Pathophysiological Insights Derived by Natural History and Motor Function of Spinal Muscular Atrophy

Michelle A. Farrar, MBBS[1,2], Steve Vucic, MBBS, PhD[1,3], Heather M. Johnston, MBChB[2], Desirée du Sart, MBBS, PhD[4], and Matthew C. Kiernan, MBBS, PhD, DSc[1,5]

Objective To examine the natural history of spinal muscular atrophy (SMA) to gain further insight into the clinical course and pathogenesis.

Study design Survival pattern, age of onset, and ambulatory status were retrospectively analyzed in 70 patients with SMA with deletions of the survival motor neuron 1 genes that presented to a specialized neuromuscular clinic. The Kaplan-Meier method was used to obtain survival curves. Hammersmith Functional Motor Scale-Expanded and abductor pollicis brevis compound muscle action potential amplitudes were assessed in 25 of the surviving cohort and correlated with survival motor neuron 2 copy number.

Results Survival probabilities at ages 1, 2, 4, 10, 20, and 40 years were 40%, 25%, 6%, and 0%, respectively, for patients with SMA type 1; 100%, 100%, 97%, 93%, 93%, and 52% for patients with SMA type 2 and all patients with SMA type 3 were alive (age range 7-33 years). There were significant associations between age of onset and long-term outcome, specifically survival in SMA type 1 ($P < .01$) and Hammersmith Functional Motor Scale-Expanded ($P < .0001$), and compound muscle action potential ($P = .001$) in SMA types 2 and 3. Motor function in patients with long-standing SMA reduced over prolonged periods or remained stable. Survival motor neuron 2 copy number related to continuing changes in motor function with age.

Conclusion The natural history of SMA suggests considerable early loss of motor neurons, with severity related to differences in the number of remaining motor neurons. As the ensuing chronic course in milder phenotypes suggests relative stability of remaining motor neurons, the maximal therapeutic window presents early. *(J Pediatr 2013;162:155-9)*.

Spinal muscular atrophy (SMA) is characterized by muscle weakness and atrophy due to degeneration of spinal and lower brainstem motor neurons.[1] The identification in most patients of homozygous disruption of the survival motor neuron 1 (*SMN1*) gene as the genetic basis of SMA[2] confirmed a monogenic disorder and thereby unified numerous historical descriptions. In addition, quantitation of the survival motor neuron 2 (*SMN2*) genes related to clinical phenotype and highlighted the variable clinical course, with a broad and continuous spectrum of severity and prognosis.[3-5] With a carrier frequency of 1 in 41, SMA remains the leading genetic cause of infant death.[6] Despite an emerging understanding of the molecular biology and pathogenesis of SMA,[7] the timing of motor neuron degeneration and rate of progression remain unresolved issues, critical to identifying therapeutic windows.

In contrast to the relentless decline expected across a spectrum of neurodegenerative diseases, for example amyotrophic lateral sclerosis, patients with SMA tend to maintain their same level of weakness over many years, some with increasing stability apparent over time.[8] An important caveat applies to infants with SMA with severe weakness. In addition, the most appreciable loss of strength is apparent initially, with varying time scales according to severity.[9] These observations have underpinned the alternate hypothesis of a disorder of neurodevelopment and apoptosis.[10] An age-dependent decline in compound muscle action potential (CMAP) amplitudes and motor unit number estimation values in SMA types 1 and 2, associated with functional decline provides objective support for denervation during childhood and adolescence,[11] yet the natural history in long-standing SMA has not been determined. The aims of the present study were to develop an understanding of the unusual clinical course of SMA by means of determining the natural history of survival motor neuron (SMN)-related SMA from a large cohort of

CMAP	Compound muscle action potential
HFMS-E	Hammersmith Functional Motor Scale-Expanded
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1
SMN2	Survival motor neuron 2

From the [1]Neurosciences Research Australia, Randwick; [2]Department of Neurology, Sydney Children's Hospital, School of Women's and Children's Health, University of New South Wales; [3]Department of Neurology, Westmead Hospital, Western Clinical School, University of Sydney, Sydney, Australia; [4]Molecular Genetics Laboratory, Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Parkville, Victoria, Australia; and [5]Prince of Wales Clinical School, University of New South Wales, Randwick, Sydney, Australia

M.F. received grant support from the National Health and Medical Research Council of Australia (Medical Postgraduate Scholarship, ID568915). S.V. serves on the scientific advisory board for Novartis, Merck Serono Australia, and Bayer Schering Australia, and as a medical consultant for Merck Serono Australia. M.K. serves as Editor in Chief of the *Journal of Neurology, Neurosurgery and Psychiatry* (BMJ Group). The other authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2012.05.067

genetically defined patients and, thereby, provide insight into the timing and processes of neurodegeneration.

