Original article

Natural history in spinal muscular atrophy Type I in Taiwanese population: A longitudinal study

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Abstract

Introduction: Spinal muscular atrophy (SMA) is caused by a defect in the survival motor neuron 1 (SMN1) gene. The Cooperative Study of the natural history of SMA Type I in Taiwan is a retrospective, longitudinal, observational study that helps in further understanding SMA disease progression in patients who have not received disease-modifying therapeutic interventions.

Methods: Case report forms were used to collect demographics; genetic confirmation; SMN2 copy number; treatment patterns; and clinical outcomes including ventilator use, endotracheal tube intubation, tracheostomy, gastrostomy, complications, and survival.

Results: A total of 111 patients with SMA Type I were identified over the study period (1979–2015). Mean (median) age of onset and age at confirmed diagnosis were 1.3 (0.8) and 4.9 (4.4) months, respectively. SMN1 deletion/mutation was documented in 70 patients and SMN2 copy number in 32 (2 copies, n = 20; 3 copies, n = 12). At 240 months, survival probability for patients born during 1995–2015 versus 1979–1994 was significantly longer (p = 0.0057). Patients with 3 SMN2 copies showed substantially longer 240-month survival versus patients with 2 SMN2 copies. Over the 36-year period, mean (median) age at death was 31.9 (8.8) months. As of December 2015, 95 patients had died, 13 were alive, and 3 were lost to follow-up. The use of supportive measures (tracheostomy and gastrostomy) was associated with improved survival.

Conclusions: These data describe the short survival of patients with SMA Type I in Taiwan in the pretreatment era, emphasizing the positive impact of supportive measures on survival.

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Keywords: Spinal muscular atrophy Type I; Natural history; Survival; SMN2 copies

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1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder and the leading inherited monogenetic cause of infant death [1]. There are 4 main clinical subtypes of SMA [1]: Type I is the most common and severe form, which affects approximately 45% of patients with SMA and presents within the first 6 months of life [2]. Infants diagnosed with SMA Type I are unable to sit independently (termed “nonsitters”), lack head control, often show abdominal breathing, and assume a “frog leg” posture when lying [3]. Apart from the recently approved SMA therapies [4,5], multidisciplinary proactive care for SMA Type I includes ventilation support; nutritional, swallowing, and gastrointestinal management; and rehabilitation assistance, with optimization of function and minimization of impairment [6,7]. The TREAT-NMD registry reported the use of invasive and noninvasive ventilation support, nasogastric feeding, and also scoliosis surgery for some patients [8].

Without efficacious intervention, patients with SMA Type I have a median survival of 7.4 months (3–56 months), with the age of onset being reported as a predictive factor of survival [9]. The onset of SMA Type II is between 6 and 18 months of age; the highest motor milestone achieved is sitting independently (termed “sitters”), and patients have a life expectancy to early adulthood [3,9]. Patients with SMA Type III and Type IV typically show onset from 18 months of age (“walkers”) and adulthood, respectively, and show survival into adulthood, with normal life span in SMA Type IV [3,8,9].

SMA results from a deletion or mutation in the survival motor neuron (SMN) 1 gene [3,10], which leads to decreased full-length SMN protein expression and the degeneration of motor neurons in the anterior horn of the spinal cord and brainstem [11]. Diagnosis of SMA now includes genetic confirmation of SMN1 gene deletion or mutation [6]. The nearly identical SMN2 gene produces an aberrantly spliced transcript that results in low levels of full-length SMN protein in those with the disease [12]. All patients with SMA have ≥1 SMN2 copy [12]; healthy individuals usually have between 0 and 3 copies of the SMN2 gene, and SMN2 copy numbers ≥3 have been reported [12,13]. In patients with SMA, disease severity and the amount of full-length SMN protein are primarily determined by the copy number of the SMN2 gene [11]. Patients with ≥3 SMN2 copies show milder symptoms of SMA than those with 2 SMN2 copies [9,11].

The US Food and Drug Administration approved nusinersen (Spinraza®) in December 2016 for the treatment of all types of SMA [4,6] and onasemnogene abeparvovec-xioi (Zolgensma®) in May 2019 for the treatment of children <2 years of age with SMA [5]. Prior to those approvals, standards of care were supportive and focused mainly on utilization of nutritional and respiratory care [6,7]. Noninvasive ventilation is generally provided as an alternative intervention that progresses to more chronic use, coupled with airway clearance techniques [2]. Noninvasive mechanical ventilation without intubation was introduced to patients with SMA in Taiwan in 2007 for acute and chronic pulmonary care [14]. Gastrostomy tube feeding, which has been shown to reduce the risk of death in patients with SMA Type I [15], can be used when insufficient calorie intake or unsafe oral feeding is of concern [2].

The birth prevalence of SMA in the United States and Europe has been estimated at 8.5–10.3 per 100,000 live births [16–18], and the population prevalence in Europe at 1.9 per 100,000 [19]. Carrier frequency, including in Taiwan, has been estimated as approximately 1/40–1/60 [16,17,20]. The population prevalence of SMA in Hong Kong, China, over 17 years was reported as 1.87 per 100,000 [21], a Japanese study reported a prevalence of 0.5–1.0 per 100,000 [22], and the birth prevalence of SMA in Japan and Taiwan were estimated at 2.7 and 5.8 per 100,000 births, respectively [23,24]. These data indicate broadly similar estimates of SMA in the US and Europe with lower burden suggested in the East Asian region.

