ARTICLE

Natural course of scoliosis and lifetime risk of scoliosis surgery in spinal muscular atrophy

Camiel A. Wijngaarde, MD, Rob C. Brink, MD, Floor A.S. de Kort, MD, Marloes Stam, MD, Louise A. M. Otto, MD, Fay-Lynn Asselman, BSc, Bart Bartels, MSc, PPT, Ruben P.A. van Eijk, MD, Joyce Sombroek, MD, Inge Cuppen, MD, PhD, Marjolein Verhoef, MD, PhD, Leonard H. van den Berg, MD, PhD, Renske I. Wadman, MD, PhD, René M. Castelein, MD, PhD, and W-Ludo van der Pol, MD, PhD

Correspondence
Dr. van der Pol
w.l.vanderpol@umcutrecht.nl

Neurology® 2019;93:e149-e158. doi:10.1212/WNL.0000000000007742

Abstract

Objective
To investigate the natural course of scoliosis and to estimate lifetime probability of scoliosis surgery in spinal muscular atrophy (SMA).

Methods
We analyzed cross-sectional data from 283 patients from our population-based cohort study. Additional longitudinal data on scoliosis progression and spinal surgery were collected from 36 consecutive patients who received scoliosis surgery at our center.

Results
The lifetime probability of receiving scoliosis surgery was ≈80% in SMA types 1c and 2. Patients with type 2 who only learned to sit (type 2a) were significantly younger at time of surgery than those who learned to sit and stand (type 2b). The lifetime risk of surgery was lower in type 3a (40%) and strongly associated with age at loss of ambulation: 71% in patients losing ambulation before 10 years of age vs 22% losing ambulation after the age of 10 years ($p = 0.005$). In type 3a, preserving the ability to walk 1 year longer corresponded to a 15% decrease in lifetime risk of scoliosis surgery (hazard ratio 0.852, $p = 0.017$). Scoliosis development was characterized by initial slow progression, followed by acceleration in the 1.5- to 2-year period before surgery.

Conclusion
The lifetime probability of scoliosis surgery is high in SMA types 1c and 2 and depends on age at loss of ambulation in type 3. Motor milestones such as standing that are not part of the standard classification system are of additional predictive value. Our data may act as a reference to assess long-term effects of new SMA-specific therapies.

MORE ONLINE

CME Course
NPub.org/cmelist

From the Department of Neurology and Neurosurgery (C.A.W., F.A.S.d.K., M.S., L.A.M.O., F.-L.A., R.P.A.v.E., J.S., I.C., L.H.v.d.B., R.I.W., W-L.v.d.P), Department of Rehabilitation (M.V.), Department of Orthopedic Surgery (R.C.B., R.M.C.), Department of Pediatrics, Child Development and Exercise Centre (B.B), and Biostatistics & Research Support Julius Centre for Health Sciences and Primary Care (R.P.A.v.E.), University Medical Centre Utrecht, Utrecht University, the Netherlands.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Dr. Sombroek is currently at the Department of Internal Medicine, Amstelland Hospital, Amstelveen, the Netherlands.

Glossary

CI = confidence interval; **SMA** = spinal muscular atrophy; **SMN** = survival motor neuron.

Hereditary proximal spinal muscular atrophy (SMA) is an important cause of infantile mortality and childhood disability. It is caused by survival motor neuron (SMN) protein deficiency due to homozygous loss of function of the *SMN1* gene. Three types of childhood SMA (i.e., types 1–3) are distinguished on the basis of age at onset and achieved motor milestones.[1–3]

The natural course of SMA is characterized by death due to respiratory insufficiency in the first years of life (i.e., in SMA type 1) or an arrest of motor function development, followed by a progressive decline of motor function and muscle strength in the more chronic forms (i.e., types 2 and 3).[1–3] Recently introduced SMN-augmenting therapies have been shown to improve survival and motor function in the short term. However, long-term effects on motor function or important SMA-related complications have not yet been elucidated.[4–7]

A progressive scoliosis due to deteriorating axial muscle strength is one of the most important complications occurring in virtually all children with SMA type 2 and a significant number with type 3. It impairs motor and respiratory function, and most patients eventually require spinal surgery for scoliosis correction.[8–13] Studies on lifetime risk of scoliosis surgery in relation to disease severity, however, are not available, and the natural course of scoliosis in SMA has not been fully investigated. Therefore, we analyzed data from 283 patients from our prospective, population-based cohort study on SMA[14] to study the prevalence, lifetime risk of scoliosis surgery, scoliosis progression, and characteristics of patients who received scoliosis surgery at our center.

Methods

Standard protocol approvals, registrations, and patients consents

Patient data were retrieved from the Dutch SMA registry, which contains data of an ongoing prospective population-based cohort study on SMA, which started in 2010. Patient characteristics are captured with standardized questionnaires and physical examinations, including muscle strength measurement and motor function assessments, as described previously.[14] The use of standardized questionnaires and physical examinations allowed us to obtain information on the presence of a scoliosis and, if applicable, information on previous scoliosis surgery.

We used the SMA classification system based on age at disease onset and acquired motor skills to define SMA phenotypes with previously published modifications to distinguish SMA types 1a through 1c, 2a, 2b, 3a, and 3b (table 1).[3,13]

We confirmed homozygous loss of function of the *SMN1* gene and determined *SMN2* gene copy numbers by multiplex ligation-dependent probe amplification analysis using the SALSA multiplex ligation-dependent probe amplification kit P021-B1-01 (MRC Holland, Amsterdam, the Netherlands) according to the manufacturer's protocol. We were unable to determine the *SMN2* gene copy number of 5 patients (1.8%) due to the lack of sufficient amounts of DNA. Further inclusion and exclusion criteria and details of all study-related procedures have been published previously.[3,14]

The study protocol was approved by the local medical ethics committee (No. 09-307/NL29692.041.09), and informed consent was obtained from all participants or their parents in case of underage children.

