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The changing natural history of spinal muscular atrophy type 1

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ABSTRACT

Background: Noninvasive ventilation has become increasingly available to spinal muscular atrophy (SMA) patients since the early 1990s. This is expected to have improved survival for SMA type 1 patients.

Objective: To assess whether there has been a change in survival in patients with SMA type 1 between 1980 and 2006.

Methods: We used deidentified, family-reported data from participants in the International Spinal Muscular Atrophy Patient Registry and obtained additional clinical information through a mail-in questionnaire. One hundred forty-three patients with SMA type 1 were included in the analysis. Survival of patients born in 1995–2006 ($n = 78$) was compared with that of patients born in 1980–1994 ($n = 65$), using the Kaplan–Meier method and Cox proportional hazards models with age at death as the outcome.

Results: Patients born in 1995 through 2006 had significantly increased survival compared with those born in 1980–1994 (log-rank test, $p < 0.001$). In a Cox model, patients born in 1995–2006 had a 70% reduction in the risk of death compared with those born in 1980–1994 (hazard ratio [HR] 0.3, 95% CI 0.2–0.5, $p < 0.001$) over a mean follow-up of 49.9 months (SD 61.1, median 22.0). However, when controlling for demographic and clinical care variables, year of birth was no longer significantly associated with age at death (HR 1.0, 95% CI 0.6–1.8, $p = 0.9$), whereas ventilation for more than 16 h/d, use of a mechanical insufflation–exsufflation device, and gastrostomy tube feeding showed a significant effect in reducing the risk of death.

Conclusion: Survival in spinal muscular atrophy type 1 patients has increased in recent years, in relation to the growing trend toward more proactive clinical care.

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GLOSSARY

BiPAP = bilevel positive airway pressure; **HR** = hazard ratio; **MI-E** = mechanical insufflation–exsufflation; **SMA** = spinal muscular atrophy; **YOB** = year of birth.

Spinal muscular atrophy (SMA) is one of the most common and devastating single gene disorders in childhood, with an incidence of approximately 1 in 6,700.¹ It is an autosomal recessive motor neuron disease caused by a homozygous deletion of the survival motor neuron gene on chromosome 5q13. Further classification of clinical subtypes is based on age at onset and highest motor milestone achieved. There is an association between age at onset and disease severity.² SMA type 1, or Werdnig–Hoffman disease, is the most severe subtype of SMA with age at onset before age 6 months. These children never acquire the ability to sit independently, and the majority were traditionally thought to die before their second birthday.^{3,4}

In recent years, more proactive management, including pulmonary and nutritional interventions, has been incorporated into clinical practice.⁵ Noninvasive pulmonary sup-

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port has been increasingly used since its introduction in the early 1990s, along with gastrostomy tube feeding that protects against aspiration and maintains adequate nutritional intake.⁶ These advances in management may have had an impact on the natural history of SMA. There is, however, a paucity of studies providing survival data for SMA patients in the past 10 years, and many of the available studies do not include a North American population. Assessment of the possible impact of recent changes in care on the survival of SMA patients is important for clinical care, counseling, and clinical trials. The objective of this study was to assess whether there has been a change in survival in patients with SMA type 1 between 1980 and 2006. Specifically, we hypothesized that survival of recently born children with SMA type 1 has

improved, and that this change is related to more proactive clinical care.

METHODS Patients and procedure. Data were obtained from the International Spinal Muscular Atrophy Patient Registry, established in 1986, which is coordinated by the Department of Medical and Molecular Genetics at Indiana University and funded by the lay organization Families of SMA. Recruitment methods for the registry include Web sites (Indiana University and links to Web sites of lay organizations) and pamphlets. The registry prospectively collects data through voluntary participation of patients and their families who provide initial and annual follow-up information. The registry collects information on the patient's medical history, family history, and survival status. Information on socioeconomic status and details of genetic testing results have not been obtained. The registry questions are easily understood and are answered by a family member knowledgeable about the patient's medical condition or the patient himself/herself. All data entry is duplicated and cross checked, and data are queried for inconsistency or invalid entries. When a query cannot be resolved based on information provided in the questionnaire, staff from the Indiana Registry contact the family for clarification. To conform to the Health Insurance Portability and Privacy Act, all information provided by the Indiana Registry for this study was deidentified.

