Scoliosis Development in Spinal Muscular Atrophy: The Influences of Genetic Severity, Functional Level, and Disease-Modifying Treatments

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Background: Spinal muscular atrophy (SMA) is caused by abnormalities of the survival motor neuron (SMN) 1 gene, leading to deficiency in SMN protein and loss of spinal cord alpha motor neurons. Newer disease-modifying agents (DMA) targeting the involved genes, including nusinersen and gene replacement therapies, have improved gross motor and respiratory function, but their impact on scoliosis development has not been established. This study aimed to determine risk factors for scoliosis development in SMA, specifically genetic severity and DMA use.

Methods: In this retrospective cohort study, children with SMA and minimum 2-year follow-up were included. The primary outcome was the prevalence of clinically relevant scoliosis. Secondary outcomes included SMA type, SMN2 copy number, Hammersmith Functional Motor Scale (HFMS), ambulatory status [functional mobility scale at 50m (FMS_{50})], DMA use, and hip displacement as risk factors. Univariate/multivariate logistic regression analyses were performed to identify dependent/independent risk factors.

Results: One hundred sixty-five patients (51% female) with SMA types I-III met the inclusion criteria, with total follow-up of 9.8 years. The prevalence of scoliosis was 79%; age of onset 7.9 years. The **major** curve angle for the entire cohort at first assessment and final follow-up was 37 degrees (SD: 27 degrees) and 62 degrees (SD: 31 degrees) ($P < 0.0001$), respectively. Significant risk factors for scoliosis by univariate analysis were SMA type (I/II, $P = 0.02$), HFMS (> 23, $P < 0.001$), nonambulatory status ($FMS_{50} = 1$, $P < 0.0001$), DMA treatment ($P = 0.02$), and hip displacement ($P < 0.0001$). Multivariate analysis revealed that HFMS > 23 ($P = 0.02$) and DMA ($P = 0.05$) treatment were independent (protective) risk factors.

Conclusions: The development of scoliosis in SMA is high, with risk factors associated with proxy measures of disease severity, including SMA type, nonambulatory status, hip displacement, and most notably, gross motor function (by HFMS). DMA use and HFMS > 23 were associated with a decreased risk of scoliosis development. Identified risk factors can be used in the development of surveillance programs for early detection of scoliosis in SMA.

Level of Evidence: Level III.

Key Words: spinal muscular atrophy, scoliosis, SMN2 copy, nusinersen, disease-modifying agents, Hammersmith functional motor scale, radiographic surveillance

(*J Pediatr Orthop* 2024;00:000–000)

Spinal muscular atrophy (SMA), an autosomal recessive condition affecting approximately 1 in 10,000, is associated with a loss of spinal cord alpha motor neurons. The survival motor neuron (SMN) 1 gene is affected, decreasing the production of SMN protein responsible for the clinical phenotype.[1,2] The SMN2 gene produces SMN protein at a lesser extent than SMN1 (5% to 10%).[3] The number of SMN2 copies has been correlated with function, secondary to additional SMN protein production.[4,5]

The associated lower motor neuron syndrome includes hypotonia, fasciculations, hyporeflexia, muscle atrophy, and muscle weakness (including decreased pulmonary function).[6] SMA is classified into 3 main types in childhood: type I has onset < 6 months and cannot sit independently, type II has onset at 6 to 18 months and can sit independently but cannot walk, and type III has onset after 18 months and can walk.[7]

The development of scoliosis is relatively common, likely secondary to truncal muscle weakness. Often accompanied by pelvic obliquity, scoliosis in SMA can negatively impact sitting balance and quality of life, though its relationship to pulmonary function is controversial.[8] As such, progressive curves > 40 to 50 degrees are typically treated surgically, with growth friendly procedures (ie, growing rods) for younger children and definitive posterior

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No funding was received for this work.

The authors declare no conflicts of interest.

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DOI: 10.1097/BPO.0000000000002759

spinal fusion and segmental spinal instrumentation for older children (Fig. 1). Other orthopaedic manifestations include muscle contractures, fractures, and hip instability (ie, displacement).[9]

Disease-modifying agent (DMA) treatments,[10] most commonly targeting SMN2 gene splicing (nusinersen and risdiplam) or SMN1 gene replacement (onasemnogene abeparvovec), have improved function and longevity for all SMA types, but their effects on the prevention of scoliosis are unknown. This study aimed to determine the prevalence and risk factors for scoliosis development in SMA. We hypothesized that reduced SMN2 copy number and increased functional impairment would increase the risk of scoliosis, whereas DMA treatment would be protective.

