The International Classification for spinal muscular atrophy (SMA) is based on age of disease onset and maximum function achieved (MFA). The onset of SMA I is less than 6 months of age and the patients sit with support only. The age of onset of SMA II is more than 6 months and the patients develop the ability to sit independently. The onset of SMA III is more than 18 months and the patients can walk independently. This classification scheme was developed for the purpose of establishing homogeneous groups of patients. For purposes of establishing a prognosis, the MFA is more helpful than the age of onset. Recognizing this principle, it is necessary to monitor the development of SMA prior to rendering a prognosis because some patients with SMA will experience improved function during toddler years.

In this paper, the SMA nomenclature will refer to MFA rather than to age of onset. SMA I will refer to patients whose MFA was sit with support, and SMA II will refer to those patients who were able to sit independently. We have added a fourth category, namely, those patients who could walk with assistance only as their MFA, which we designate as SMA IIIa. SMA IIIb will refer to patients who could walk independently. Predicting the course of SMA I (Werdnig-Hoffmann disease) has been well established. Predicting the course of SMA II, SMA IIIa and SMA IIIb, on the other hand, has not been well delineated. This inability to establish a prognosis at the time of diagnosis, or shortly thereafter, has been a serious problem for patients, families, and physicians. The purpose of this study is to establish guidelines for predicting functional changes in SMA patients who walk, walk with assistance, and sit independently as their MFA. We also offer some observations about other function changes in SMA.

Methods. Patients with SMA were enrolled in a three institution project over a 2-year period to study prospectively the natural course of disease. (DCN/SMA group; Texas Scottish Rite Children's Hospital, Cincinnati Children's Hospital and Medical Center, Newington Children's Hospital). Each subject fulfilled the following criteria: onset of weakness before age 5 years; evidence of denervation by EMG or muscle biopsy; normal nerve conduction velocity; no sensory deficit; and a signed informed consent. The patients were evaluated serially during a 6-year period. Strength, range of motion, and forced vital capacity measurements as well as function evaluations (table) were performed during each visit. The patients were given an unlimited amount of time to accomplish the requested functions, which were evaluated by observation.

Most patients refused to cooperate with rolling and crawling functions (Table items 3, 4, 8 to 10, 18, 21); thus these were eliminated from the analyses. We analyzed the age of disease onset and the length of time that the participants continued to perform a particular function. Kaplan-Meier survival curves were developed for those patients who walked (SMA IIIb), walked or stood with assistance (SMA IIIa), and sat independently when placed (SMA II). A log rank test was used to compare age of onset and function loss within each of these three groups.

Results. One hundred fifty-nine patients were enrolled during the first 2 years of the project. Fourteen patients were examined prior to age 1; 59 between 1 and 5 years; 46 between 5 and 15 years of age; and 40 were more than 16 years old when first examined. There were 75 males and 84 females in the study group. Subjects were classified in four groups according to the maximum function achieved: walk independently (SMA IIIb), walk with assistance (SMA IIIa), sit independently (SMA II), and sit with support (SMA I). History or observation determined that 59 patients were able to walk independently at some time in their lives. 27 patients could walk with assistance. 53 patients were able to sit
Fifty-nine patients who walked independently as their best function achieved were arbitrarily divided into two categories, those whose disease onset was prior to age 2 years and those whose disease onset was after age 2 years. The log rank test showed a significant difference between the two groups (p=0.001). The former group lost walking ability at a median age of 12 years; the median for walking loss for the latter group was 44.2 years (figure 1). Twenty seven patients who walked with assistance were divided arbitrarily into those whose disease onset was after age 2 years. The log rank test showed a significant difference between the two groups (p=0.001). The former group lost walking ability at a median age of 12 years; the median for walking loss for the latter group was 44.2 years (figure 1.) Twenty -seven patients who walked with assistance were divided arbitrarily into those whose disease onset was after age 2 years. No significant differences were detected - the Kaplan - Meier curve showed that 50% lost this ability by a median age of 7 years; no one was walking with assistance after age 14 years (figure 2). Fifty-three patients who could sit independently as their best function achieved were divided into the same two groups. A statistically significant difference between age of onset and length of time in these categories was not achieved. The Kaplan-Meier curve showed that 75% of patients in this category were still sitting after age 7 years; the median age before sitting independently was lost was 14 years (figure 3).
Figure 1. Kaplan-Meier plot showing the proportion of patients who could walk as their best function and are still maintaining that function. Two distinct plots are noted as determined by age of onset in years. (<2 Years and >=2 Years)

Figure 2. Kaplan-Meier plot showing the proportion of patients whose best function was walk with assistance and are maintaining that function at the indicated age in years.
Discussion. We developed this study to understand the natural course of SMA II and III. All patients were asked the same questions and examined according to a methodology that is valid and reliable. This obviates some of the flaws in previous studies that were performed retrospectively, by questionnaire, or by different protocols and methodologies.

Patients with SMA lose function over time. This function loss occurs slowly and appears to be related primarily to MFA, although knowledge of age of onset provides helpful information. In those patients who walked independently (SMA IIIb) and whose age of onset was more than 2 years, walking was maintained for a median of 44 years. If the age of onset was less than 2 years, independent walking ability was lost at a median age of 12 years. Patients whose best function was walk with assistance (SMA IIIa) lost this ability by the median age of 7 years. Patients whose best function was sitting independently (SMA II) maintained this ability until a median age of 14 years.

As walking was lost, the patients also lost the ability to raise hands above the head. With few exceptions, most patients in this category could not negotiate the stairs without the help of a rail. As the patients lost the ability to walk independently, they also lost the ability to negotiate stairs. We have been unable to calculate how long patients who walked independently as their highest function will maintain independent sitting skills. We observed one patient in the project whose onset was age 5, who walked until age 45 years, and who lost the ability to sit at age 55 and died of pneumonia and respiratory failure at age 62.

The International Classification was developed primarily to provide a rational basis for gene linkage studies. The system has also been used for prognosis, especially for life expectancy. This study, as well as that by Zerres and Rudnik-Schoneborn clearly demonstrates that MFA, in addition to age of onset, better predicts a patient's ability to maintain one of the major functions such as walking, standing, and sitting independently than does age of disease onset. The results of these studies suggest that the clinician providing the parent/patient advice about the natural course of disease wait until the patient has attained maximum function.
Our conclusions must be considered with the following precautions. Our patients may have been less disabled or different from the general population of SMA patients, although, based on our clinical experience, we think that this concern is of minimal importance. Only six patients were less than age 6 years at the time of this analysis. Their function might improve in the future since patients with SMA in this age group may improve functional abilities; however, if function in these patients did improve, the results and conclusions would not change. The results of this paper are also limited because some of the data used in calculating the Kaplan-Meier curves are determined retrospectively.

Guidelines for the rehabilitation needs and counseling for SMA can be developed, within the limitations discussed above, with a knowledge of age of onset and maximum function reached. These data should provide help to the clinician who will be asked to render a functional prognosis to patients at the time of the diagnosis.

References


5. Thomas NH, Dubowitz V. The natural history of type I (severe) spinal muscular atrophy. Neuromuscul Disord 1994;4:497-502


Editor's note: The following numbers reflect the percentages of patients tested for SMN deletion since this study was complete: Connecticut site: 100% SMN deleted; Texas site: 90% SMN deleted; Cincinnatti site: no figures available.

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