In addition to the demographic, clinical, and survival status information prospectively collected on all registry participants, a one-page retrospective questionnaire was developed to obtain more detailed clinical information, including relevant clinical care interventions, and to update the survival data obtained through the registry. Before sending the questionnaire to participants in this study, the questions were reviewed by SMA parents and improvements to clarity and language were made according to parent feedback. Questionnaires were mailed by registry staff to parents of all patients registered as having SMA type 1. The questionnaires were returned to the registry, where the information was deidentified before being sent for analysis. Information collected included SMA type (1, 2, or 3, based on highest motor milestone achieved), date of birth and death (month and year), age at symptom onset, age at diagnosis, genetic confirmation, tracheostomy, use of noninvasive [e.g., bilevel positive airway pressure (BiPAP)] or invasive ventilation (age started, number of hours used, age ventilation was used for more than 16 h/d), use of a mechanical insufflation-exsufflation (MI-E) device, gastrostomy tube feeding, and use of a "special amino acid diet." This diet has been advocated by parents who suggested this term to describe a diet based on elemental amino acids.⁷

Only patients with SMA type 1 were included in the analysis, defined as those with onset before age 6 months and who were never able to sit unsupported. The questionnaire was mailed to 391 registry patients who were reported as having SMA type 1. One hundred ninety-two questionnaires were returned, resulting in a 49.1% response rate. Of these 192 patients, 151 patients met the definition of SMA type 1; 9 patients had onset after age 6 months, and 32 patients did not meet the definition of SMA type 1 based on highest motor milestone achieved. One additional patient was excluded because no ventilatory support was used until age 21 years, making an SMA type 1 diagnosis clinically implausible. The remaining 150 patients included two pairs of twins, three

Table 1 Demographic and clinical characteristics of spinal muscular atrophy type 1 patients who remained alive and who died as of the censoring date

Variable	Alive (n = 63)	Deceased (n = 80)	Total (n = 143)
Male, %	47.6	52.5	50.3
Continent, %*			
North America	77.8	95.0	87.4
Other	22.2	5.0	12.6
Ethnicity, %			
White	84.1	82.5	83.2
African American	0.0	6.3	3.5
Hispanic	3.2	1.3	2.1
Other	12.7	10.0	11.2
Age at symptom onset, mean (SD), mo*	3.3 (1.7)	2.0 (1.5)	2.5 (1.7)
Age at diagnosis, mean (SD), mo*	6.1 (2.6)	3.4 (2.5)	4.6 (2.9)
Genetic testing, %*	92.1	53.8	70.9
Tracheostomy, %*	44.4	13.8	27.3
Ventilation, %**	92.1	32.5	58.7
Ventilation > 16 h/d, %**	52.4	18.8	33.6
MI-E device, %*	68.3	13.8	37.8
Gastrostomy tube feeding, %*	90.5	37.5	60.8
Amino acid diet, %*	56.5	10.0	30.3
YOB 1995–2006, %*	79.4	35.0	54.5

Total n: 141 for age at symptom onset, 142 for age at diagnosis, 141 for genetic testing, and 142 for amino acid diet.

* $p < 0.05$ for the comparison deceased vs alive.

* Includes noninvasive (e.g., bilevel positive airway pressure) and invasive ventilation.

MI-E = mechanical insufflation-exsufflation; YOB = year of birth.

other pairs of siblings, and a set of three siblings. For each set of siblings, we retained the sibling first enrolled in the registry and excluded the other seven siblings from the analysis. Thus, the analysis included 143 SMA type 1 patients.