Scoliosis progression

To study scoliosis progression, we identified patients in our database who underwent scoliosis surgery at our tertiary referral center between 1991 and 2015. We reviewed all available patient charts and extracted relevant details, including radiographs of the spine, surgical techniques applied (i.e., segmental spinal instrumentation or surgical techniques that allow for continued spinal growth after surgery), and perioperative and postoperative reports. Radiographs of the spine were made following a standardized procedure at our center. If possible, the radiographs were made in the upright, standing position. If a patient was unable to stand, radiographs were made in a sitting position without support. If a patient was unable to sit, the supine position was used.

The magnitude of the curve, vertebrae that were included in the scoliosis, curve shape, and convexity were obtained from all available radiographs. Curve characteristics, including the coronal Cobb angle,[15] were reassessed by 1 observer (R.C.B.) using multiple radiographs per patient to evaluate progression of the curve and taking the patient's position, for example, sitting or lying, into account. Both analog and digital anteroposterior and posteroanterior radiographs were included because previous studies showed very low variability in Cobb angle measurements between digital and analog radiographs and between anteroposterior and posteroanterior radiographs.[16,17]

Effect of surgery on scoliosis

Scoliosis correction of the main curve was defined as the difference in Cobb angle between the last available preoperative and the first available postoperative radiograph. Postoperative radiographs were used only if made within 6 months after surgery. This time criterion was selected to take the progressive nature of scoliosis in SMA, even after spinal surgery, into account.[18]

Table 1 Clinical classification of SMA

SMA type and subtypes	Age at onset	Highest achieved motor milestones
1	0–6 mo	Never acquires ability to sit unsupported
0/1a	Prenatal/neonatal	Symptoms in prenatal and/or neonatal (first month) period, no head control
1b (classic)	1–6 mo	No head control and no ability to roll over
1c	3–6 mo	Will usually acquire additional motor skills such as head control or rolling from supine to prone or at least to 1 side at any stage in life. Patients with SMA type 1c are reported to survive into adulthood with or without respiratory support
2	6–18 mo	Able to sit unsupported, not able to walk
2a		Unsupported sitting but not able to stand or walk with help
2b		In addition to unsupported sitting, able to stand or walk with help but not unassisted
3	>18 mo	Able to walk unsupported
3a	18–36 mo	
3b	>36 mo	
4	During adulthood, i.e., ≥18 y	Able to walk unsupported

Abbreviation: SMA = spinal muscular atrophy.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Lifetime surgery probability was analyzed with Kaplan-Meier survival curves. Patients who did not undergo surgery were censored at the end of the follow-up period, i.e., their most recent study visit to our center. To detect differences between SMA types, we used the log-rank test. Median survival times, expressing the median patient age at surgery, were calculated. To correct for multiple testing, p values were adjusted with Bonferroni correction. Cox regression was used to assess the impact of age at loss of ambulation on the lifetime surgery probability in patients with SMA type 3a. The 95% confidence intervals (CIs) for the size of each reported effect are shown.

Age at surgery between SMA types within the subgroup of patients who received surgery at our center was compared by use of a Kruskal-Wallis analysis because data followed a non-normal distribution. To analyze the presence of a trend of increasing age at surgery with milder SMA phenotypes, the Jonckheere-Terpstra test was used. Mann-Whitney U analysis was used to compare age at surgery between groups who received surgery before vs after introduction of new surgical techniques because data followed a non-normal distribution. Values of $p < 0.05$ were considered statistically significant. We used R software (R-3.4.3 for Windows with RStudio version 1.1.383, R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.[19]

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

In total, we included 283 patients with SMA types 1 through 4 (age range 0–82.2 years). In our cohort, 170 patients (60%) had scoliosis, and 95 (34%) underwent scoliosis surgery. Patient characteristics are presented in table 2.

Lifetime risk of scoliosis surgery in SMA

The lifetime probability of scoliosis surgery differed between SMA types ($p < 0.0001$). Surgery probability was high for SMA types 1c and 2 at 77% and 84%, respectively (95% CI 26.2–92.9 and 72.0–90.6). The lifetime probability was similar for SMA types 2a and 2b at 85% and 83%, respectively (95% CI 68.2–92,5 and 60.7–92.2, $p = 0.598$). In SMA type 3a, the probability was 40% (95% CI 20.7–54.4), considerably lower compared to SMA types 1c ($p = 0.0093$), 2a ($p = 3.3 \times 10^{-9}$), and 2b ($p = 3.9 \times 10^{-5}$). The lifetime probability of scoliosis surgery for SMA types 3b and 4 was very low: only 1 of 44 patients with SMA type 3b (2%, 95% CI 0.0–6.6) and none of the 6 patients with SMA type 4 in our cohort underwent scoliosis surgery (figure 1).