Methods

The present study incorporated patients that presented to a specialized combined pediatric and adult neuromuscular clinical service from 1995-2010. These dates were selected as diagnostic genetic testing identifying homozygous deletions of exons 7 and 8 of the *SMN1* gene commenced in 1995.[2] As such, inclusion criteria were the clinical and genetic diagnosis of SMA, with SMN-related disease. Other forms of SMA, unlinked to the SMN gene, have very different natural histories and consequently were excluded. The study was approved by the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee.

The classification of SMA was based on age of onset and achievement of motor milestones as follows[12]: children with SMA type 1 never attained independent sitting and had hypotonia within the first 6 months; SMA type 2 manifested during the first 18 months and children were able to maintain sitting unassisted but they never walked independently; and SMA type 3 attained the ability to walk unaided. Patients with SMA type 3 were subdivided into SMA type 3a with onset before 3 years of age and those with onset after 3 years into SMA type 3b. Routine clinic evaluations incorporated clinical assessment of strength, functional, respiratory, nutritional, and orthopedic functions. Noninvasive ventilation has been routinely offered and introduced as a standard of care for patients with SMA types 2 and 3 over the past decade.

The following outcome variables were documented: classification of SMA, sex, parental report of age of onset, age of death, disease duration, and respiratory and nutritional management. Ambulation status and age of loss of ambulation was recorded in patients with SMA type 3.

Cross-sectional assessments of motor function and *SMN2* copy number [6,13] were determined in a subset of patients with SMA type 2 and 3 with long-standing disease. Motor function was assessed using the Hammersmith Functional Motor Scale-Expanded (HFMS-E),[14] possible score range 0-66, and abductor pollicis brevis CMAP amplitude, with median nerve stimulation at the wrist and measurement of the negative peak.[15] Bipolar electrodes were used to locate the optimal stimulation site for each patient. The CMAP was recorded using surface electrodes (4620 M; Unomedical Ltd, Birkerød, Denmark) positioned over the abductor pollicis brevis muscle with the active electrode at the motor point and the reference electrode 4 cm distal. All neurophysiological testing was performed by a single experienced neurophysiologist.

Data Analyses

Survival data were censored on December 31, 2010. Survival probabilities were calculated by the Kaplan-Meier method and the Mantel-Hansel test was used to compare curves. Demographic data were expressed as mean ± SD of the mean. Differences in means were tested with Student unpaired *t* test. A probability (*P*) value of <.05 was considered statistically significant. Correlations between neurophysiologic, genetic, and clinical assessments were analyzed by Spearman rank correlation coefficient. A probability (*P*) value of <.05 was considered statistically significant.

Results

A clinical and genetic diagnosis of SMA was confirmed in 70 patients during the study period from 1995-2010. Patient demographics, classifications, disease course, and functional status for the entire study cohort are summarized in the Table. There were no significant sex differences among patients with SMA types 1 or 2. Patients with SMA 3b demonstrated a female predominance (4:1).

As might have been expected, qualitative and subjective parental reports of the initial clinical manifestations of SMA varied, particularly between SMA types. Hypotonia and poor head control were universal early concerns among SMA type 1 parents. Slow attainment of early gross motor milestones and failure to walk were common initial parental concerns among infants with SMA type 2. Frequent falls, associated with difficulties walking or climbing stairs were frequently reported as initial symptoms among patients with SMA type 3a. In contrast, patients with SMA type 3b generally reported difficulties in actitivies as early manifestations.

Survival Probabilities

The survival probabilities for the entire SMA cohort are depicted as survival curves (Figure 1). At the time of censoring, 95% of patients with SMA type 1 had died from respiratory failure and 1 patient was alive aged 29.6 months without respiratory support. Among the deceased patients with SMA type 1, 5% were managed with noninvasive respiratory support and gastrostomy nutrition; 1 patient died aged 56 months. Interestingly, 95% of families with

Table. Demographics, classification, and functional status of patients with SMA

SMA type	Number	Sex M:F	Age of onset (mo)	Deceased (%)	Nonambulatory (%); censor age (y)	Ambulatory (%); censor age (y)
1	20	11/9	2.1 ± 2.2	95	5; 2.5	0
2	31	16/15	11.7 ± 4.1	15	84; 17.3 ± 9.4	0
3a	14	6/8	18.0 ± 5.4	0	79; 27.5 ± 10.9	21; 20.4 ± 15.2
3b	5	1/4	137 ± 26	0	0	100; 26.7 ± 4.7

Ages are displayed as mean ± SD. The age of the surviving patients in each subgroup at conclusion of the study is termed "censor age."