The protocol for this study was approved by the Columbia University Medical Center Institutional Review Board, the Indiana University Institutional Review Board, and the International Spinal Muscular Atrophy Patient Registry Oversight Committee.

Data analysis. Survival data were censored on September 1, 2006. Given that BiPAP was increasingly used after its introduction in the early 1990s, we dichotomized the sample by year of birth in patients born in 1980–1994 and those born in 1995–2006. This resulted in two groups of similar size (65 vs 78 patients). We compared demographic and clinical characteristics of SMA patients according to alive/deceased status as of the censoring date and according to year of birth using Student's *t* test for continuous variables and χ^2 test or Fisher exact test for categorical variables.

The Kaplan–Meier method was used to calculate survival probabilities and plot survival curves of patients born in 1980–1994 and those born in 1995–2006, and the log-rank test was used to compare survival in the two groups. These analyses were conducted using two outcomes: 1) age at death and 2) either age at death or age at ventilation for more than 16 h/d (includes noninvasive ventilation [e.g., BiPAP] and invasive ventilation). In each case, age as of the censoring date (September 1, 2006) was used for patients who did not

experience the respective events, i.e., death and either death or ventilation for more than 16 h/d. In addition, Cox proportional hazards models were used to evaluate the association of year of birth (1995–2006 vs 1980–1994) with age at death. We first included only year of birth as a predictor variable in the model, and then repeated the analysis controlling for demographic and clinical care variables that were significantly different when comparing patients according to alive/deceased status and year of birth. A two-sided 0.05 level of significance was used in all analyses.

RESULTS Patients whose parents did not respond to the mail-in questionnaire (*n* = 199) were not significantly different from patients whose parents responded to the questionnaire (*n* = 192) in sex, ethnicity, year of birth (1980–1994 vs 1995–2006), age at diagnosis, and proportion with genetic testing. Patients whose parents did not respond to the questionnaire were more commonly from continents other than North America (24.6% vs 16.1%, *p* = 0.04) than patients whose parents responded to the questionnaire.

The demographic and clinical characteristics of the 143 patients who met inclusion criteria are summarized in table 1. Of the 143 patients, 38 (26.6%) were deceased at the time of enrollment into the registry (47.7% among patients born in 1980–1994 and 9.0% among those born in 1995–2006). Eighty patients (55.9%) died before the censoring date, September 1, 2006 (mean age at death 20.2 months, SD 35.4, median 8.0, range 1.0–193.5). Patients who remained alive as of the censoring date had significantly higher age at onset and age at diagnosis, were significantly less often from North America, and were significantly more likely to have had respiratory or nutritional interventions than those who died (table 1). Similarly, when comparing patients according to year of birth, those born in 1995–2006 had significantly higher age at onset and age at diagnosis, were significantly less often from North America, and were significantly more likely to have had respiratory or nutritional interventions than those born in 1980–1994 (table 2). Among patients born in 1980–1994, 52 (80.0%) had died as of the censoring date (mean age at death 19.1 month, SD 38.7, median 7.3, range 1.0–193.5), and among those born in 1995–2006, 28 (35.9%) had died as of the censoring date (mean age at death 22.1 month, SD 28.6, median 10.0, range 2.5–112.0).

Survival plots are shown in the figure. When using death as the event, there is a significant difference in survival between patients born in 1980–1994 and those born in 1995–2006 (log-rank test statistic 22.9, *p* < 0.001). Median survival time was 8.5 months for patients born in 1980–1994 and indeterminate for those born in 1995–

Table 2 Demographic and clinical characteristics of spinal muscular atrophy type 1 patients born in 1980–1994 and born in 1995–2006

