Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 415–421

www.elsevier.com/locate/nmd

Thoracic circumference: A new outcome measure in spinal muscular atrophy type 1?

Juliette Ropars[a,b,*], Christine Barnerias[c], Marie Hully[c], Delphine Chabalier[c], Sylviane Peudenier[a], Audrey Barzic[a], Pierrick Cros[a], Isabelle Desguerre[c]

[a] *Service de pédiatrie, CHRU de Brest, 2 Avenue Foch, 29609 Brest, France*
[b] *Laboratoire de Traitement de l'Information Médicale INSERM U1101, Brest, France*
[c] *Hôpital Necker Enfants Malades, APHP, Paris*

Received 5 October 2018; received in revised form 20 December 2018; accepted 10 March 2019

Abstract

Since respiratory insufficiency is the first cause of morbidity and mortality in spinal muscular atrophy type 1 (SMA 1), specific respiratory outcome measures are needed to evaluate changes and assess innovative therapies. In this study, thoracic circumference (TC) was used as a proxy for chest growth and an indirect measurement of respiratory function. The anthropometric parameters including TC and head-circumference (HC) were evaluated from birth to 13 months in 19 infants with SMA 1 and 124 control infants. TC was significantly decreased in the SMA 1 group from the first weeks of life. The control group TC/HC ratio = 1 (± 0.04), and was not found to be associated with age. By contrast, it decreased with time in all infants with SMA 1 and those with a TC/HC ratio <0.85 died within 3 months. TC is a simple measurement that provided an index of chest growth and was used as evidence of early, progressive respiratory failure and under-development of the rib-cage in SMA 1. The TC/HC ratio decreased in all patients over time, reflecting the progression of the disease suggesting that TC/HC ratio could be a new measure for SMA 1 for measuring disease severity and prognosis.

Keywords: Spinal muscular atrophy; Neuromuscular disorder; Outcome measure; Respiratory function; Disease progression.

1. Introduction

Proximal Spinal Muscular Atrophy (SMA) is one of the most common neuromuscular diseases, with an incidence of about one in 10,000 live births [1]. It is a progressive motor neuron disorder caused by deletion of exon 7 or other mutations in the survival motor neuron (*SMN) 1* gene, resulting in SMN protein deficiency [2]. The almost identical *SMN2* gene produces a small amount of functional SMN protein, and *SMN2* copy number is recognized as a major modulator of the SMA phenotype. Although the role of SMN protein in motor neurons is incompletely understood, the phenotype of spinal muscular atrophy is largely related to the number of SMN2 gene copies present [3].

The type of SMA is defined by the onset and severity of disease [4], from SMA type 0, in which the onset is in utero with reduced or absent movements, muscle contractures and ventilatory support at birth, to SMA type 4 with onset in adult life. About 60% of patients with SMA have SMA type 1 [1]. This type begins early, with generalized progressive muscle weakness and atrophy occurring before 6 months of age. The infants are unable to support their heads and do not achieve independent sitting. Cognitive function is normal. Respiratory failure is due to hypoventilation and poor cough, in addition to bulbar dysfunction. This is the major cause of mortality in patients with SMA I. Respiratory insufficiency mainly involves the intercostal muscles, with relative sparing of the diaphragm. This produces a bell-shaped chest and a pattern of paradoxical breathing or "belly-breathing" [5].

* Corresponding author at: Service de pédiatrie, CHRU de Brest, 2 Avenue Foch, 29609 Brest, France.
E-mail address: juliette.ropars@chu-brest.fr (J. Ropars).

https://doi.org/10.1016/j.nmd.2019.03.003
0960-8966/

Children with SMA 1 develop respiratory insufficiency before the age of 2 years, and in the past, most did not survive beyond this age without invasive ventilatory support [6,7]. However, there is a paucity of data, regarding longitudinal changes in respiratory muscle function in children with SMA 1 because of the difficulty in measuring respiratory function at this age.

