Clinical factors as predictors of survival in spinal muscular atrophy type I

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Conflict of Interest: *none declared*

Funding from #ISTRI6PQA1 TREAT-NMD Network of Excellence and Telethon. No involvement of sponsors in the study design; collection, analysis or interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication.

Abstract

The aim of this study was to establish whether clinical factors may help to identify subgroups of infants with spinal muscular atrophy (SMA) type I. A questionnaire was retrospectively proposed to 38 families of infants with SMA type I. It included questions regarding possible prenatal and early neonatal signs of motor and/or respiratory weakness, onset and progression of clinical signs, and age at death for those infants who had not survived beyond the age of 30 months. As we also wished to establish whether the severity of onset of clinical signs and their progression are predictors of outcome, and in order to have a homogeneous group, we only included families where the affected child had not received any respiratory support or noninvasive ventilation. In the population of SMA type I patients, statistical analysis of the questionnaire allowed to identify three subgroups of the disease: (1) neonatal SMA; (2) classical SMA type I; (3) SMA intermediate between type I and type II. This would be useful for correct stratification of patient groups and should be considered when establishing inclusion criteria for future trials in SMA type I patients.

Keywords spinal muscular atrophy type I; clinical predictors of survival; questionnaire

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects the spinal cord motor neurons, and is clinically characterised by progressive generalised muscle weakness. There is a wide range of severity, the most severe form being Werding–Hoffman disease (or SMA type I), in which affected children are unable to sit unsupported. In the mildest form (SMA type III), independent ambulation is achieved but mild to moderate proximal muscle weakness may be experienced, causing difficulty with stairs and rising from the floor. Children with the intermediate form (SMA type II) are, in contrast, able to sit but not to walk independently.[1] Although this clinical classification based on severity of maximum motor achievement has several advantages, it appears to be restrictive for use in clinical trials because it lumps together patients with most different degrees of severity.

SMA is due to homozygous absence of a functional *SMN1* gene and it has been demonstrated that the disease severity inversely correlates with *SMN2* copy number in patients,[2,3] and in mice models.[4] It has also been reported, however, that the number of copies does not always predict the progression or the severity of the disease and has a limited prognostic value in individual cases.

Due to the recent discovery of potential drugs for SMA, there is increasing evidence that one of the most crucial problems in the design of clinical trials is the lack of clinical tools for classifying homogeneous groups of patients into each form of SMA, which would allow proper stratification in therapeutic trials and reduce bias in sampling of patients.[5]

The classical definition of SMA type I includes all infants with genetically proven SMA who are unable to sit independently, ranging from those with the very severe neonatal onset

form who do not survive beyond the age of 6 months, to those who are able to sit with minimal support and who may survive for several years without any need of supported ventilation. Ioss *et al*[6] suggested separating SMA type I into two forms: a classic form – with onset of symptoms before the age of 3 months and with 'floppy' children never able to raise their head; and an intermediate form – with onset between 3 and 6 months of age and with children who are able to raise their head.

The aim of this retrospective study was to identify, by means of a questionnaire distributed to 38 families of infants with SMA type I, any clinical factors that could help identify subgroups of infants with this disease. We also wanted to establish whether the severity of onset of clinical signs and their progression are predictors of outcome.

Methods

A total of 38 paediatric patients with SMA type I, who had been cared for in 2001–2003 at four Italian neuromuscular disease centres (two in Rome, one in Milan and one in Messina), were included in the study. All the children had a genetically confirmed SMA type I. At the time of the study, all but two patients were dead and had never received respiratory support. The two long-term survivors began to receive respiratory support at 35.3 and 49.6 months respectively; as we were interested in the natural history of the disease, they were excluded from the analysis when respiratory support was started.

A questionnaire was devised to investigate the clinical signs of disease onset as reported by parents. It included six questions concerning: (1) history of reduced foetal movements; (2) respiratory problems (ie distress or abnormal respiratory pattern) at birth; (3) weakness detected in the neonatal period (first 21 days of life by definition); (4) head control achieved by 4 months of age; (5) head control achieved later; and (6) partial trunk control (ie sitting with support). All questions allowed for a dichotomous (yes/no) answer.

The questions were posed by telephone. Before the telephone interview, all families received a letter explaining the aims and methods of the study, and asking for their collaboration. The letter was signed by the physician in charge of the patient, and by a representative of the parent support group *'Families for SMA'*.

The telephone interviews were conducted by the centre's principal investigator or by a trained research fellow. At the time of the telephone call, the interviewer asked for confirmation that the preliminary letter had been received, and that the responding parents were aware of the aims of the study and agreed to participate. The study protocol was reviewed by the Ethics Committees of the participating centres.