Disease progression in SMA type 3a leads to loss of ambulation in a significant proportion of patients. It is likely that the progression of weakness not only leads to loss of ambulation but also increases the risk of scoliosis progression that ultimately requires surgery.[8] To assess its effect in SMA type 3a, we stratified by age at loss of ambulation (figure 2). Lifetime probability of scoliosis surgery was 71% (95% CI 19.2–89.7) in patients with early (≤10 years) and 22% (95% CI 0–41.4) with later (>10 years) loss of ambulation ($p = 0.005$, data available from 28 patients). The age at which independent walking was lost greatly affected the probability of scoliosis surgery: losing the ability to

Table 2 Baseline characteristics

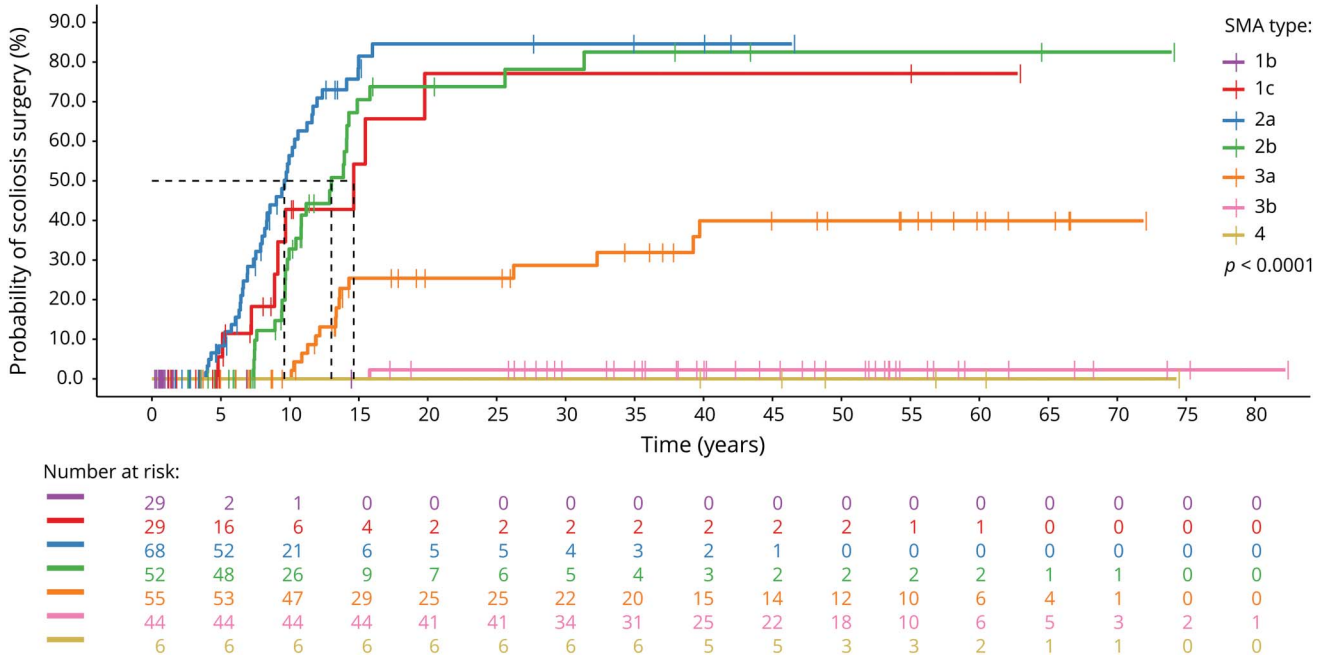
	SMA type						
	Type 1b (n = 29)	**Type 1c (n = 29)**	**Type 2a (n = 68)**	**Type 2b (n = 52)**	**Type 3a (n = 55)**	**Type 3b (n = 44)**	**Type 4 (n = 6)**
Age, y	0.5 (0–14.3)	7.9 (1.0–62.8)	17.6 (1.5–46.4)	18.9 (2.4–73.9)	34.1 (3.5–71.9)	44.6 (17.1–82.2)	52.6 (39.6–74.3)
M:F	10:19	17:12	26:42	18:34	23:32	25:19	2:4
***SMN2* copies, n**							
1	3	0	0	0	0	0	0
2	23	4	1	1	1	1	0
3	2	25	61	44	26	6	0
4	1	0	4	6	28	32	6
5	0	0	0	0	0	4	0
NA	—	—	3	1	—	1	—
Scoliosis surgery, n (%)	0 (0)	9 (31)	42 (62)	28 (54)	15 (27)	1 (2)	0 (0)
Age at scoliosis surgery, y	—	9.1 (4.8–19.8)	8.2 (3.9–16.0)	10.6 (7.4–31.3)	13.4 (10.1–39.7)	15.8	—

Abbreviations: NA = not available; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2
Data are presented as median (range) when appropriate.

walk independently 1 year later corresponded roughly to a 15% decrease in the lifetime risk of scoliosis surgery (hazard ratio 0.852, 95% CI 0.748–0.97, $p = 0.0166$, n = 28).

