Author's response to reviews

Title: Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa. Descriptive clinical study with retrospective data collection of 126 patients

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Author's response to reviews: see over
Dear Mr. Aldea,

Thank you for the review and your editorial comments. Please find enclosed our corrected manuscript.

We have no “Acknowledgements”. The authors examined the patients, collected, prepared and interpreted the data and prepared the manuscript. We had no special funding.

A native English speaker with scientific expertise checked the paper without significant revision of the manuscript.

We have corrected all points raised by the referees and marked the revisions in the text yellow:

Reviewer 1

1. In this manuscript, the data are presented in both tabular and graphical formats. As I see it, this presentation is redundant. Table 2 = Figures 1 and 2; Table 3 = Figure 3. Please present these data as either tables or graphs.

   We prefer to present these data as tables because the tables contain more information (n, Ø, ±, min – max, median).
   We removed the figures.

2. If the authors elect to present these data as graphs, then please use bar graphs instead of line graphs as line graphs imply repeated measures of the same set of patients (which I do not believe is the case here). Also, please be sure to include error bars (standard error).

   We removed the figures / graphs.

3. There is no mention of statistical analysis in the methods sections. Please describe how you completed your statistical analysis.

   We have no special statistical analysis in our study.

4. In the methods, it is mentioned that the diagnosis of SMA was "confirmed either genetically or by muscle biopsy and neurophysiology." Why were all of the subjects' diagnoses not confirmed genetically given that 1) there is a reliable genetic test for proximal SMA

   This is a study with retrospective data collection. We collected our data from 1999 to 2010. The diagnosis in the older patients was confirmed by muscle biopsy and neurophysiology because genetic diagnostics in SMA developed gradually.
SMN1 and SMN2) and 2) there are multiple types of SMAs with different genetic causes (i.e. SMN1 for 5q proximal SMA, DYNC1H1 for SMA-LED, AR and UBE1 for X-linked SMAs). after 1995. 

**We completed:** The diagnosis in the older patients was confirmed by muscle biopsy and neurophysiology because genetic diagnostics in SMA developed gradually after 1995.

5. In those patients whose diagnoses were confirmed genetically, was there a correlation between SMN2 copy number and the severity of scoliosis/pelvic obliquity/relative vital capacity?

The correlation between SMN2 copy number and the severity of scoliosis, pelvic obliquity and relative vital capacity was not evaluated in this study. An analysis was not possible. The SMN2 copy number was known only in a few patients. It is not examined routinely.

6. Are there relationships between sex and a) the type of scoliosis observed, b) maximum curvature, c) pelvic tilt and d) relative vital capacity?

The relationships between sex and the type of scoliosis, maximum curvature, pelvic tilt and relative vital capacity were not evaluated in this study. The number of patients in the age groups is too small for such analysis, especially in the SMA IIIa group.

7. In the figure and table legends, the authors describe their measures in patients “not operated on”. The wording is difficult to read. Please reword.

We changed: “non-surgery patients”

**Reviewer 2**

Please use the classification system put forward by the ENMC: type I, II and III. Your classification is not in agreement with that used by SMA researchers. 

The classification system in our study is very similar and compatible with the ENMC system. The classification we use is shown in table 1. The definitions of type I, II and III are the same as the ENMC system. Additionally we use the subdivision of types I and III in our study. The subdivision of types I and III is very important for children’s orthopaedics in our opinion. The course of the disease, treatment strategies and the use of orthopaedic and assistive devices are different in types Ia and Ib, and in types IIIa and IIIb. There are only patients with type II and IIIa in our study. If we were to use the ENMC system there would be patients with type II and III. We think it should be no problem to compare the results for authors who use the ENMC system without subdivisions of type III. And for authors who use the subdivisions it is important to find it also in our study. If possible we would like to stay with our classification.

The study population is not well described. The authors should state how many SMA patients in the same age group (?1-20 years) did NOT have scoliosis and how many had surgery and so were not included in this study. 

