coughing up secretions, however 30 persons mentioned that the problem only occurred once a month or even more seldom. Ten persons did not consider coughing a problem; five of these were tracheostomised and received suction to relieve secretion accumulation.

There was significant inter-correlation among the following assessments: muscle strength measured by means of MMT, Dynamometry, FVC, Brooke Upper Limb Scale, EK scale, HFMS for spinal muscular atrophy.

Correlation coefficients are shown in Table 7.

5. Discussion

Our study subjects were predominately male, which corresponds to other studies [21,38].

In our study population we found a range of SMN2 copies between 2 and 4. The number of SMN2 copies is described as having influence on survival and function [5,6]. In our study, however, the number of SMN2 copies related neither to the level of functional ability as measured with HFMS, Brooke, EK nor to muscle strength or FVC%.

Tiziano et al. found a significant correlation between the HFMS score and the number of SMN2 copies in 87 children with SMA II

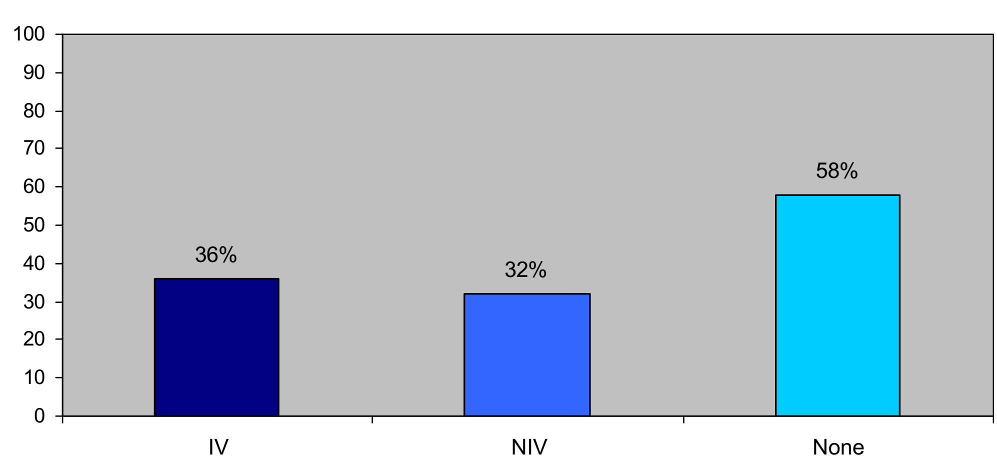

Fig. 4. Pneumonia/lung infection during the past 12 months reported by patients on IV (invasive ventilation), ($n = 4/11$), NIV (non-invasive ventilation) ($n = 6/19$), or None which is patients without assisted ventilation ($n = 14/24$). The bars present the number of patients in percentages of the individual groups (IV, NIV, None).

Table 7
Inter correlation coefficients for functional ability scores, muscle tests and FVC in sitting position. *N* = number of persons that entered in the correlation calculation. Only 51 persons were examined by dynamometry and only 42 persons could perform a FVC. *Correlation is significant.

	Brooke U.L	HFMS	EK scale	MRC total	Dynamometry
Brooke U.L					
N					
HFMS	−.753*				
N	54				
EK	.896*	−.762			
N	54	54			
MRC total % of normal value	−.885*	.734*	−.845*		
N	54	54	54		
Dynamometry total score	−.689*	.576*	−.690*	.693*	
N	51	51	51	51	
FVC% of normal value	−.627*	.677*	−.754	.655*	.514*
N	42	42	42	42	42

between the ages of 2½ and 12 [39], and Arkblad et al. found a clear correlation between SMN2 copy numbers and HFMS scores in 26 children with SMA II and -III [3]. Although we did not find such a relationship, the two persons with the least muscle strength were also those with the fewest number of SMN2 copies and the two oldest participants were among those with the most copies. In our study we had relatively many persons with four SMN2 copies (27%), whereas in the Tiziano study, the children with SMA II had only two or three SMN2 copies and in the Arkblad study, only one of the children with SMA II had four SMN2 copies, the rest had three.

The composition of our study population might explain this: forty-three percent were over 20 years old and the fact that this group includes 12 of those 14 patients who had four copies could indicate that these individuals have been stronger and, for that reason, have survived; and later, when respiratory insufficiency became a problem, their treatment was augmented with respiratory support.

Another explanation for the difference between our study and others could be the difficulties in general in drawing a clear-cut line between the different SMA types.

The study showed a correlation between age and functional ability and a significant difference was found between the younger and the older group with respect to functional ability (assessed with Brooke, HFMS and EK), muscle strength (measured with MMT or with a dynamometer) and contractures.