In recent years, considerable advances have been made in the understanding of the pathogenesis of SMA, leading to the emergence of pharmacological treatments [8]. A new treatment has recently been developed based on antisense oligonucleotides (Nusinersen), which alters splicing of *SMN2* pre-mRNA and thus increases production of functional SMN protein. Recent studies showed this treatment is promising [9–11]. Effects on respiratory function are not specified.

Outcome measures should take small changes in the natural history of the disease into account, as well as being sufficiently sensitive to measure treatment-related changes. In the design of clinical trials, the primary outcome measure is usually survival or permanent ventilatory support. The ENMC international workshop highlighted the lack of a defined minimal clinically important difference for measures and the need to consider age specific changes in respiratory function [4]. Clinically relevant and reproducible, simple and non-invasive measures that are sensitive to change are required. There are obvious clues in motor development to clinically relevant responses to new therapies in spinal muscular atrophy type 1 (SMA 1). Since respiratory insufficiency is the first cause of morbidity and mortality, pulmonary function might be a pertinent marker of the clinical status of children with SMA 1 [12,13]. Specific respiratory outcome measures are therefore needed to objectively evaluate the effects of interventions in children with SMA 1.

The aim of this study was to assess the pertinence of thoracic circumference as a new outcome measure of respiratory insufficiency, and predictor of mortality in SMA 1. The anthropometric parameters of children with SMA 1 were compared with those of a group of paired, children who had normal development. We hypothesized that chest growth would be abnormal in SMA 1 and that the ratio between thoracic circumference and head circumference in children with SMA 1 would reflect the disease progression and predict the age of death, if ventilatory support was not initiated.

2. Materials and method

2.1. Participants

Children with SMA 1 were recruited at Necker hospital, Paris, between January 2011 and December 2014. The inclusion criteria were: (1) confirmed SMA 1 (typical phenotype genetically confirmed with a homozygous deletion/point mutation of exon 7 in the *SMN 1* gene), (2) presence of two copies of the *SMN2* gene (3) followed by a neuropaediatrician as an in- or out-patient in the Paediatric Neurological department of Necker hospital, with death occurring during the study period. Infants with other known co-morbid medical factors, lung disease or premature birth were excluded.

Control children with normal development and aged from new-born to 13 months were included in the study. They were enrolled by four paediatricians (CM, CF, AS, MV) during routine medical visits. Children with chronic pathologies or acute respiratory pathologies were excluded.

This observational, single site, non-interventional, control study was approved by the ethics committee “comité de protection des personnes Ile de France 2. The parents received an information letter and provided written consent form before their child could participate in the study, in accordance with French legislation.

2.2. Data collection

The following anthropometric parameters were recorded at each medical visit: height, weight, head circumference (HC) and thoracic circumference (TC) for both patients with SMA 1 and control infants. TC was measured with a tape measure, on the nipple line, during inspiration. Three measures were performed and the highest value was used for further analysis. Medication, enteral nutrition, ventilatory support, pulmonary infection and age at the time of death were also recorded for the SMA 1 group.

2.3. Data processing

The number of medical visits differed across the patients with SMA 1, therefore the main analysis was carried out on the final visit before the death of the patient. This analysis included age at the time of visit, time from visit till death, body mass index (BMI), TC/weight, TC/height, TC, BMI, TC/HC.

Each infant in the control group participated in one visit during which the following parameters were analysed: age at the time of visit, body mass index (BMI), TC, BMI, TC/HC.

In order to assess changes in parameters with age, sub-group analyses were carried out: <3 months old; <6 months old and >6 months old.

Associations between the following parameters were tested: age, weight, height, BMI, HC, TC and TC/HC in either group (SMA 1 and control). Then, correlations were compared between both groups.

Survival analysis was performed.

Finally, data from the visits prior to the final visit were analysed. The association between TC/HC ratio and time from final visit till death was assessed. The time from final visit till death was calculated for each of the TC/HC values.