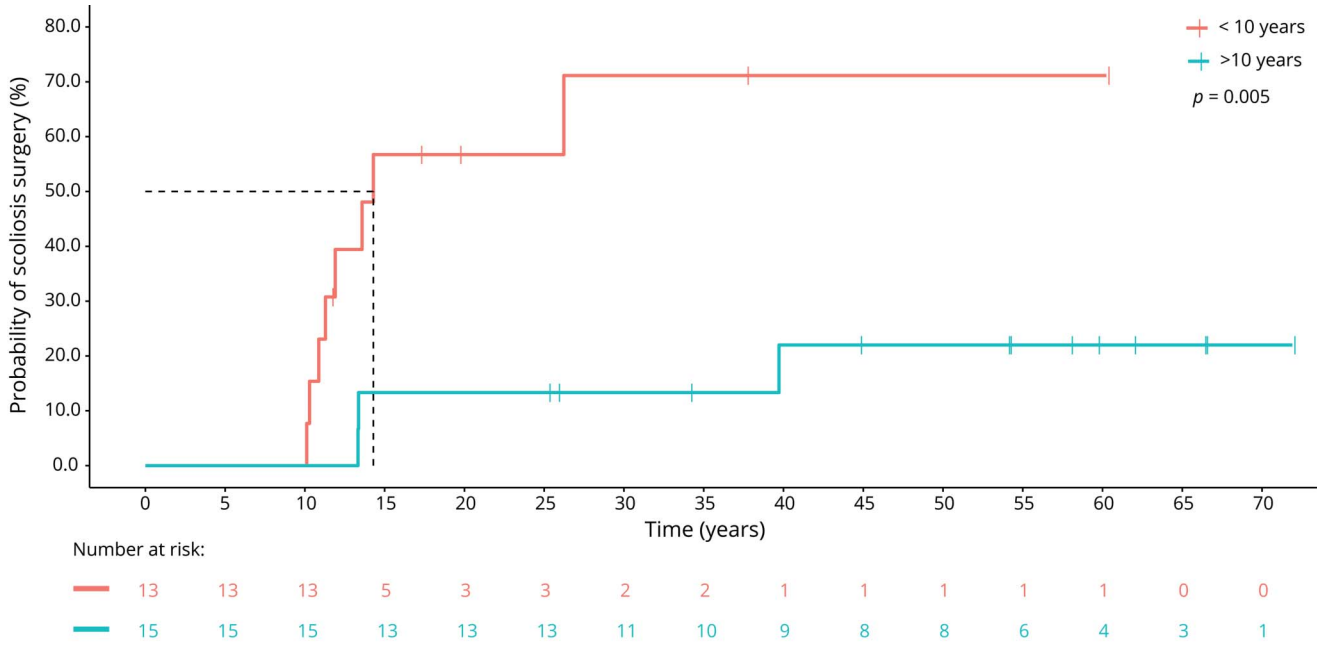
Stratification by *SMN2* copy numbers within the group of SMA type 3a patients showed no clear differences in surgery probabilities ($p = 0.31$), although a trend of higher surgery

Figure 1 Lifetime probability of scoliosis surgery in SMA



Probability of scoliosis surgery by age (in years). Colored lines represent the different spinal muscular atrophy (SMA) phenotypes. Small vertical lines indicate censoring. Horizontal and vertical dashed black lines indicate the median times to scoliosis surgery per SMA type.

Figure 2 Lifetime probability of scoliosis surgery and ability to walk independently in SMA type 3a



Probability of scoliosis surgery by age (in year). Colored lines represent the different groups of patients with spinal muscular atrophy (SMA) type 3a: early (red) vs late (blue) loss of ambulation and corresponding lifetime probabilities of scoliosis surgery. Small vertical lines indicate censoring. Horizontal and vertical dashed black lines indicate the median time to scoliosis surgery.

probability in patients with 3 vs 4 *SMN2* copies was present (58% and 22%, respectively).

Patients' age at scoliosis surgery

The median ages at scoliosis surgery differed between SMA types: 14.6, 9.6, and 13 years in SMA types 1c, 2a, and 2b, respectively ($p < 0.0001$, figure 1). For patients with SMA type 3a who lost ambulation before the age of 10 years, the expected median age at surgery was 14.3 years (figure 2). A clear trend of increasing age at surgery with milder SMA phenotypes was present when we assessed all patients with SMA types 1c through 3a who underwent scoliosis surgery ($J = 2{,}139$, $p = 2.226 \times 10^{-6}$).

Natural course of scoliosis in SMA

To assess scoliosis in more detail and to study its natural progression in patients with SMA, we studied 36 consecutive patients who underwent scoliosis surgery at our tertiary referral center in the 25-year period between 1991 and 2015. Patient and scoliosis characteristics are presented in table 3, including the reasons for surgery. Because of the limited number of patients, no subgroup analyses to assess differences in reasons for surgery between SMA subtypes were performed.

The progression rate of scoliosis was studied with the use of serial preoperative radiographs. Sufficient data were available from 15 of 36 (42%) patients. Scoliosis progression was 7.2°/y with a marked increase to an average of 10.1°/y in the 18 months before spinal surgery (figure 3).

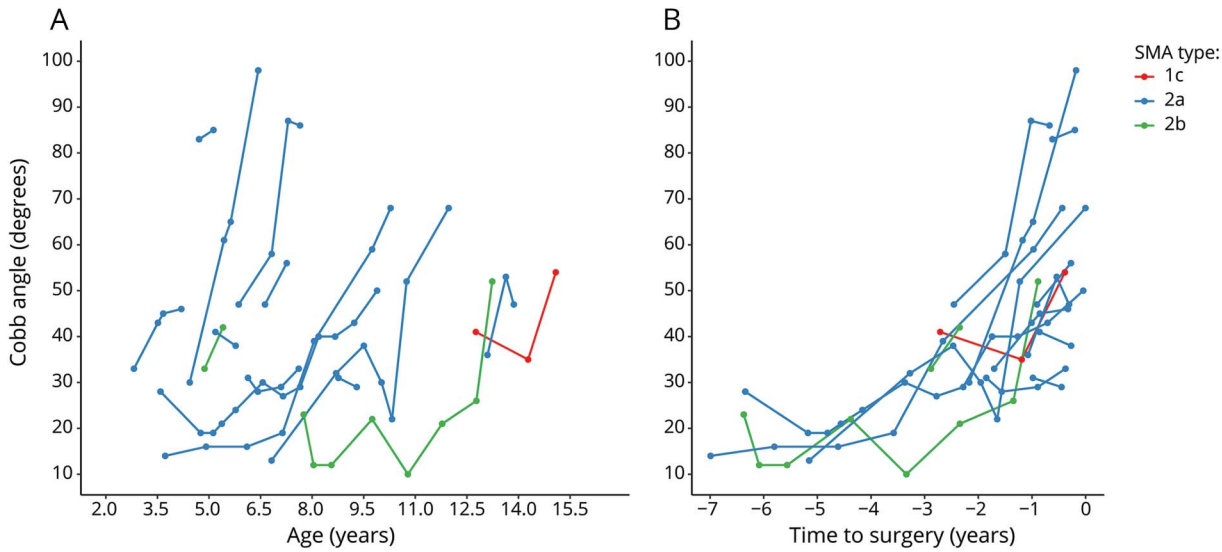
Age at surgery, scoliosis characteristics, and surgery techniques from 1991 to 2015