We have not evaluated how many SMA patients did not have scoliosis. It was not possible in our study. We examined SMA patients during special orthopaedic consultations where the patients visited us because of orthopaedic problems like contractures and scoliosis. In our study we evaluated only patients with evident scoliosis without surgery. 41 patients, 37 with SMA type II and 4 with type IIIa, were excluded because they had already had spinal surgery.

**We completed:** 41 patients, 37 with SMA type II and 4 with type IIIa, were excluded because they had already had spinal surgery.
The authors need to remember that they are presenting CROSS SECTIONAL data, not longitudinal data. Therefore, they cannot conclude that every SMA patient in these categories would experience "progression" as they describe it.

We completed: This study presents cross sectional data, so that it cannot be concluded that every SMA patient with SMA type II or IIIa would experience exactly the same course as described. Significant individual differences are observed.

In terms of writing style, on page 6, 3rd paragraph from top, are you talking about all patients from 0-4 yrs or only 4 year olds? You must be more precise about age groups.

We changed: We regularly observed scoliosis and pelvic obliquity in the group with SMA II, even in children in the age group 0 to 4 years old.

Reviewer 3

1) It is important to know over what period of time these data were examined, and what methods they used to ensure that all patients evaluated during that time period were included.

We completed: The data were collected during special nationwide orthopaedic consultations for patients with neuromuscular disorders from 1999 to 2010. All SMA patients with evident scoliosis without surgery examined during that time period were included in this study. 126 patients with SMA, 99 with SMA type II and 27 with SMA type IIIa, 61 male patients and 65 female were evaluated. 41 patients, 37 with SMA type II and 4 with type IIIa, were excluded because they had already had spinal surgery.

2) Similarly, it would be of value to know how many patients were excluded because they had already had surgery, if possible.

We completed: 41 patients, 37 with SMA type II and 4 with type IIIa, were excluded because they had already had spinal surgery.

3) The mean age of sitting independently was surprisingly late for their type 2 cohort, indicating they likely had a biased cohort of patients, referred to their group for evaluation due to the fact that scoliosis had already developed. This is to be expected, but the authors should put this caveat to highlight weaknesses in methodology. In point of fact, this is valuable, since delayed sitting may be predictive of the severity of weakness indicating a higher risk for scoliosis.

We completed: The mean age of sitting independently at an average age of one year seems to be surprisingly late for SMA II patients. It could be an indication for a biased cohort of patients, referred to the evaluated group due to the fact that scoliosis had already developed. Delayed sitting may be predictive of the severity of weakness indicating a higher risk for scoliosis.

And: This is a biased cohort of patients because our patients had visited us because of orthopaedic problems like contractures and scoliosis.

4) This study highlights the need for a comprehensive strategy to prospectively identify and follow all patients from an early age and monitor them for disease progression; give the expertise of these authors, some suggested guidelines as to when to refer such patients and how frequently to monitor them, particularly with regard to frequency of xray evaluation, would be of value.

We completed: This study highlights the need for a comprehensive strategy to prospectively identify and follow all SMA patients from an early age and monitor them for the course of disease, development and progression of scoliosis, pelvic obliquity and respiratory insufficiency. We recommend starting to monitor SMA patients regularly by clinical examination in special orthopaedic consultations as early as possible to determine an individual strategy in the provision of corsets, orthoses and orthopaedic technical devices and to determine the time for operative spine stabilisation [3]. The aims of the orthopaedic management are to stabilise, optimise and maintain the sitting and standing position and the ability to walk [3]. If scoliosis is diagnosed in the clinical examination, the radiographs in two planes in a sitting position without corset should be done to verify the
scoliosis [24]. The course of scoliosis and pelvic obliquity could be monitored and documented by clinical examination. We recommend monitoring the patients every 3 to 12 months depending on the dynamics of the disease and child development and growth. Usually radiographs are not necessary with each examination. We recommend radiographs for special circumstances, such as the provision of corsets or an indication for spinal surgery [3, 24].

We hope that you are happy with our corrections and thank you very much for your assistance and cooperation.

With best regards

Albert Fujak and co-authors