2.4. Statistical analysis

BiostaTGV (version 2014) software was used for statistical analyses

The analyses were carried out on the means of the variables for both groups (control and SMA 1).

Table 1
Subject characteristics.

	Total			<3 months			<6 months			>6 months		
	SMA	Control	p	SMA	Control	p	SMA	Control	p	SMA	Control	p
Number of infants	19	124		5	32		10	78		9	46	
Age (year) (mean, SD)	0.52 (0.31)	0.43 (0.27)	0.26	0.16 (0.06)	0.12 (0.06)	0.39	0.29 (0.15)	0.26 (0.14)	0.62	0.77 (0.23)	0.72 (0.18)	0.5
(median, IQR)	0.50 (0.28–1.22)	0.39 (0.22–1.09)										
Weight (kg) (mean, SD)	6.16 (1.46)	6.89 (1.87)	0.12									
(median, IQR)	6.2 (5.02–8.8)	6.87 (5.49–1.09)										
BMI (kg/m2) (mean, SD)	13.83 (1.43)	16.5 (1.29)	***				14.47	16.26	0.054	13.55	17.14	***
(median, IQR)	14.4 (12.6–15.6)	16.47 (15.53–18.53)					(1.38)	(1.31)		(1.43)	(1.02)	
HC(cm) (mean, SD)	42.27 (3.12)	42.13 (3.3)	0.70	38.10 (1.14)	38.38 (1.95)	0.84	40.02 (2.50)	40.39 (2.42)	0.85	44.3 (2.06)	45.08 (2.25)	0.45
(median, IQR)	43 (40–47.5)	42.25 (40–49.9)										
TC (cm) (mean, SD)	37.53 (2.79)	42.34 (3.85)	***	34.4 (1.39)	37.99 (2.6)	**	36.65 (2.77)	40.43 (3.09)	**	38.5 (2.62)	45.59 (2.65)	***
(median, IQR)	37.5 (35.25–42)	42.25 (40–50.8)										
TC/HC (mean, SD)	0.889 (0.06)	1.005 (0.04)	***	0.9 (0.05)	0.99 (0.004)	**	0.91 (0.04)	1 (0.004)	***	0.87 (0.07)	1.01 (0.04)	***
(median, IQR)	0.88 (0.84–1)	1.005 (0.98–1.12)										

BMI, body mass index; HC, Head Circumference; TC, thoracic circumference; SD standard deviation; IQR, Inter Quartile Range; $p < 0.05$.
** $p<0.01$.
*** $p<0.001$.

A Mann-Whitney test was used to compare the variables of the control children and the children with SMA 1.

Spearman's rank correlation was used to test the association between age and anthropometric parameters, and between TC/HC ratio and time from final visit to death.

Correlation coefficients were compared between the 2 groups (control and SMA 1) using a Fisher transformation. To analyse the influence of TC/HC ratio on death, a Cox model was used.

The threshold for significance was set to $p < 0.05$.

3. Results

Nineteen children with SMA 1 were enrolled in the study. All died during the observational period. Fifty-seven medical visits were analysed.

Subject characteristics at enrolment are shown in Table 1. Median age at baseline study visit was 6 months (range 1–15 months). Median age at death was 7 months (range 2.4–15.5 months). Respiratory failure was the cause of all deaths.

None of the infants with SMA 1 were under non-invasive mechanical ventilatory support and none had in/exsufflation therapy or a tracheotomy.

One-hundred and twenty-four control children were included in the study. The group of children with SMA 1 and control children were similar in terms of age and sex ratio. There was no significant difference between the weight at the baseline study in the SMA 1 group (mean 6.14 kg, 3° percentile for age) and control group (mean 6.89 kg, 50° percentile for age).