Median age at scoliosis surgery in the cohort of 36 patients was 7.9 years and not different between SMA types [$H(_3) = 7.0612$, $p = 0.06997$, table 3], although we observed a trend of increasing age at surgery with milder SMA phenotypes within this cohort ($J = 246$, $p = 0.00809$).

Scoliosis shape was determined using radiographs of the spine from 25 (69%) patients. Eleven patients were excluded because their radiographs were of insufficient quality (e.g., incomplete imaging of the spine). Fifteen (60%) patients had a C-shaped scoliosis; 10 (40%) had an S-shaped scoliosis. Median preoperative Cobb angle was 50° (range 29°–104°), and scoliosis surgery resulted in a median correction of 50% (table 3).

In our cohort, segmental spinal instrumentation using the Luque[20] method was used predominantly until 2008. From 2009 on, this method was largely replaced by surgical techniques that allow for continued spinal growth after surgery. From 2009, patients in our cohort underwent surgery at older ages (median 10.2 years, range 6.6–15.5 years, n = 10) compared to before 2009 (median 7.3 years, range 3.9–14.9 years, n = 26) ($U = 64$, $p = 0.019$, $r = 0.39$). However, when we

Figure 3 Scoliosis progression in SMA



(A) Individual scoliosis progression in patients of different ages. (B) Progression of scoliosis before spinal surgery (at t = 0). Lines represent the individual progression patterns, and colors indicate different spinal muscular atrophy (SMA) phenotypes as specified in the legend.

compared age at surgery before and after 2009 for all patients with SMA types 1c through 3a in our population-based registry (n = 94, table 2), the median age did not differ between groups (9.9 and 10.0 years, respectively, $U = 653$, $p = 0.42$, $r = 0.082$).

Discussion

This study describes the lifetime risk of scoliosis and its surgical treatment in relation to SMA type and the acquisition and loss of specific motor milestones, as well as the characteristics and rate of progression of scoliosis in a large cohort of patients with SMA. SMA type is associated with the cumulative lifetime risk of scoliosis that requires surgery. Acquired milestones and their loss are associated with the age at which surgery is necessary. Combined, these data reflect the natural history of scoliosis development in SMA.

Scoliosis probably reflects the inability of axial muscle to support the growing vertebral column and is one of the most important complications of SMA, affecting the majority of patients with types 1c and 2 and, as we have shown, those with type 3a with early loss of ambulation.[8–12] Scoliosis development negatively affects the ability to sit and to balance, respiratory function, and several other functions.[12] Despite its importance, very few large cohort studies have addressed the issue in detail, and scoliosis progression has not been included as an outcome measure in clinical trials.

We found high lifetime probabilities of scoliosis surgery in SMA types 1c, 2a, and 2b (≈80%), a lower probability in SMA type 3a (≈40%), and a very low probability in SMA types 3b and 4. Previous studies that described lifelong risk of scoliosis surgery had much smaller sample sizes or had significant limitations.[8–12,21,22] The majority of literature on the topic was published in the 1970s and 1980s, before genetic testing for SMA became available. This raises the possibility that some patients included in those studies did not have hereditary proximal SMA.[8,9,23–31] Furthermore, most of the more recent work focused on orthopedic management, surgical techniques, and postoperative outcomes rather than scoliosis development, prevalence, or surgery probability.[32–35] A cross-sectional analysis of >5,000 patients with SMA derived from a large number of national SMA databases that used the Translational Research in Europe: Assessment and Treatment of Neuromuscular Disorders format[36] reported that 9% of patients had received scoliosis surgery, a number that is much lower than the 34% demonstrated in our cohort. We think that these differences are most likely explained by large differences in median ages between the studies; that is, except for SMA type 1, the median age in our cohort of patients with SMA types 2a through 4 was >17 years (table 2), much higher than in most other studies. Because spinal growth is nearly complete at this age and thus later scoliosis development is highly unlikely,[37] we believe that our data represent a more reliable estimation of scoliosis prevalence and, especially, lifetime risk of scoliosis surgery.