Variable	YOB 1980–1994 (n = 65)	YOB 1995–2006 (n = 78)
Male, %	52.3	48.7
Continent, %*		
North America	96.9	79.5
Other	3.1	20.5
Ethnicity, %		
White	84.6	82.1
African American	3.1	3.8
Hispanic	1.5	2.6
Other	10.8	11.5
Age at symptom onset, mean (SD), mo*	2.2 (1.7)	2.8 (1.7)
Age at diagnosis, mean (SD), mo*	3.9 (2.9)	5.1 (2.7)
Genetic testing, %*	44.4	92.3
Tracheostomy, %	24.6	29.5
Ventilation, %**	30.8	82.1
Ventilation > 16 h/d, %**	21.5	43.6
MI-E device, %*	7.7	62.8
Gastrostomy tube feeding, %*	40.0	78.2
Amino acid diet, %*	7.7	49.4
Deceased, %*	80.0	35.9

Total *n*: 141 for age at symptom onset, 142 for age at diagnosis, 141 for genetic testing, and 142 for amino acid diet.

**p* < 0.05 for the comparison year of birth (YOB) 1995–2006 vs YOB 1980–1994.

† Includes noninvasive (e.g., bilevel positive airway pressure) and invasive ventilation.

MI-E = mechanical insufflation-exsufflation.

Table 3 Survival probabilities (%)* at different ages (in months) of spinal muscular atrophy type 1 patients born in 1980–1994 and born in 1995–2006, for events death and death or ventilation† for more than 16 h/d

Event, by YOB	12 mo	24 mo	48 mo	120 mo	240 mo
Death					
YOB 1995–2006	79.3	73.9	65.1	50.3	—
YOB 1980–1994	36.9	30.8	26.2	24.6	18.1
Death or ventilation > 16 h/d					
YOB 1995–2006	58.6	47.0	28.2	15.7	—
YOB 1980–1994	26.2	18.5	13.8	10.8	4.6

* Kaplan–Meier method.

† Includes noninvasive (e.g., bilevel positive airway pressure) and invasive ventilation.

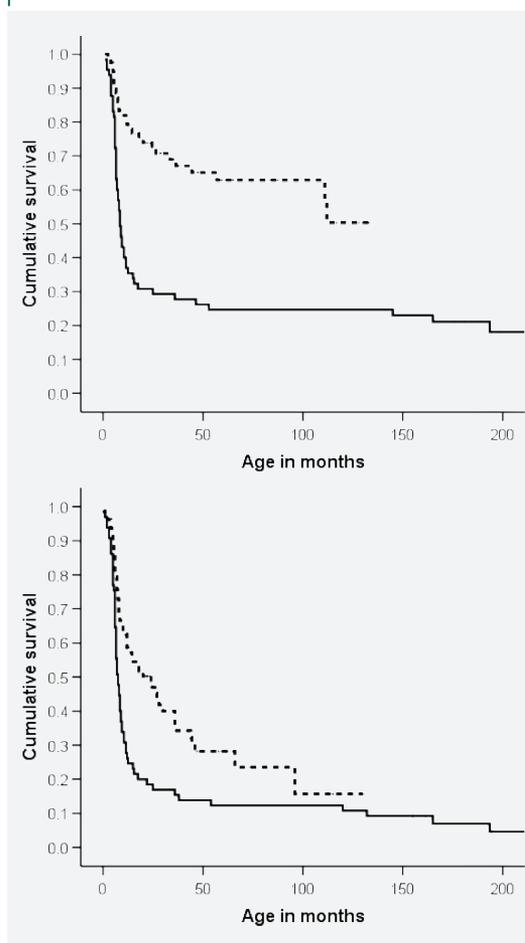
YOB = year of birth.

2006. The survival plot using death or ventilation for more than 16 h/d as the event shows a smaller difference between the two groups, but the difference remained significant (log-rank test statistic 11.2, $p = 0.001$). Median survival time was 7.5 months for patients born in 1980–1994 and 24.0 months for those born in 1995–2006. Survival probabilities for both events by year of birth are provided in table 3.