The study also indicated that the severity of scoliosis increases by age in spite of spinal fusion, Table 1. Our study was not able to clarify whether spinal fusion had any influence on functional abilities. In the younger group, median scores on functional scales were lower in persons with spinal fusion compared to persons without spinal fusion whereas it was quite opposite in the older group. The cause of this might be that the persons with spinal fusion in the younger group had already scored lower on the functional scales before their spinal fusion. In the older group the oldest persons had perhaps had better function from the start – and spinal fusion was not performed when they were young.

Whether or not SMA II is a disease with progressive loss of muscle strength has been widely discussed. Individuals with SMA II can lose functional ability, not only because of loss of muscle strength but also as a consequence of contractures, scoliosis or growing. Interventions such as spinal surgery also influence the functional level. A study by Iannacone [22] of 73 children and adults with SMA II and III assessed over 2–6 years found loss of functional abilities but no loss of muscle strength when measured with dynamometry of 14 muscle groups. Carter [9] found a significant mean decline of 0.24 units per 10 years in muscle strength measured as MMT of 32 muscle groups in 18 children and adults with SMA II, and Steffensen et al. [24] found a small but significant decline of muscle strength measured as MMT of 34 muscle groups and FVC% among 12 adults with SMA II over a five- year period, but no significant change of functional abilities when scored with the EK. Although our study has a cross-sectional study design and is therefore not able to inform about loss of muscle strength over time, it supports the observations by Carter and Steffensen that since MRC scores showed a difference between younger and older persons, there is a slow decline of muscle strength with advancing age.

The discrepancies among the findings could be caused by the methods used in the individual studies to determine changes over time and the time span studied. It is important that the tools we use are sensitive enough to identify both differences among the individuals of the entire SMA group as well as changes over time.

For this study we chose to use assessment instruments that had been used in other studies on SMA and preferably validated for the assessment of patients with SMA II.

Functional ability scales frequently used for examining SMA II patients are the Brooke-, HFMS- and EK scales. We also considered evaluating our patients by some of the more recent devised functional scales for neuromuscular diseases, but we had to account for the amount of time in which especially younger children were able to cooperate.

The Brooke Upper Limb Scale is a rather crude scale with large intervals between each level of function. When used on very weak persons, it cannot differentiate between persons who are unable to hold a pencil or pick up coins but still have sufficient hand or finger function to operate their wheelchair, use a computer, type and send text messages, etc. This results in a ceiling effect among weak persons, and in our study this was clearly reflected in the older group.

The Hammersmith Functional Motor Scale for SMA is designed and validated for non-ambulant children with SMA. It tests movements that are basic for human beings independent of their age. The reason for including it in this study was to examine whether the scale might be useful in life- long prospective studies. However, we have subsequently concluded that the test will not be suitable for this, partly because it does not account for severely limited functional abilities. Since several persons in our study did not have an independent sitting balance and could not lift their forearms, almost half of the entire group could not perform any tasks on the scale.

The EK scale was suitable for measuring all persons, but showed only minor, although significant, differences between the two age groups. The most likely reason for this is that the last items on the scale measure the need for respiratory intervention and this part of the score changes when the intervention has taken place.

A person who shows signs of hypoventilation has a higher score before the respiratory intervention than after it has taken place, and like the Brooke scale, the EK scale does not offer sufficient differentiation on the level of hand function in weak persons. There was no ceiling and floor effect in our SMA II group.

The Manual Muscle Test as a means to assess muscle strength has been used as outcome measure in several studies, although it is known that the 0–5 scale is controversial because scores of individual muscle groups are unable to express subtle differences in muscle strength and there might be a high degree of inter- and intrarater variability, especially among untrained evaluators, and in muscle groups graded more than 3 on the MRC scale [40]. In our study we used trained evaluators and using the sum of scores of the individual muscle groups and calculating a percentage of normal value increased the sensitivity of the Manual Muscle Test.

A total muscle test is time-consuming and difficult to perform in persons with SMA II because the test person has to be transferred from his wheelchair and back again. It also requires the patients to concentrate and collaborate which may be difficult for younger children. We therefore wanted to study whether or not a scaled-down muscle test of the upper limbs could be informative and found that such a reduced version of the muscle test might be even more descriptive than a total muscle test, because differences among individuals with SMA II were more clearly shown. Whether a scaled-down muscle test also has a higher sensitivity than a comprehensive test in terms of identifying change over time remains to be examined. Describing the motion performed in the thumb test as 'opposition' might be a little controversial, because a combination of muscle weakness and hyper mobility may make it difficult to determine whether the patient is performing a true opposition movement. We did, however, find it important to have an expression for strength in this finger, as the thumb is very often active when writing text messages, operating a joystick, etc.