METHODS

This retrospective cohort study was conducted at an academic tertiary-level children's hospital and was approved by our institutional review board. Children presenting between June 2005 and January 2024 with diagnostic codes specific to SMA [*International Classification of Diseases, Ninth Revision* (335.1) and *International Classification of Diseases, Tenth Revision* (G12.9)] were identified from our institution's electronic medical record. Inclusion criteria were a genetically confirmed diagnosis of SMA, at least 1 confirmatory anteroposterior scoliosis radiograph for cases with scoliosis and 2-year minimum follow-up. Exclusion criteria were no genetic confirmation of SMA diagnosis and incomplete scoliosis data from the medical record.

The primary outcome variable was the prevalence of clinically relevant scoliosis, defined as a major curve angle ≥ 40 degrees from erect scoliosis radiographs and/or having undergone scoliosis surgery. We chose a major curve angle ≥ 40 degrees based on the value commonly utilized as an indication for potential operative intervention in SMA.[10]

Secondary outcome variables, considered as potential risk factors for scoliosis development, included SMA type (I, II, or III), SMN2 copy number (< 3, more severe; ≥ 3, less severe),[11] presence of hip displacement (migration percentage $> 40\%$),[10] ambulatory status at final follow-up [defined by the functional mobility scale[12] grading at 50m (FMS_{50}) as 1 for nonwalkers and > 1 for walkers], utilization of DMA for at least 1 year (including nusinersen, risdiplam, or onasemnogene abeparvovec), and Hammersmith functional motor scale (HFMS).[13] The HFMS has 33 items (2 points total per item; maximum score = 66)