In a Cox proportional hazards model including only year of birth as a predictor variable, patients born in 1995–2006 had a 70% reduction in the risk of death compared with those born in 1980–1994 (hazard ratio [HR] 0.3, 95% CI 0.2–0.5, $p < 0.001$) over a mean follow-up of 49.9 months (SD 61.1, median 22.0). However, in a model controlling for demographic and clinical care variables, year of birth was no longer significantly associated with age at death (HR 1.0, 95% CI 0.6–1.8, $p = 0.9$). Whereas ventilation for more than 16 h/d, use of MI-E device, and gastrostomy tube feeding showed a significant effect in reducing the risk of death, the amino acid diet did not reach significance (table 4). When the analysis was repeated including only patients with genetic confirmation ($n = 100$), results were similar except for the amino acid diet (HR 0.6, 95% CI 0.2–1.6, $p = 0.3$).

DISCUSSION This study shows that survival of children with SMA type 1 born in 1995–2006 has increased compared with those born in 1980–1994. Although to a substantially smaller degree, this was also observed for survival time free of respiratory insufficiency (analysis using death or ventilation for more than 16 h/d as the event), suggesting that chronic ventilation accounts for part but not all of the recent improvement in survival. Further analyses indicated that ventilation for more than 16 h/d, use of MI-E device, and

Figure Kaplan–Meier survival plots of spinal muscular atrophy type 1 patients born in 1995–2006 (dashed line) compared with those born in 1980–1994 (solid line), for events death (top panel) and death or ventilation for more than 16 h/d (bottom panel)



gastrostomy tube feeding had independent effects on survival and accounted for the observed effect of year of birth (1995–2006 vs 1980–1994) on survival.

Fifty percent of patients born in 1995–2006 have followed a special amino acid diet. This diet has become increasingly popular in recent years among parents of children with SMA, but its efficacy has not been studied. In our study, the amino acid diet had no significant effect on survival in the analysis including all patients, and even less so when the analysis was limited to those patients with genetic confirmation.

Previous studies providing survival data on SMA type 1 patients are summarized in table 5. Comparisons with our study are limited by methodologic differences. The studies before 1995 have reported a mean age at death of 8.8 to 10 months and outliers surviving up to 10 years.^{8–10} In one study published in 1995, survival probab-

Table 4 Lack of association of year of birth (1980–1994 vs 1995–2006) with age at death in spinal muscular atrophy type 1 patients, when controlling for demographic and clinical care variables*

Variable	HR (95% CI)	p Value
Age at symptom onset, mo	0.6 (0.5–0.7)	<0.001
Ventilation > 16 h/d†	0.3 (0.1–0.6)	0.002
MI-E device	0.2 (0.1–0.5)	0.001
Gastrostomy tube feeding	0.5 (0.3–1.0)	0.04
Amino acid diet	0.4 (0.2–1.1)	0.06
YOB, 1995–2006 vs 1980–1994	1.0 (0.6–1.8)	0.9

* All variables were included in the same Cox proportional hazards model; because age at symptom onset and age at diagnosis were correlated ($r = 0.7, p < 0.001$), only age at symptom onset was included in the model; continent (other vs North America) was included in an initial model but was excluded from the final presented model because its effect was not significant.

† Includes noninvasive (e.g., bilevel positive airway pressure) and invasive ventilation.

HR = hazard ratio; MI-E = mechanical insufflation-exsufflation; YOB = year of birth.

ities were 32% at 2 years, 18% at 4 years, 8% at 10 years, and 0% at 20 years.¹¹ The studies published after 2000 have reported an increased mean age at death ranging from 10.4 months to 4 years^{12,13} and outliers surviving up to 24 years.¹⁴ In a 2004 study, the survival probabilities were higher than those reported in 1995: 50% at 1 year, 40% at 2 years, 30% at 4 years, 30% at 10 years, and 30% at 20 years.¹⁵ We found greater survival in our group of patients born in 1980–1994 as well as in the group born in 1995–2006 compared

with the 1995 and 2004 studies, respectively (table 3). This suggests that the sample in our study may differ from the general SMA type 1 population.