The median age at surgery was 9.9 years in our cross-sectional population-based study and 7.9 years in the subgroup of patients who received surgery at our center between 1991 and 2015. Ages at surgery have previously been reported predominantly in small case series and are

Table 3 Characteristics of SMA patients who underwent scoliosis surgery at our center (1991–2015)

Patient characteristics (n = 36)	
SMA types, n	
Type 1c	4
Type 2a	23
Type 2b	8
Type 3a	1
M:F	13:23
***SMN2* copies, n**	
2	1
3	31
4	3
NA	1
Age at surgery, y	7.9 (3.9–15.5)
Type 1c	6.2 (5.1–15.5)
Type 2a	7.4 (3.9–14.2)
Type 2b	9.8 (7.6–14.9)
Type 3a	14.3
Scoliosis characteristics (n = 25)[a]	
C-shaped, n (%)	15 (60)
Left convex	8
Right convex	7
S-shaped, n (%)	10 (40)
Left convex	6
Right convex	4
Scoliosis level, n (%)	
Lumbar	9 (36)
Thoracolumbar	16 (64)
Preoperative Cobb angle, °	50 (29–104)
Postoperative Cobb angle, °	24 (8–60)
Absolute correction, °	28 (6–66)
Relative correction, %	50 (21–88)
Reasons for scoliosis surgery (n = 36), n (%)[b]	
Rapid progressive scoliosis	24 (67)
Deterioration of pulmonary function	7 (19)
Pain or discomfort	6 (17)
Instability when seated	3 (8)
Reduced supine bending	2 (6)
Parental request	1 (3)
Scoliosis with severe kyphosis	1 (3)
Stabilizing current situation	1 (3)
Not reported	3 (8)

Abbreviations: NA = not available; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2
Data are presented as median (range) when appropriate.
[a] Scoliosis characteristics are based on radiographs of the spine, which were available for 25 of 36 patients. In 11 cases, radiographs were incomplete or of insufficient quality.
[b] As indicated by the orthopedic surgeon. For some patients, >1 reason was noted.

largely comparable to our data.[8,21,22,33,34] Age at scoliosis surgery correlated significantly with SMA type: patients with milder SMA phenotypes received surgery later compared to those with more severe phenotypes (figure 1). In the full cohort (n = 283), patients with SMA type 1c had a slightly higher age at surgery than patients with type 2 SMA. This may be explained by a paradoxical delay of surgery due to SMA severity, e.g., caused by doubts about life expectancy or pulmonary status. In addition, the number of patients with SMA type 1c in our cohort who received surgery was small (n = 9, table 2).

Acquisition and loss of motor milestones were also associated with the need for and timing of surgery. Patients with milder SMA type 2 (those who learned to stand in addition to sit, i.e., type 2b) were significantly older when they received surgery compared to those with SMA type 2a. Patients with SMA who also learned to walk (i.e., type 3a) had a significant higher age at surgery than those with type 2b. Furthermore, early loss of ambulation in SMA type 3a was associated with a much higher lifetime probability of scoliosis surgery (71%), almost comparable to that for type 2b (83%). In contrast, those with SMA type 3a who lost ambulation after the age of 10 years had a dramatically lower lifetime probability of receiving scoliosis surgery (22%). Thus, long-term preservation of the ability to walk may significantly lower the lifetime probability of scoliosis surgery. Our data reaffirm that the use of developmental stages defined by several motor milestones, including rolling and standing, which are not part of the SMA classification system, is of additional predictive value.[2,3,14]

Estimates of scoliosis progression in SMA vary widely. The available follow-up data from 15 patients (predominantly SMA type 2a) in our cohort suggest an average progression of 7.2°/y with a marked acceleration in the 18 months before surgery, up to ≈10°/y (figure 3). A number of previous studies report comparable figures of 8°/y, but higher progression rates up to 20°/y also have been reported, with faster

progression in SMA type 2a compared to type 2b.[8,9,21,22,38] Accelerated scoliosis progression in SMA type 2 has been reported previously, occurring at ≈10 years of age.[9] This roughly correlates with our findings, although we observed the increase at a much younger age (figure 3). Furthermore, the specific acceleration of scoliosis progression at ≈10 years of age was not shown in a large cohort with data of 61 untreated patients with SMA type 2.[21]

Taking the high variability of reported data into account, we estimate that scoliosis progression in SMA type 2 is ≈5°/y to 12°/y, most likely following a biphasic pattern of initial slower annual progression, followed by a period of increased scoliosis progression in the 1.5 to 2 years preceding surgery. The available data suggest slower scoliosis progression in SMA type 2b compared to type 2a.

Scoliosis progression data for SMA type 3 are less clear. The reported range in small cohort studies is between 2.9°/y and 15°/y, but data on remaining motor function in these patients were not presented.[8,9,21] Scoliosis progression in SMA type 3 is likely to be slower compared to type 2, although our data indicate that early loss of ambulation in SMA type 3 predicts faster scoliosis progression because this causes a dramatic increase in the lifetime probability of scoliosis surgery.

We studied level and curve shape of scoliosis in a subgroup of patients who received surgery at our center. Previous studies have indicated that a thoracolumbar C-shaped scoliosis is characteristic of SMA and other neuromuscular disorders.[10,11,22,39,40] Although this was true for the majority of our patients, a significant number had a lumbar or S-shaped scoliosis (table 3). The observed differences with previous studies may be attributable to the relatively small size of our cohort or inclusion or other bias. However, it seems safe to assume that levels and shape may differ between patients.

Different surgical techniques have been used for the correction of scoliosis in SMA. Segmental spinal instrumentation using the Luque[20] method was the most used technique in our cohort of patients until approximately 2008. Thereafter, it was largely replaced by surgical techniques that allow for continued spinal growth, in accordance with current guidelines.[13] The introduction of these growth-friendly techniques also allows earlier surgical interventions, leading to a decline in age at surgery and earlier increased support in patients with severe scoliosis.[41,42] In our cohort, however, the introduction of these techniques did not lead to lower median ages at surgery, possibly attributable to the relatively small size of our cohort.