Statistical analysis

Data analysis was done at the coordinating centre, the Ospedale Pediatrico Bambino Gesù in Rome. Proportions were computed for categorical variables, and means and medians for continuous ones, together with appropriate variability measures. The probability of survival and 95% confidence interval (CI) around the survival curve were estimated according to the Kaplan–Meier method.[7] Multivariate Cox's proportional hazards analysis[8] was used to establish the association between the clinical signs of disease onset and length of survival. The multivariate model included gender and all the variables from the clinical questionnaire except partial trunk control. The latter was positive in only three cases, and was associated with achievement of head control. Achievement of head control, coded as yes (at normal time or later) versus never, was treated as a time-dependent factor since it is normally absent before 2–4 months of age.

Finally, a cluster analysis was performed in order to determine the natural grouping of observations (ie patients) according to the clinical signs. All the factors explored by the clinical questionnaire were included in this analysis. Subsequently, the mean and median lengths of survival were computed for each 'cluster' of patients. The non-parametric Kruskal–Wallis test was used to assess the differences in median survival time across the clusters.

Data analysis was carried out using the Stata statistical package, version 9.0 (StataCorp.2005. Stata Statistical Software: Release 9.0. College Station, TX: StataCorp).

Results

Patients' gender, clinical signs, and survival time are presented in Table 1. A total of 23 of the 38 patients were male. Neonatal neurological signs were the most common symptom (21 patients). In 10 cases, parents recalled reduced foetal movements, while five patients showed respiratory distress at birth. A total of 11 patients were able to achieve head control, either at about normal time (ie by 3–4 months of age: two patients only) or subsequently. Of these 11 patients, three were able to sit with support (partial trunk control). Most patients, however, were never able to sit, even with support, or to control their head.

The survival curve, with 95% confidence limits, is presented in Figure 1. The two patients who were still alive at the time of the study were 'censored' (ie excluded from the survival analysis) as of the time at which they started respi-

Gender and clinical signs of the study sample

	No.	%
Male gender	23	60.5
Reduced foetal movements	10	26.3
Respiratory distress at birth	5	13.2
Neonatal neurological signs (early neonatal weakness?)	21	55.3
Head control		
– at normal time	2	5.3
– later than normal	9	23.7
– never	27	71.1
Sits with support	3	7.9
Alive at time of interview	2	5.3
Survival up to time of interview (months)		
mean (SD)	9.88	(9.15)
Median (range)	6.25	(2–49.6)

Table 1

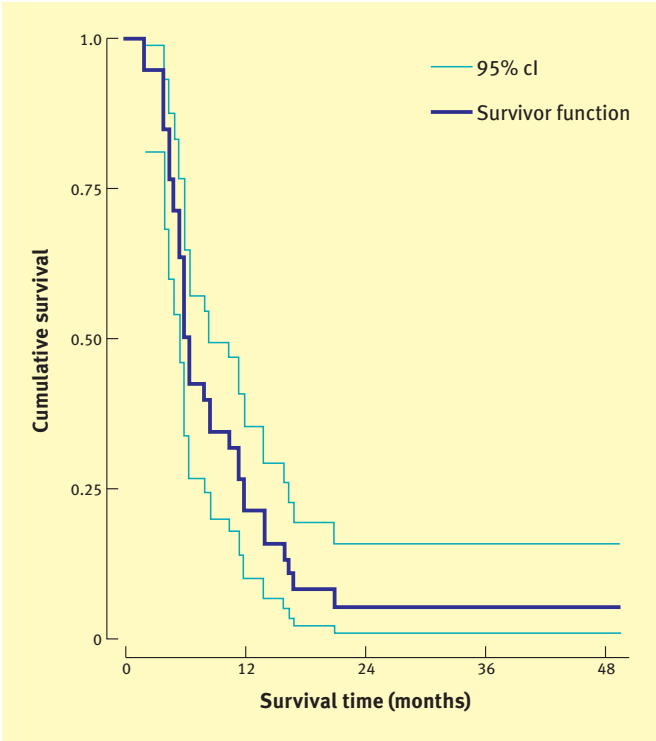

Figure 1 Survival curve estimated according to the Kaplan–Meier method. The probability of survival was: 50% (95% CI 33–65%) at 6 months of age; 21% (CI 10–35%) at 1 year; and 5% (CI 1–16%) at 2 years.