All in all, we found that manual muscle testing of the upper limbs was an acceptable tool for life-long testing of individuals with SMA II, allowing as it does for individual differences and being suitable for testing individuals with very little muscle strength. We found no ceiling or ground effects in our study population.

Muscle strength measured as quantitative muscle test (QMT) by means of a hand held-dynamometer is easy to perform and appropriate for wheelchair-bound individuals. This method and the results it generates are found to be reliable in persons with SMA, although not equally reliable in all muscle groups. Moreover, QMT can be complicated because very weak persons might not be able to overcome the activation threshold of the dynamometer [41–43] rendering it therefore less sensitive [22]. In our study, two thirds of the persons tested were not able to overcome the activation threshold in elbow extension and gripping and the majority of the remaining participants achieved very low scores. Elbow flexion was easier to perform, with 82% of the tested persons able to achieve a score, indicating that it might be the most useful test of QMTs in studies of SMA II patients of all ages; it should be noted, however, that 18% were unable to perform any of the QMT tests.

Elbow flexion contractures are common and this fact might contribute to better strength in the elbow flexors and thus also improve functional abilities of the upper limbs – such as eating.

Upper limb- and jaw contractures seem to accelerate with age and should therefore be given special attention during physical treatment. The limited mouth opening that we found in our study corresponds to the problems described in a recent survey by Messina et al. [21]. Like them, we also found the limitation to be more severe in older individuals than in younger ones. This is an important issue, as a limited mouth opening can lead to problems with such daily routines as eating, brushing teeth and talking.

We believe it is important to measure mouth opening and to focus on techniques to prevent contractures at an early stage of the disease. However relating MMO in patients to a normal value as we did in our study may not give a correct impression on the problem as there is large variability in normal MMO. MMO may be related to the subject's body size and is found to be highly correlated to the ability to position three fingers vertically in the mouth [36].

Assessments of respiratory function with Forced Vital Capacity% showed no significant difference between the younger and the older groups. Since respiratory insufficiency is the most frequent cause of death, and since assisted ventilation was not a generally accepted intervention 20 years ago, it is possible that those with SMA II who reached adulthood were those who had stronger respiratory muscles and thus better able to cope with their respiratory infections. A longitudinal study by Steffensen et al. [24], in a sample of 12 adults with SMA II who were examined once a year showed that Forced Vital Capacity decreased significantly over 5 years. Carter et al. [9] found similar data in seven persons over a 10-year period. Since our study has a cross sectional design, it cannot provide information on the sensitivity of FVC% as a tool for monitoring change over time.

Furthermore, FVC% is not only a measure of respiratory muscle strength. Such factors as scoliosis, stiffness of the ribcage and reduced pulmonary compliance can overload the respiratory muscles and influence the volume of air that can be exhaled in one breath. It has been shown that spinal surgery postpones loss of FVC [11]. In the older group, the majority (57%) had had spinal surgery, which could provide some explanation for the lack of difference between the younger and the older group. However, other studies show a continuous decline of lung function postoperatively [44].

The significant difference between FVC% when measured in sitting as compared to supine position has been observed by other authors and interpreted as a mechanical advantage to the diaphragm during in- and expiration because in the supine position, it is pushed upwards into the thorax by the abdominal content and in this position it facilitates lower rib movements during inspiration [16].

More than half of the study participants were ventilated by either non-invasive or invasive ventilation. All SMA patients and their relatives had received instruction in secretion removal by means of equipment and by helpers giving manual support to improve coughing. Those who used invasively assisted ventilation also used air stacking and suctioning. One person had learned glossopharyngeal breathing in order to improve coughing. It is remarkable that the frequency of infections was not significantly higher among those who were invasively ventilated compared to those who were non-invasively ventilated. It is a frequently used argument against invasively assisted ventilation that in comparison to non-invasive ventilation, infections are more frequent in this approach.

Evaluation of future clinical trials stresses a more thorough understanding of the natural history of SMA and we think that this study contributes to this understanding. The study also emphasizes that in an era where individuals with very limited muscle strength achieve normal longevity, the need for clinical tools that are able to measure severely reduced functional ability is increasing. Persons with SMA II have very different functional abilities in their distal function: the ability to move and use their forearms and hands. In order to register any gain or loss of function in this area it is therefore important to use clinical tools that are sensitive enough to measure these differences and meaningful for the patients evaluated at the same time.

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