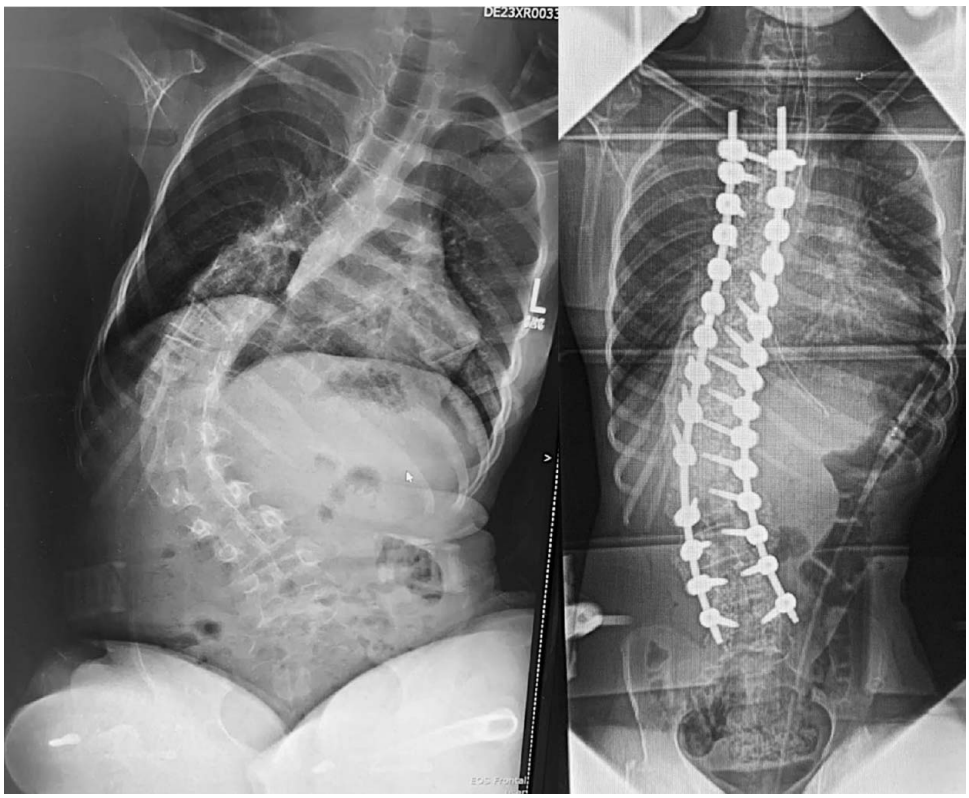

FIGURE 1. Radiographs of a 12-year-old girl with type II spinal muscular atrophy and a progressive thoracolumbar scoliosis. This patient was treated with intrathecal nusinersen preoperatively for 6 years and has maintained some walking ability using Lofstrand crutches. Left image: preoperative anteroposterior erect scoliosis radiograph with major curve angle, 84 degrees. Right image postoperative anteroposterior erect scoliosis radiograph following posterior instrumentation and fusion from T3 to L5, major curve angle corrected to 36 degrees. The pelvis was not instrumented to allow for pelvic motion when walking.

and has been shown to be valid and reliable for measuring gross motor function in SMA. Other secondary outcome variables included age at first scoliosis surveillance radiograph, duration of radiographic scoliosis surveillance, number of scoliosis surveillance radiographs, age at onset of scoliosis, and curve magnitude.

Statistical Analysis

Descriptive statistics using Mann-Whitney *U* and Kruskal-Wallis tests were performed to analyze secondary outcomes. Frequencies and chi-square testing for comparisons between scoliosis versus no scoliosis groups were tabulated. To determine risk factors for scoliosis development, the analysis included proportions of both categorical and continuous variables, applying univariate and multivariate-backward tests, with a significance level *P* of 0.05. A receiver operating characteristic analysis was performed to determine the HFMS cutoff that predicted scoliosis development, but the area under the curve (AUC) was not robust (AUC = 0.16). In our prior analysis of risk factors for hip displacement in SMA, an HFMS score cutoff of 23 was determined to be robust (AUC = 0.78),[10] relating major orthopaedic manifestations to functional severity. As such, we chose HFMS > 23 as a risk factor in the current analysis.

RESULTS

One hundred sixty-five patients [SMA type: I, n = 51 (31%); II, n = 72 (44%); III, n = 42 (25%); 51% female] met the inclusion criteria. A patient flow diagram is provided (Fig. 2). The follow-up duration was 9.8 years (SD: 4.6 y).

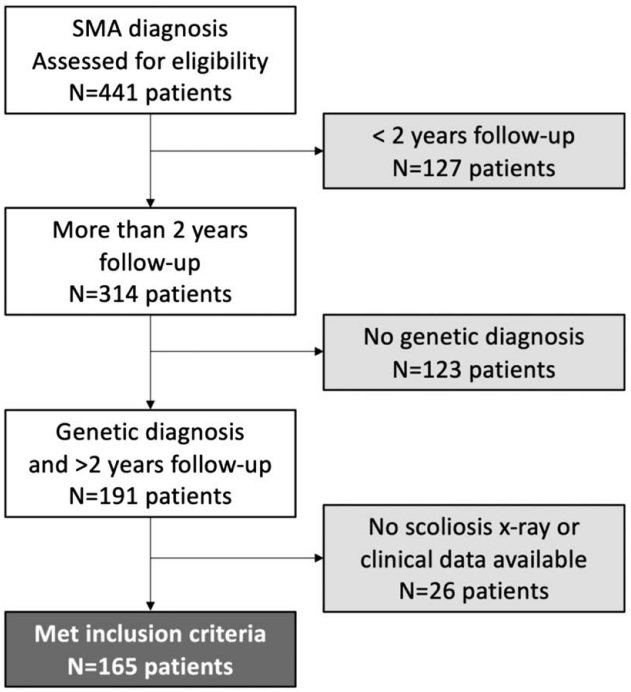

FIGURE 2. Patient flow diagram depicting reasons for inclusion/exclusion in the study. SMA indicates spinal muscular atrophy.

The age at first scoliosis radiograph was 6.5 years (SD: 3.8 y), with a mean of 2.7 (SD: 1.7) scoliosis surveillance radiographs over the study duration. The mean age at genetic diagnosis was 2.0 years (SD: 2.4 y).

Ambulatory status information was available for 162 (98%) patients. FMS_{50} grading for the entire cohort was 1: 121 (75%), 2: 14 (9%), 3: 4 (2%), 4: 15 (9%), 5: 4 (2%), 6: 2 (1%), and 2 (1%) unable to classify. Stratified by ambulatory status, 121 (75%) were nonambulatory ($FMS_{50} = 1$), and 41 (25%) were ambulatory ($FMS_{50} > 1$).