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Table 2 presents the univariate and multivariate Cox proportional hazard's analyses exploring the association between clinical signs and probability of death. Respiratory distress at birth and neonatal neurological signs increased the likelihood of death four- and two-fold respectively. The effect of neurological signs, however, was only marginally significant ($P = 0.065$). In contrast, achievement of head control, either within normal time or later, appeared to be strongly protective ($P < 0.001$).

Figure 2 shows the results of the cluster analysis, grouping patients according to the presence and/or absence of specific clinical signs. Three main groups (or 'clusters') could be identified, whose characteristics and survival time are shown in the table below the graph.

The first group ($n = 10$ patients) included infants with reported normal foetal movements, and no respiratory distress at birth. All 10 children achieved head control, either before 4 months of age or later, and three of them also achieved partial trunk support. Two patients from this group achieved head control in time and were able to sit with support: they were still alive at the start of the study and were put on respiratory care and non-invasive ventilation. The remaining eight children achieved head control later than 4 months and were all dead by the age of 21 months (data not shown in table).

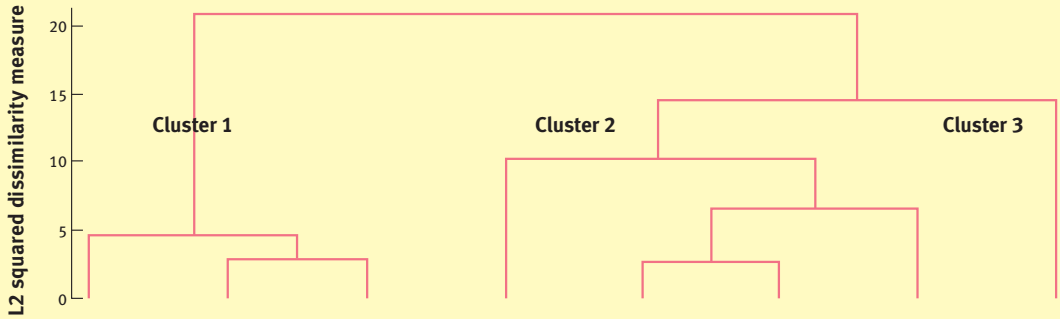
Another group (cluster 3) consisted of the five patients with respiratory distress at birth; they all also had reduced foetal

Univariate and adjusted death hazard ratios according to patient characteristics

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value*	Adjusted hazard ratio (95% CI)	Adjusted *P* value*
Gender		0.935		0.777
Male	1.0†		1.0†	
Female	0.97 (0.49–1.92)		1.12 (0.52–2.37)	
Reduced foetal movements		0.059		0.895
No	1.0†		1.0†	
Yes	2.06 (0.97–4.39)		1.07 (0.39–2.97)	
Respiratory distress at birth		0.000		0.046
No	1.0†		1.0†	
Yes	8.06 (2.62–24.82)		4.10 (1.02–16.40)	
Neonatal neurological signs		0.001		0.065
No	1.0†		1.0†	
Yes	3.15 (1.55–6.39)		2.11 (0.95–4.69)	
Head and/or trunk control‡		0.000		0.000
No	1.0†		1.0†	
Yes	0.09 (0.03–0.27)		0.11 (0.03–0.32)	

Hazard ratios and *P* values were determined by Cox proportional hazards regression analysis. CI, confidence interval. **P* values refer to the overall statistical significance of the factor. †Indicates reference category; ‡This variable is time-dependent (from month 2.5.

Table 2



	Cluster 1 (N=10)	Cluster 2 (N=23)	Cluster 3 (N=5)
	No. (%)	No. (%)	No. (%)
Reduced fetal movements	0 (–)	5 (21.7)	5 (100)
Respiratory distress at birth	0 (–)	0 (0)	5 (100)
Neonatal neurological signs	2 (20)	14 (60.9)	5 (100)
Head control	10 (100)	1 (4.3)	0 (0)
Sits with support	3 (30)	0 (0)	0 (0)
Mean survival (sd)*	**19.9(12.7)**	**6.8 (3.1)**	**3.6(1.6)**
Median survival (IQR)*	**15 (12.7)**	**6 (12.5)**	**4 (3.5)**

*months

Figure 2 Cluster analysis. Three clusters could be identified, according to the presence and/or absence of specific clinical signs. Characteristics and survival time are shown in the table below the graph.

movements and neonatal neurological signs. None of them ever achieved head or trunk control.

Finally, an intermediate larger group (cluster 2 – 23 patients) was identified. Most of the patients in this group [14 (61%)] had neonatal neurological signs of muscle weakness, but none had respiratory distress at birth. Five had reduced foetal movements. Only one achieved (late) head control, and none trunk control. Six patients (26%) had neither pre- nor neonatal signs of muscle disease, or any motor achievement at follow-up.