There was a significant difference in the rate of change in TC in the SMA1 group when compared to the control group whereas there was no difference for HC (Table 1). TC was significantly lower in the SMA 1 group compared to the control group (37.53 cm ±2.79 vs. 42.34 cm ±3.85, $p < 0.001$. This was true for all age groups (<3 months, <6 months, >6 months) and the magnitude of the difference increased with age.

The TC/HC ratio was significantly lower in the SMA 1 group than in the control group (0.89 ±0.06 vs. 1 ± 0.04, $p < 0.001$), and this was true across all age groups.

The analysis of correlations between TC, HC and age (Fig. 1) showed that HC was significantly correlated with age in both the SMA 1 group (Rs 0.87, $p < 0.001$) and the control group (Rs 0.90, $p<0.001$). There was no significant difference between the correlation coefficients of each group (Fisher transformation, $p = 0.46$).

TC was significantly associated with age in the control group (Rs 0.85, $p < 0.001$). In the SMA 1 group, the correlation coefficient between TC and age was 0.58 ($p < 0.1$). There was a significant difference between the correlation coefficients of each group (Fisher transformation, $p < 0.05$).

There was no significant association between the TC/HC ratio and age in the children with SMA 1 (Rs −0.3, $p = 0.21$).

A threshold value was estimated for the TC/HC ratio that predicted imminent death in patients with SMA 1 (Table 2, Fig. 2). Qualitative analysis of the TC/HC curves by age in patients who had undergone successive measurements of TC and HC showed that the TC/HC ratio decreased with