HFMS scores were available for 56 (34%) patients. The mean HFMS score for the total cohort was 20.7 (SD: 17.1) at first assessment and 19.5 (SD: 17.4) at final follow-up ($P = 0.45$). By SMA type, HFMS scores at first assessment/final follow-up for types I, II, and III were 10.8 (SD: 9.7)/11.0 (SD: 10.4), ($P = 0.80$); 15.6 (SD: 13.0)/12.8 (SD: 12.2), ($P = 0.13$); and 34.8 (SD: 7.9)/34.8 (SD: 18.1), ($P = 0.89$), respectively.

Genetic severity by SMN2 copy number was more severe (< 3 copies) in 30 (37%) patients and less severe (≥ 3 copies) in 51 (63%) patients. For patients with < 3 versus ≥ 3 SMN2 copies, there were no significant differences in HFMS scores at first assessment [15.8 (SD: 17.8) vs. 23.0 (SD: 17.0), ($P = 0.13$)] nor at final follow-up [19.1 (SD: 18.8) vs. 20.2 (SD: 17.6), ($P = 0.84$)].

Regarding DMA, 84 (51%) of the total cohort [SMA type I: 25 (49%), II: 34 (47%), and III: 25 (59%)] underwent treatment of mean duration 4.7 years (SD: 1.9 y), with 44 (27%) receiving treatment before scoliosis development [SMA type I: 12 (24%), II: 17 (24%), III: 15 (36%)] for a mean duration 3.4 years (SD: 1.5 y). Nusinersen was utilized by 21 (48%), risdiplam by 16 (36%), and onasemnogene abeparvovec by 7 (16%). The mean age (y) at the start of DMA treatment for the entire cohort was 4.9 (SD: 4.6). Stratified by SMA type, the mean age (y) at the start of DMA treatment for types I, II, and III, was 1.1 (SD: 1.3), 4.6 (SD: 2.3), and 8.3 (SD: 5.7), respectively.

The prevalence of scoliosis for the entire cohort was 79%, with mean age of onset 7.9 years (SD: 3.5 y). When stratified by SMA type, the prevalence (%)/age of onset (y) were 90/6.9 (SD: 4.2), 88/8.2 (SD: 2.4), and 50/9.7 (SD: 3.8) for types I, II, and III, respectively.

The major curve angle for the entire cohort at first assessment and final follow-up was 37 degrees (SD: 27 degrees) and 62 degrees (SD: 31 degrees), ($P < 0.0001$), respectively. There were no significant differences in curve progression between SMA types from first assessment to final follow-up ($P = 0.16$). Stratified by DMA treatment, there were also no significant differences in curve progression between the non-DMA and DMA groups from first assessment to final follow-up [31 degrees (SD: 25 degrees) vs. 27 degrees (SD: 21 degrees), respectively ($P = 0.69$)]. The breakdown of major curve angle by SMA type, for the entire cohort and by DMA treatment, at first assessment and final follow-up, can be found in Table 1.

Frequencies of risk factors for patients with and without scoliosis are reported in Table 2. By chi-square analyses, all risk factors were found to be significant except SMN2 copy number. Significant risk factors for scoliosis

TABLE 1. Major curve angle by SMA type and DMA Treatment

	Major curve angle [mean (SD) degrees] First assessment/final follow-up, *P*		
	Type I	**Type II**	**Type III**
Overall	41 (23)/72 (25), < 0.0001*	44 (30)/62 (28), 0.004*	24 (22)/49 (37), 0.006*
Non-DMA treatment	44 (24)/77 (22), < 0.0001*	54 (29)/71 (27), 0.04*	21 (24)/52 (44), 0.03*
DMA treatment	32 (19)/59 (28), < 0.04*	17 (11)/45 (20), < 0.001*	26 (21)/46 (28), 0.08

*Statistical significance.
DMA indicates disease-modifying agent; SMA, spinal muscular atrophy.

development by univariate analysis were SMA type (I/II, $P = 0.02/0.02$), nonambulatory status ($FMS_{50} = 1$, $P < 0.0001$), and hip displacement ($P < 0.0001$), while HFMS (> 23, $P < 0.001$) and DMA treatment ($P = 0.02$) were protective. Multivariate analysis revealed that HFMS > 23 ($P = 0.02$) and DMA treatment ($P = 0.05$) were independent (protective) risk factors (Table 3).