When average survival time was computed separately for the three groups, a clear-cut trend appeared with shorter survival in cluster 3 (median: 4 months), longer in cluster 1 (median: 15 months), and intermediate (6 months) in cluster 2. The difference in survival was statistically significant (Kruskal–Wallis chi-squared with 2 df 19; $P = 0.0001$).

Discussion

Using a simple questionnaire, we were able to obtain useful clinical information about the heterogeneity of clinical presentation and progression in infants with SMA type I. Analysis of the retrospective data identified three different subtypes of SMA type I based on onset and progression of clinical signs and outcome, that is, age at death or survival after 2 years without ventilation. The presence of prenatal and neonatal signs and the achievement of head control appear to be the most sensitive indicators of severity and survival. Patients in cluster 3 in our series had the most severe type of neonatal SMA. These children had prenatal signs, with reduced foetal movements and both motor and respiratory signs in the neonatal period. This group of patients may also include the so-called neonatal form of SMA type 0.[9] According to our statistical analysis, neonatal respiratory distress appears to be the most significant predictor of severity and short survival. The children in cluster 2 had clinical signs corresponding to the classical form of SMA type I. They often had a history of reduced foetal movements and of hypotonia and/or motor signs in the neonatal period but did not have neonatal respiratory distress. They often gained no obvious motor achievements during the follow-up and only one achieved head control. The survival of these children was better than those with the most severe form and the mean age at death of 6.8 months corresponded to previous reports by Dubowitz.[10]

A small subgroup of patients (cluster 1) appeared to have later (after the neonatal period) onset of signs of muscle weakness, and better motor achievements. They usually achieved head control in time or later than normal motor milestones. These children had a longer life expectancy with a mean age at death of 19.9 months. In this group, only two children clearly had head control by the age of 4 months, were able to sit with support and had the mildest progression, without developing swallowing impairment during the follow-up of 35.3 and 49.6 months, respectively. The remaining eight patients achieved head control later than the age of 4 months and, although they had a better clinical course than children in cluster 2, they did not survive beyond the age of 21 months. The mildest form of SMA seen in two patients in our series probably corresponds to the form proposed by Dubowitz as SMA type 1.9, at the extreme limit of the mild severity range of the SMA type I spectrum,[10] also referred to by Ioos *et al* as the intermediate form

between type I and type II.[6] It is easily detectable clinically and is relatively rare.

Our results, therefore, confirm previous studies suggesting clinical heterogeneity in infants with SMA type I and suggest that a more careful evaluation of the infants' ability, onset and progression of signs is mandatory in these children. This information is not only of important prognostic value, but is also essential for the planning of therapeutic trials. So far, although there have been a few clinical trials in SMA type II and III, less has been done in infants with SMA type I. This is partly due to a combination of factors, such as the clinical heterogeneity of infants with SMA type I, the lack of validated assessments for this form of the disease, and the heterogeneity of standards of care.

The use of a questionnaire like the one used in this study is far from being the ideal tool for assessing the natural history of the disease. However, it has its advantages. For instance, it can also be used retrospectively to interview families of deceased infants, and allows the collection of information on cohorts that have received no active respiratory treatment with invasive or non-invasive ventilation. Thus, data can be assembled that may form the baseline for future studies aimed at evaluating different modalities of care such as non-invasive ventilation or early gastrostomy, which are now often used routinely in infants with SMA type I.

The use of the questionnaire in our cohort allowed us to identify three major subgroups that each has significantly different disease progression and survival. Our results suggest that any future clinical trials should take into account the possibility that among paediatric patients suffering from the most common form of SMA type I, there are some infants who are more likely to have early abnormal outcome and others who are more likely to have longer survival, and that the various subgroups should be stratified and balanced equally in the different arms of a clinical trial in order to avoid biases in randomisation. These findings, however, are still limited, and more appropriate tools such as functional scales or other indicators of clinical severity and survival should be used prospectively to define the natural history of the disease.

More complete information could be achieved in a prospective study by direct observation of the patient using a structured assessment of various aspects of function. However, it would be necessary in this case to set up a motor function scale to measure motor breakdown or motor achievements over time, assessed during serial examinations of patients.

Acknowledgements

Funding from Ricerca Corrente of the Italian Ministry of Health and support from Telethon onlus (grant #ISTR16PQA1 for TREAT NMD neuromuscular network) are gratefully acknowledged. We would also like to extend sincere thanks to the Associazione Italiana Famiglie SMA and all the families that agreed to reply to the questionnaire.

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