We acknowledge several limitations of our work. The cross-sectional design is an important limitation of this study because it underestimates the true prevalence of scoliosis in SMA since some patients are still young and will develop a scoliosis later. Longitudinal follow-up of patients would obviously be superior, but such an approach would require an effort over long periods of time, which no longer seems feasible since the introduction of SMN-augmenting therapies. In addition, the lack of power for some of our observations is an important limitation. For example, estimates of natural scoliosis progression were based on a relatively limited number of available radiographs. This also limits the possibility of assessing differences between boys and girls with respect to their patterns of scoliosis progression.

Despite these limitations to some aspects of our work, the focus and size of this study are relative strengths; most of the conclusions are based on a large population-based cohort of genetically and clinically well-defined patients with SMA.

Although standardized and longitudinal follow-up studies of scoliosis in patients with SMA will remain necessary, our data may be helpful as a reference for assessing long-term effects of therapy.

Acknowledgment

The authors are grateful to the patients with SMA who participated in this study and for the support of the Dutch patient organization for neuromuscular diseases (Spierziekten Nederland).

Study funding

This study was supported by grants from the Prinses Beatrix Spierfonds (WAR13-07 and WAR14-26) and Stichting Spieren voor Spieren.

Disclosure

C. Wijngaarde, R. Brink, F. de Kort, M. Stam, L. Otto, F. Asselman, B. Bartels, R. van Eijk, J. Sombroek, I. Cuppen, and M. Verhoef report no disclosures relevant to the manuscript. L. van den Berg reports grants from Netherlands ALS Foundation, Prinses Beatrix Spierfonds, Netherlands Organization for Health Research and Development (Vici scheme), and the European Community's Health Seventh Framework Program (FP7/2007-2013, grant agreement 259867), as well as personal fees from Baxter and Biogen (scientific advisory boards). R. Wadman and R. Castelein report no disclosures relevant to the manuscript. W-Ludo van der Pol receives research support from the Prinses Beatrix Spierfonds, Stichting Spieren voor Spieren, and Netherlands ALS foundation. His employer receives fees for consultancy services to Biogen, Avexis (scientific advisory board), and Novartis (data monitoring committee). Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* August 1, 2018. Accepted in final form February 20, 2019.

Appendix Authors

Name	Location	Role	Contribution
C.A. Wijngaarde, MD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Design and conceptualization of the study; acquisition of data; data analysis and interpretation; statistical analysis; drafting and revising the manuscript for intellectual content.
R.C. Brink, MD	Department of Orthopedic Surgery, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; drafting and revising the manuscript for intellectual content.
F.A.S. de Kort, MD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; revising the manuscript for intellectual content.
M. Stam, MD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; revising the manuscript for intellectual content.
L.A.M. Otto, MD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; revising the manuscript for intellectual content.
F. Asselman, BSc	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; revising the manuscript for intellectual content.
B. Bartels, MSc, PPT	Department of Pediatrics, Child Development and Exercise Center University Medical Centre Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; revising the manuscript for intellectual content.
R.P.A. van Eijk, MD	Department of Neurology and Biostatistics & Research Support, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, the Netherlands	Author	Data analysis and interpretation; statistical analysis; revising the manuscript for intellectual content.
J. Sombroek, MD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; revising the manuscript for intellectual content.
I. Cuppen, MD, PhD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Data interpretation; revising the manuscript for intellectual content.
M. Verhoef, MD, PhD	Department of Rehabilitation, Physical Therapy Science, and Sports, University Medical Center Utrecht, the Netherlands	Author	Data interpretation; revising the manuscript for intellectual content.
L.H. van den Berg, MD, PhD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Design of the study; data interpretation; revising the manuscript for intellectual content.
R.I. Wadman, MD, PhD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Acquisition of data; data interpretation; revising the manuscript for intellectual content.
R.M. Castelein, MD, PhD	Department of Orthopedic Surgery, University Medical Center Utrecht, the Netherlands	Author	Data interpretation; revising the manuscript for intellectual content.
W-L. van der Pol, MD, PhD	Department of Neurology, University Medical Center Utrecht, the Netherlands	Author	Design and conceptualization of the study; acquisition of data; data analysis and interpretation; drafting and revising the manuscript for intellectual content.

References

1. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120–2133.
2. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol 2012;11:443–452.
3. Wadman RI, Wijngaarde CA, Stam M, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol 2018;25:512–518.
4. Bertini E, Dessaud E, Mercuri E, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:513–522.
5. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017;377:1713–1722.
6. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–1732.
7. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–635.
8. Rodillo E, Marini ML, Heckmatt JZ, Dubowitz V. Scoliosis in spinal muscular atrophy: review of 63 cases. J Child Neurol 1989;4:118–123.
9. Granata C, Merlini L, Magni E, Marini ML, Stagni SB. Spinal muscular atrophy: natural history and orthopaedic treatment of scoliosis. Spine 1989;14:760–762.
10. Mullender M, Blom N, De Kleuver M, et al. A Dutch guideline for the treatment of scoliosis in neuromuscular disorders. Scoliosis Engl 2008;3:14.
11. Mesfin A, Sponseller PD, Leet AI. Spinal muscular atrophy: manifestations and management. J Am Acad Orthop Surg 2012;20:393–401.
12. Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. Appl Clin Genet 2013;6:113–120.
13. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018;28:103–115.
14. Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0–4. J Neurol Neurosurg Psychiatry 2017;88:365–367.
15. Cobb JR. Outline for the study of scoliosis, instructional course lectures. Am Acad Orthop Surg 1948;5:261–275.
16. DeSmet AA, Goin JE, Asher MA, Scheuch HG. A clinical study of the differences between the scoliotic angles measured on posteroanterior and anteroposterior radiographs. J Bone Joint Surg Am 1982;64:489–493.
17. Shea KG, Stevens PM, Nelson M, Smith JT, Masters KS, Yandow S. A comparison of manual versus computer-assisted radiographic measurement. Intraobserver measurement variability for Cobb angles. Spine 1998;23:551–555.
18. Zebala LP, Bridwell KH, Baldus C, et al. Minimum 5-year radiographic results of long scoliosis fusion in juvenile spinal muscular atrophy patients: major curve progression after instrumented fusion. J Pediatr Orthop 2011;31:480–488.
19. R. Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria. R Foundation for Statistical Computing; 2017. Available at: r-project.org/.
20. Luque ER. Segmental spinal instrumentation for correction of scoliosis. Clin Orthop Relat Res 1982:192–198.