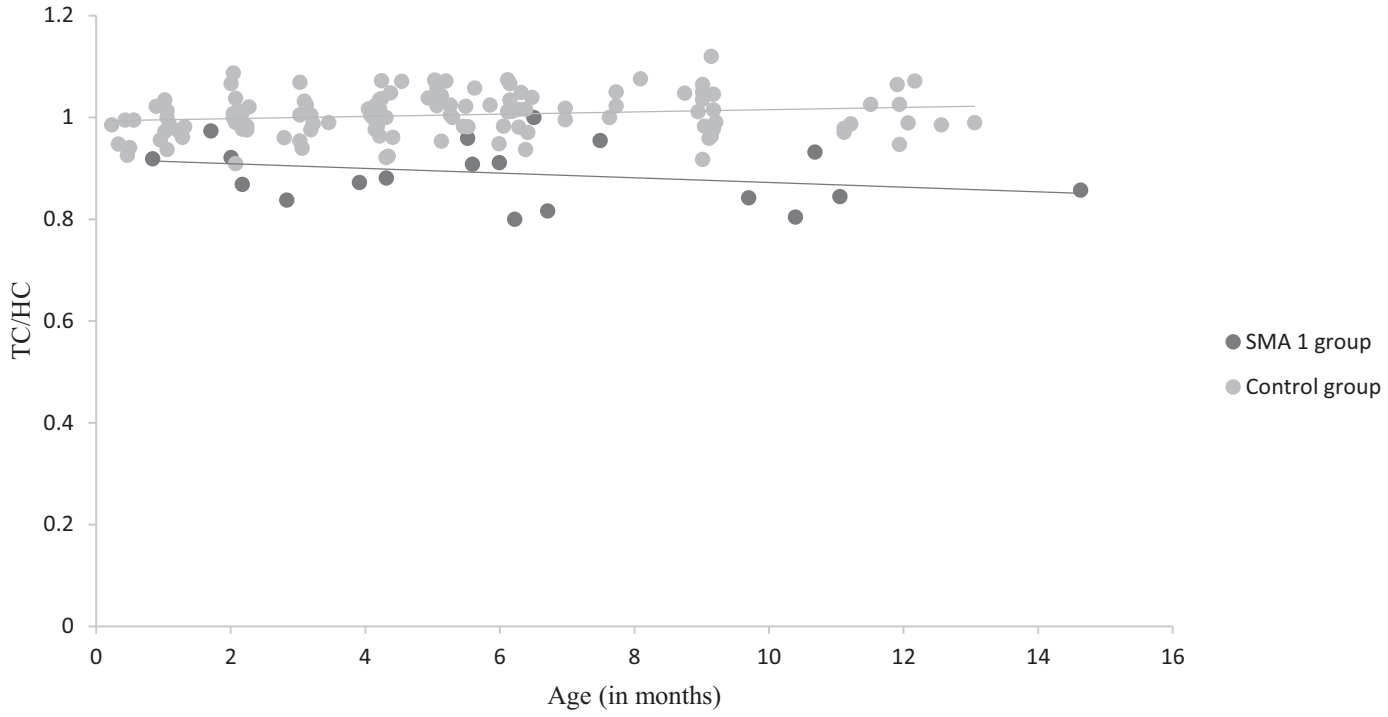

Fig. 1. TC/HC ratio as a function of age in each group.
Age is presented on the *X*-axis and the HC/TC value on the *Y*-axis. Grey represents control infants and black represents infants with SMA1. Trend lines are presented in each group.