Regarding pulmonary function, percent of forced vital capacity (%FVC) at first assessment and final follow-up for the entire cohort was 67% (SD: 25%) and 52% (SD: 28%), respectively ($P < 0.0001$). By SMA type, %FVC at first assessment/final follow-up was 57% (SD: 9%)/43% (SD: 20%) for type I ($P = 0.19$), 62% (SD: 26%)/49% (SD: 27%) for type II ($P = 0.03$), and 86% (SD: 13%)/74.1% (SD: 25%) for type III ($P = 0.52$), respectively. Stratified by DMA use prior to scoliosis development, %FVC for first assessment/final follow-up was 60% (SD: 22%)/44% (SD: 24%), ($P = 0.001$) and 87% (SD: 23%)/81% (SD: 17%), ($P = 0.29$) for the non-DMA and DMA groups, respectively.

DISCUSSION

The development of scoliosis in SMA is thought to be secondary to "deteriorating axial muscle strength" resulting in a lack of support for the spinal column that worsens in nonambulatory children.[14] Most previous studies investigating the prevalence of scoliosis in SMA were small case series preceding DMA treatment. Since the introduction of nusinersen in 2016, functional improvements have increased lifespan and decreased medical complications, although the impact of DMA treatment on scoliosis development remains unknown. The purpose of the current study was to determine the prevalence and risk factors associated with scoliosis development in SMA and to assess the role of DMA treatments.

The prevalence of scoliosis in the current study was linked to SMA type, with nonambulatory types I and II having similar rates (90% and 88%, respectively) and a substantially lower rate for ambulatory patients, classified as type III (51%). Because patients classified as type II are sitters with improved trunk strength, we expected the prevalence for type I to be higher than type II. In other neuromuscular conditions, such as cerebral palsy, the incidence of scoliosis (> 40 degrees) for Gross Motor Function Classification System level IV (with improved trunk strength and sitting capacity) was 19%, whereas level V (with poor trunk control and unsupported sitting capacity) had a higher risk at 62%.[15] Despite similar prevalence in the current study, the age at onset was earlier for type I (6.9 y) versus type II (8.2 y), conferring a relative functional advantage to type II with later scoliosis development.

In a prospective study of 283 Dutch patients with SMA, the overall scoliosis incidence was 60%, substantially less than the 79% prevalence of the current study.[16] Unlike the current study, they included patients identified from an all-surgical cohort, which may not reflect the true prevalence and timing of scoliosis development, potentially excluding those who did not have surgery due to surgeon discretion, disease severity, or geographic access.[14] The current study includes all genetically confirmed patients with SMA, regardless of surgical intervention.

In a pre-DMA natural history study by Granata et al,[17] the mean age of scoliosis onset was 4 years for SMA type II and 10 years for type III. Type I SMA has not been represented in pre-DMA treatment studies given the high disease burden and decreased lifespan that precluded orthopaedic management. For the current study, the age of onset of scoliosis development was considerably higher for type II, possibly due to the influence of DMA treatments that were associated with a decreased risk of scoliosis development overall.

DMA treatments have resulted in improved quality of life and longevity, improved motor milestones, decreased disease progression, and reduced use of healthcare resources.[18] Given the observed relationship to functional impairment, it would seem logical that DMA treatment would reduce scoliosis risk in SMA. Despite functional gains, nusinersen treatment did not prevent scoliosis in a Brazilian study of 41 patients with types II and III SMA at 2-year follow-up.[19] Conversely, we found that DMA treatment was associated with reduced scoliosis development as an independent risk factor. This difference may be due to our much larger sample size (165 patients) and longer follow-up (∽10 y) in the current study.

TABLE 2. Frequencies of Risk Factors for Scoliosis Development

Risk factor	Scoliosis not present [n (%)]	Scoliosis present [n (%)]	*P*
SMA type I	5 (19)	46 (69)	< 0.0001*
SMA type II	9 (30)	63 (75)	< 0.0001*
SMA type III	21 (60)	21 (16)	< 0.0001*
< 3 SMN2 copies	7 (29)	23 (40)	0.48
HFMS > 23	10 (71)	7 (17)	< 0.001*
Nonambulatory ($FMS_{50} = 1$)	18 (51)	107 (84)	< 0.001*
Hip displacement	6 (22)	63 (59)	0.001*
DMA treatment	15 (43)	29 (22)	0.03*

*Statistical significance by chi-square testing.
DMA indicates disease-modifying agent; FMS_{50}, functional mobility scale at 50m; HFMS, Hammersmith functional motor scale; MP, migration percentage; SMA, spinal muscular atrophy; SMN, survival motor neuron.