21. Fujak A, Raab W, Schuh A, Kreß A, Forst R, Forst J. Operative treatment of scoliosis in proximal spinal muscular atrophy: results of 41 patients. Arch Orthop Trauma Surg 2012;132:1697–1706.
22. Fujak A, Raab W, Schuh A, Richter S, Forst R, Forst J. Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. BMC Musculoskelet Disord Engl 2013;14:283.
23. Schwentker EP, Gibson DA. The orthopaedic aspects of spinal muscular atrophy. J Bone Joint Surg Am 1976;58:32–38.
24. Benady SG. Spinal muscular atrophy in childhood: review of 50 cases. Dev Med Child Neurol 1978;20:746–757.
25. Evans GA, Drennan JC, Russman BS. Functional classification and orthopaedic management of spinal muscular atrophy. J Bone Joint Surg Br 1981;63B:516–522.
26. Riddick MF, Winter RB, Lutter LD. Spinal deformities in patients with spinal muscle atrophy: a review of 36 patients. Spine 1982;7:476–483.
27. Aprin H, Bowen JR, MacEwen GD, Hall JE. Spine fusion in patients with spinal muscular atrophy. J Bone Joint Surg Am 1982;64:1179–1187.
28. Shapiro F, Bresnan MJ. Orthopaedic management of childhood neuromuscular disease: part I: spinal muscular atrophy. J Bone Joint Surg Am 1982;64:785–789.
29. Daher YH, Lonstein JE, Winter RB, Bradford DS. Spinal surgery in spinal muscular atrophy. J Pediatr Orthop 1985;5:391–395.
30. Merlini L, Granata C, Bonfiglioli S, Marini ML, Cervellati S, Savini R. Scoliosis in spinal muscular atrophy: natural history and management. Dev Med Child Neurol 1989;31:501–508.
31. Phillips DP, Roye DPJ, Farcy JP, Leet A, Shelton YA. Surgical treatment of scoliosis in a spinal muscular atrophy population. Spine 1990;15:942–945.
32. Chua K, Tan CY, Chen Z, et al. Long-term follow-up of pulmonary function and scoliosis in patients with Duchenne's muscular dystrophy and spinal muscular atrophy. J Pediatr Orthop 2016;36:63–69.
33. Holt JB, Dolan LA, Weinstein SL. Outcomes of primary posterior spinal fusion for scoliosis in spinal muscular atrophy: clinical, radiographic, and pulmonary outcomes and complications. J Pediatr Orthop 2017;37:e505–e511.
34. Chou SH, Lin GT, Shen PC, et al. The effect of scoliosis surgery on pulmonary function in spinal muscular atrophy type II patients. Eur Spine J 2017;26:1721–1731.
35. Colombo L, Martini C, Bersanini C, et al. Effects of magnetically controlled growing rods surgery on pulmonary function in young subjects with spinal muscular atrophy type 2 and other neuromuscular scoliosis. J Neurosurg Sci Epub 2017 May 31.
36. Bladen CL, Thompson R, Jackson JM, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol 2014;261:152–163.
37. DiMeglio A, Dimeglio A, Canavese F, Charles YP, Charles P. Growth and adolescent idiopathic scoliosis: when and how much? J Pediatr Orthop 2011;31:S28–S36.
38. Catteruccia M, Vuillerot C, Vaugier I, et al. Orthopedic management of scoliosis by Garches brace and spinal fusion in SMA type 2 children. J Neuromuscul Dis 2015;2:453–462.
39. Kouwenhoven JW, Ommeren PM, Pruijs HE, Castelein RM. Spinal decompensation in neuromuscular disease. Spine 2006;31:E188–E191.
40. Abul-Kasim K, Ohlin A. Curve length, curve form, and location of lower-end vertebra as a means of identifying the type of scoliosis. J Orthop Surg (Hong Kong) 2010;18:1–5.
41. Chandran S, McCarthy J, Noonan K, Mann D, Nemeth B, Guiliani T. Early treatment of scoliosis with growing rods in children with severe spinal muscular atrophy: a preliminary report. J Pediatr Orthop 2011;31:450–454.
42. Dede O, Demirkiran G, Yazici M. 2014 Update on the "growing spine surgery" for young children with scoliosis. Curr Opin Pediatr 2014;26:57–63.

Natural course of scoliosis and lifetime risk of scoliosis surgery in spinal muscular atrophy

Camiel A. Wijngaarde, Rob C. Brink, Floor A.S. de Kort, et al.

Neurology 2019;93;e149-e158 Published Online before print June 4, 2019
DOI 10.1212/WNL.0000000000007742