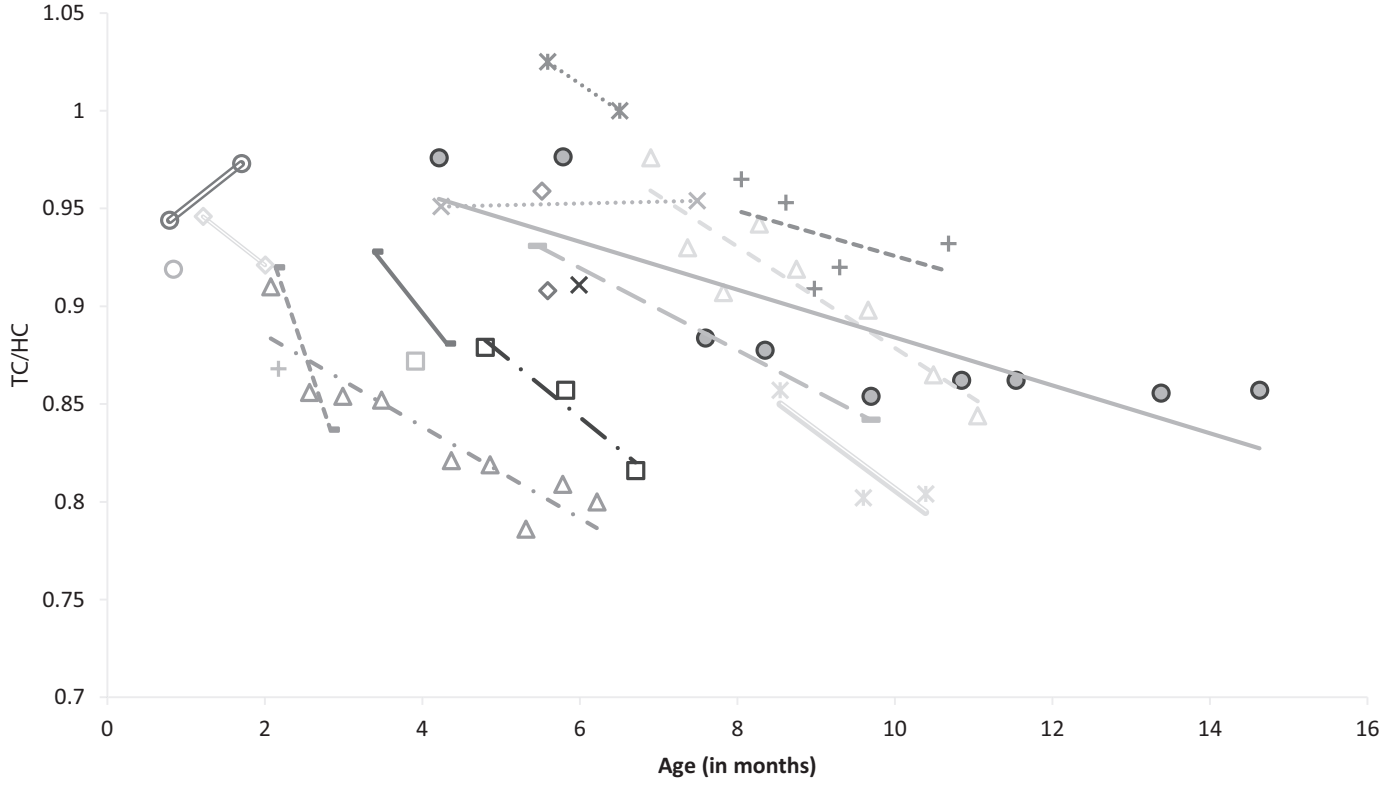

Fig. 2. Change in TC/HC with age in the infants with SMA 1.
Age is presented on the *X*-axis and the HC/TC value on the *Y*-axis. Data available for each infant with SMA 1 are presented. Each infant is represented by a different symbol. Fit lines are shown for patients with 3 or more values.

Table 2
TC/HC ratio in infants with SMA 1 and time till death.

TC/HC	Number of values	Time from final visit till death (months)		
		Mean (SD)	Minimum	Maximum
>0.95	11	4.51 (3.74)	0.6	11.4
0.9–0.95	17	2.88 (2.44)	0.3	9.56
0.85–0.9	18	3.34 (2.09)	0.4	7.99
<0.85	11	1.33 (0.79)	0.01	2.47

SD, standard deviation; HC, head circumference; TC, thoracic circumference. The available data were analyzed (57 visits).

age. The TC/HC ratio was not statistically associated with time to death (Rs 0.22, $p=0.11$), however all infants with a TC/HC ratio below 0.85 died within 3 months (median 1.37, range 0.01–2.47). The effect of TC/HC ratio on death in the Cox model was not statistically significant (HR 0.6 IC95% [0.22–1.68], $p=0.329$).

4. Discussion

Several studies have described the clinical features and natural history of SMA [14,15] and some outcome measures have been developed to measure different aspects of SMA [4]. Nevertheless, few outcomes measures are specific for SMA 1 and those that exist mainly evaluate survival rather than age-specific changes [4]. Electrophysiological examinations, including motor-unit number estimation (MUNE) and maximal compound muscle action potentials (CMAPs) [16], do not evaluate the function of the motor neuron pools that control bulbar or respiratory function, and results may be limited by severe denervation [14]. Several measures of movement and function have been validated to assess changes in muscle weakness over time: the CHOP INTEND and TIMPSI scales are clinically useful SMA1 outcome measures that are used in clinical trials [4]. The aims of treatment interventions aim range from slowing disease progression to improving function, both of which are difficult to capture in a single measurement. Specific and relevant outcome measures are thus needed to improve the validity and utility of clinical trial results as well as for use in monitoring and follow-up patient care.

Few studies of respiratory function in patients with SMA have been reported in the literature [5,17], despite the fact that respiratory failure is the most common cause of death. Finkel et al. performed exploratory studies of respiratory muscle function in children with SMA 1 using invasive tests (maximal inspiratory pressures and respiratory inductive plethysmography) and found that their results reflected the progressive respiratory muscle weakness [12]. However, these measurements require time, effort, expensive specialized equipment, and are limited by the age and the fragility of the patients. Children with SMA 1 have intercostal muscle weakness with relatively preserved diaphragm strength, resulting in a bell-shaped chest and under-development of the lungs in some cases [13]. It was for this reason that we chose to assess respiratory muscle function by measuring thoracic circumference: the measurement was simple, cheap, well tolerated and reproducible in extremely fragile infants.