Indeed, the possibility of selection bias is one limitation of our study: parents voluntarily signing up for a national registry and responding to questionnaires may be more likely to pursue proactive medical management. The same is also true, however, of parents signing up for clinical trials. A further limitation of the study is that the validity of the information obtained through the registry and the mail-in questionnaire has not been assessed against in-person interviews or medical records. Whereas the registry enrolled and followed SMA patients prospectively, the information obtained through the mail-in questionnaire was retrospective and relied on parents' recall of past medical events. Recall of specific events for patients born in 1980–1994 would tend to be less accurate than for those born in 1995–2006. Age at symptom onset and age at diagnosis were significantly lower in patients born in 1980–1994 than in those born in 1995–2006. Although we cannot exclude the possibility that patients born in 1980–1994 were more severely affected (as reflected by an earlier onset), the differences in age at symptom onset and age at diagnosis may also reflect recall bias due to the advent of genetic testing. When genetic testing was not available, the diagnosis was made clinically. For patients born in recent years, parents' recall may be driven by the age when genetic confirmation was obtained after the clinical diagnosis.

The changes in care over time suggest a shift in attitude among parents of SMA patients partici-

Table 5 Review of literature

Reference	Country	n	Survival data
Byers and Banker, 1961 (8)	United States	25	Age at death (n = 23): mean 10 mo, range 17 d–52 mo; survival (n = 2): mean 17 mo, range 10–24 mo
Ignatius, 1994 (9)	Finland	71	Age at death (n = 69): mean 8.8 mo, median 7 mo, range 2 mo–10 y
Thomas and Dubowitz, 1994 (10)	England	36	Age at death (n = 29): mean 9.6 mo, median 7 mo, range 1–24 mo
Zerres and Rudnik-Schoneborn, 1995 (11)	Germany	197	Survival probability: 32% at 2 y, 18% at 4 y, 8% at 10 y, 0% at 20 y
Borkowska et al., 2002* (14)	Poland and Germany	36	Age at death (n = 18): mean 11 y, range 5–24 y
Bach et al., 2002 (12)	United States	56	Age at death (n = 10): mean 10.4 mo, SD 3.4; survival (n = 46): mean 50.8 mo, SD 42.3
loos et al., 2004 (13)	France	68	Onset 0–3 months: age at death (n = 27): mean 18 mo, SD 29; onset 3–6 mo: age at death (n = 9): mean 4 y, SD 4
Chung et al., 2004 (15)	Hong Kong	22	Survival probability: 50% at 1 y, 40% at 2 y, 30% at 4 y, 30% at 10 y, 30% at 20 y

* Patients alive at the end of the study.

† Included only patients surviving >36 months.

pating in the International Registry, paralleling a shift in physician practice and attitude toward respiratory support in SMA type 1.¹⁶ Major advances have been made in the past 10 years in our understanding of SMA, with identification of the SMN gene, development of animal models, and improved understanding of the SMN protein function. This research progress has translated into increased hope for therapeutic advances among families of children with SMA, who are more willing to pursue active medical management.

The results of this study are important for planning future clinical trials in SMA type 1. The recent change in survival time suggests that historic controls may not be suitable and that concurrent controls are likely needed for SMA type 1 trials. Comparing outcomes in current patients with data from historical controls may falsely suggest a treatment benefit. The association of ventilatory support with longer survival may indicate the need to use outcome measures other than time to death. Time to death or ventilation greater than 16 h/d may prove to be a better outcome measure in this patient population.

The results of this study may also impact clinical care. Physicians should be aware of the prolonged survival in SMA type 1 patients and offer families updated prognostic information when counseling. Now surviving into school age, more attention should be placed on assisting these children with adaptive measures to enable them to participate successfully in school and their environment.

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