TABLE 3. Determination of Risk Factors for Scoliosis Development

	Univariate analysis		Multivariate analysis*	
	EXP (B) OR	Sig. *P*	EXP (B) OR	Sig. *P*
SMA type I	3.3	0.02†	851.9	1.0
SMA type II	2.7	0.02†	0.29	0.42
< 3 SMN2 copies	1.6	0.34	-	-
HFMS > 23	0.08	< 0.001†	0.03	0.02†
Nonambulatory ($FMS_{50} = 1$)	5.0	< 0.0001†	-	-
Hip displacement	6.5	0.001†	0.51	0.62
DMA treatment	0.38	0.02†	0.08	0.05†

*Backward multivariate regression analysis. SMA type III is the reference for SMA types I and II risk factors.

†Statistical significance.

DMA indicates disease-modifying agent; FMS_{50}, functional mobility scale at 50m; HFMS, Hammersmith functional motor scale; MP, migration percentage; OR, odds ratio; SMA, spinal muscular atrophy; SMN, survival motor neuron.

The reduction of scoliosis development by DMA use found in the current study contrasts a study that found an increased risk of hip displacement in SMA for those under DMA treatment.[10] Although both documented functional impairment by SMA type, increased periarticular muscle forces were thought to increase the risk for hip displacement, whereas improved trunk strength may be protective for scoliosis development.

Unlike SMA type, a static and ordinal functional classification, HFMS is a continuous and validated functional measure, responsive to improvements via DMA treatment or deterioration through disease progression.[20] Accordingly, for the current study, an HFMS score > 23 was an independent protective factor against scoliosis development in SMA. Using data from a randomized controlled trial of nusinersen treatment for types II and III SMA (CHERISH and its extension study, SHINE),[21] scoliosis development reportedly has an inverse relationship to HFMS score. Thus, as for other neuromotor disorders (eg, cerebral palsy), the degree of functional impairment in SMA is the primary determinant of orthopaedic manifestations.[15]

Despite prior studies suggesting its use as a predictor of functional impairment, the number of SMN2 copies was not a risk factor for scoliosis development in the current study. There were no significant differences identified between HFMS scores for < 2 versus ≥ 3 SMN2 copies at first assessment or final follow-up. Similar findings were identified for the development of hip displacement in SMA.[10] This lack of correlation may be related to genetic heterogeneity induced by epigenetic modifiers.[22]

A link between declining pulmonary function and scoliosis has been widely proposed, though evidence in the literature varies. For those with scoliosis development, the current study reports a decline in pulmonary function for all SMA types, yet DMA treatment was shown to be protective against %FVC deterioration. This contrasts with scoliosis surgery outcomes, where improvements in pulmonary function postoperatively are not assured. In a recent systematic review investigating the impact of scoliosis surgery on pulmonary function in SMA, most studies reported a decline in pulmonary function, with some suggesting early postoperative stabilization of % FVC followed by an eventual decline.[8]

Although this is the largest study investigating the prevalence and risk factors for scoliosis development in SMA to date, the relatively small sample size and non-population-based methodology are the main limitations. In addition, due to the span of years for patient inclusion, many patients were assessed before the current era of DMA treatments, limiting the power of our statistical analysis. Study strengths include its long follow-up of almost 10 years and assessments by validated functional outcomes, including the HFMS and the FMS.

In conclusion, the prevalence of scoliosis development in SMA is high, with risk factors related to functional impairment, most notably for types I and II. DMA treatments had a protective effect, decreasing the risk of scoliosis, and deterioration in pulmonary function in SMA. Prospective studies are needed to determine the most appropriate timing of radiographic surveillance, with validated quality-of-life measures to assess the impact of scoliosis on patients with SMA.

ACKNOWLEDGMENTS

The authors would like to thank Dr Kenneth Rogers for help with statistical support.

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