To our knowledge, this was the first study to evaluate TC in children with SMA 1 and to compare the results with healthy age- and gender-matched children with normal development. TC and TC/HC ratio were significantly decreased in the SMA 1 group, compared to the control group, from the very first weeks of life. In the infants with SMA 1, although the TC/HC ratio was not significantly associated with age, it decreased over time and all of those who had a TC/HC ratio <0.85 died within 3 months.

These original results have provided new information about the ontogeny of SMA 1 and suggested that the TC/HC ratio could be a new and clinically pertinent outcome measure for this disorder.

Increases in TC may reflect rib-cage growth. We have shown that TC was more closely associated with age in the control group than in the SMA 1 group. Differences in TC between the groups were clear before 3 months of age and, moreover, they increased with age. These results corroborate those of Finkel et al. who found that infants under 3 months of age already have significant respiratory muscle weakness [12]. We therefore propose that this weakness is present from birth and the resultant absence of chest expansion seems likely to adversely affect chest growth.

Another anthropometric parameter that has been found to be reduced in infants with SMA 1 is BMI which can reflect nutritional status but also reduced muscle mass. It can be affected by medical management (e.g., type of nutrition, use of gastrostomy, etc.) [18–20].

Furthermore, no differences in HC were observed between the groups, probably because infants with SMA 1 have normal cognitive function. HC increased with age in both groups, indicating normal head growth in both the SMA 1 and control groups. We therefore calculated the ratio between TC and HC to avoid biases due to age or nutritional status. The TC/HC ratio was constant (around 1) from birth to the age of two years in the control group while it significantly decreased in the SMA1 group from the first weeks of life. This indicated that use of the TC/HC ratio successfully overcame the confounding influence of age whilst highlighting respiratory function impairment in children with SMA 1, and was also sensitive to changes in respiratory function over time. We concluded that the TC/HC ratio, which decreased over time in all children with SMA 1, provided a measure of disease-progression, regardless of their age. This was further supported by qualitative analysis of changes in the ratio over time in the infants who had undergone successive measurements.

The lack of significance of the death analysis could be related to the relatively small sample size, the heterogeneous respiratory functions of patients or the different durations of survival due to the different causes of death. The main causes of death in SMA type 1 are respiratory insufficiency and bulbar dysfunction, although unexplained sudden death can also occur [5]. Although the association between the TC/HC ratio and time from final visit till death was not significant,

the qualitative analysis in Fig. 2 shows that the TC/HC ratio decreased over time for all of the children with SMA 1. Since this ratio was not associated with age in the SMA 1 group, it seems likely that it instead reflected the natural course of the disease. All the infants with a TC/HC ratio below 0.85 died within 3 months. Children with a TC/HC ratio over 0.9 are still at risk of upcoming death but this study estimated a threshold value of 0.85 that predicted imminent death in patients with SMA 1. It seems plausible therefore that this ratio could be used in clinical practice to help determine the prognosis of the infant, allowing clinicians to inform parents accordingly and to organize appropriate palliative care.

This study has several limitations. The SMA 1 group was unavoidably small and a lack of statistical power could have explained the absence of statistical significance for some results. The small sample size also made it impossible to assess the impact of other factors that could influence TC, such as nutritional status. None of the infants were under mechanical ventilatory support therefore the effect of ventilation on TC could not be evaluated. The results indicated that a larger, statistically powerful and longitudinal study of infants with SMA 1 is warranted to validate the TC/HC ratio as a useful outcome measure, as well as to analyse the impact of different care and management strategies, such as ventilation or nutrition. The goal of this study was to analyse a homogeneous group of children with SMA 1 who were being cared for in the same centre, therefore only infants under 13 months of age were included. Since recent studies have reported an increase in survival rates of children with SMA 1 [6,7], we believe that this study should also be repeated in older children to validate use of the TC/HC ratio as an outcome across all ages. A recent observational study of SMA 1 showed that ventilatory support is initiated at a median age of 11 months in the USA [14]. It seems reasonable to suppose that this would also increase rib cage growth and it would therefore be interesting to compare the TC/HC ratio after the age of 12 months, in normally-developing children and in children with SMA 1 in countries with different care standards and ventilation strategies [21]. Future studies could also assess the reliability of TC as a developmental index in other neuromuscular diseases of early life that have different patterns of respiratory involvement such as nemaline myopathy or congenital muscular dystrophy.

5. Conclusion

Measurement of TC is simple and reproducible. TC may reflect rib cage growth and thus indirectly, pulmonary growth. TC was found to be significantly decreased in infants with SMA 1 compared to control infants, from the first weeks of life, and was found to be associated with early and progressive respiratory failure. The TC/HC ratio provided information about the clinical course of the disease, regardless of age. A larger longitudinal multicentre study is warranted to confirm the use of TC and TC/HC as new outcome measures in SMA 1 for clinical practice as well as for in clinical trials for the evaluation of recent therapies.

Acknowledgements

The authors wish to thank all parents of the children with SMA 1 for their participation. We also thank the paediatricians who included the control children: Marie Varigny, Angèle Salles, Caroline Marteau, Cécile Floch

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.03.003.

References

[1] Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120–33.
[2] Melki J, Abdelhak S, Sheth P, Bachelot MF, Burlet P, Marcadet A, et al. Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q. Nature 1990;344:767–8.
[3] Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68.
[4] Finkel R, Bertini E, Muntoni F, Mercuri E, Group ESWS. 209th ENMC International workshop: outcome measures and clinical trial readiness in spinal muscular atrophy 7–9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord 2015 1–10.
[5] Ioos C, Leclair-Richard D, Mrad S, Barois A, Estournet-Mathiaud B. Respiratory capacity course in patients with infantile spinal muscular atrophy. Chest 2004;126:831–7.
[6] Cobben JM, Lemmink HH, Snoeck I, Barth PA, van der Lee JH, de Visser M. Survival in SMA type I: a prospective analysis of 34 consecutive cases. Neuromuscul Disord 2008;18:541–4.
[7] Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Ravà L, Bignamini E, et al. Survival of patients with spinal muscular atrophy type 1. Pediatrics 2013;131:e1509–14.
[8] Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. Gene Ther 2017;24:529–33.
[9] Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: preliminary results on motor function. Neuromuscul Disord 2018;28:582–5.
[10] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35.
[11] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32.
[12] Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. Pediatr Pulmonol 2014;49:1234–42.
[13] Schroth MK. Special considerations in the respiratory management of spinal muscular atrophy. Pediatrics 2009;123(4):S245–9 Suppl.
[14] Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014;83:810–817.

[15] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology 2012;79:1889–97.
[16] Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol 2005;57:704–12.
[17] LoMauro A, Aliverti A, Mastella C, Arnoldi MT, Banfi P, Baranello G. Spontaneous breathing pattern as respiratory functional outcome in children with spinal muscular atrophy (SMA). PLoS ONE 2016;11:e0165818.
[18] Barnérias C, Quijano S, Mayer M, Estournet B, Cuisset J-M, Sukno S, et al. Multicentric study of medical care and practices in spinal muscular atrophy type 1 over two 10-year periods. Arch Pediatr 2014;21:347–54.
[19] Roper H, Quinlivan RWorkshop Participants. Implementation of "the consensus statement for the standard of care in spinal muscular atrophy" when applied to infants with severe type 1 SMA in the UK. Arch Dis Child 2010;95:845–9.
[20] Durkin ET, Schroth MK, Helin M, Shaaban AF. Early laparoscopic fundoplication and gastrostomy in infants with spinal muscular atrophy type I. J Pediatr Surg 2008;43:2031–7.
[21] Finkel RS, Sejersen T, Mercuri EENMC SMA Workshop Study Group. 218th ENMC international workshop:: revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19–21 February 2016. Neuromuscul Disord 2017;27:596–605.