In Taiwan, the identification of homozygous deletion of exons 7 and 8 of SMN1 gene for SMA commenced in 1995 [25]. Genetic documentation of SMN1/SMN2 gene dosage for patients with SMA in Taiwan became widely available in 2005 [26,27]. To our knowledge, this is the first time SMA natural history data have been published for the Taiwanese population. The objectives of this study are to describe and characterize disease onset, disease course, and outcomes, including impact of respiratory and nutritional intervention, of patients with SMA Type I in the Taiwanese population during 1979–2015.

2. Materials and methods

2.1. Study design and standard protocol approvals

The Cooperative Study of the natural history of SMA Type I in Taiwan (NCT02466529) is a retrospective study conducted to better understand the progression of patients with SMA Type I—specifically, patients with SMA Type I identified by pediatric neurologists in 17 tertiary centers and 2 secondary care centers throughout Taiwan.

From a total of 19 tertiary centers in Taiwan, 17 tertiary centers were selected based on the following criteria: each center should have a full-time pediatric neurologist on duty, who can provide care for the patients with SMA Type I, and have a pediatric intensive care unit. The other 2 tertiary centers did not meet these criteria, and it was confirmed that there were no
reported cases of SMA (data from the rare disease integrated information management system website by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan). The 17 tertiary centers included in the study are located in the northern, central, southern, and eastern parts of Taiwan. Of the 2 secondary care centers that qualified, one is located in northern and the other in southern Taiwan.

The study was conducted in compliance with the Declaration of Helsinki and regulatory requirements, with approval obtained from Institutional Review Board-II, Kaohsiung Medical University, Chung-Ho Memorial Hospital (KMUHIRB-F(II)-20150011). Owing to the nature of this chart review study, in which information was not linked to individual patients, informed consent was not required.

2.2. Patients

Patients from both urban and rural regions throughout Taiwan were identified at tertiary and secondary care centers with experience of caring for patients with SMA Type I. The diagnostic criteria of enrolled patients with SMA Type I changed upon the advent of widespread SMN genetic testing in 2005 in Taiwan.

The inclusion criteria of this study were consistent with clinical criteria for SMA Type I, and all 111 patients met the following criteria: (1) disease onset at younger than 6 months of age; (2) generalized hypotonia and symmetric weakness, with weakness more severe in the proximal than in the distal part of extremities, and with weakness in the legs greater than weakness in the arms; and (3) absence of tendon reflexes. Besides typical SMA Type I clinical presentation, before 2005, SMA Type I was diagnosed in 41 patients based on additional features: 35 patients showed neurogenic changes in biopsied muscles, 3 showed neurogenic changes in electromyogram, and 3 showed tongue fasciculation and refused to undergo muscle biopsy or electromyogram. After 2005, SMA Type I was confirmed in 70 patients who were found with SMNI gene deletion or mutation in genetic testing.

The study exclusion criteria were disease onset after 6 months of age; SMA Type II, Type III, or Type IV; and non-5q SMA (absence of deletion or mutation of SMN1 gene) after 2005.

2.3. Data collection, analyses, and statistical methods

Data were collected via retrospective chart review through the use of clinical case report forms and medical records for each patient, and included age at symptom onset, age at death, motor milestones (e.g. achieving head control), respiratory intervention, loss of function, and survival time. Survival data are reported from January 1979 through December 2015. The survival probabilities of patients were evaluated for 1979–1994 and then 1995–2015, due to improved access to ventilator or respiratory support from 1995 onward.

Ventilator support data describe the use of airway clearance therapy, including mechanical insufflation/exsufflation (e.g. cough assist devices) and ventilation methods both noninvasive (e.g. bilevel positive airway pressure ventilation) and invasive (e.g. tracheal intubation or tracheostomy ventilation).

Methodologic steps were taken to ensure accurate, complete, and reliable data. The study team was instructed on the study procedures and on how to complete a case report form. All data were entered twice, cross-checked, and queried for inconsistency or invalid entries. When a query could not be resolved based on information provided in the case report, staff contacted the doctor for clarification.

Demographic data were compared using an unpaired t-test. Survival probabilities were calculated using the Kaplan-Meier method; p-values were calculated using log rank, and values <0.05 were considered significant.

3. Results

3.1. Patient characteristics and demographics

Patients were observed over the period 1979–2015, for an overall study duration of 36 years. A total of 111 patients with SMA Type I were identified over this period; data collected up to December 2015 are included in the analysis. Half (57/111; 51.4%) of patients with SMA Type I were male (Table 1). Symptom onset occurred within 2 months of age for 69.4% (77/111) of the total cohort. SMNI gene deletion or mutation was confirmed in 63.1% (70/111) of patients with SMA Type I; however, only 28.8% of patients (32/111) had a documented SMN2 copy number. Of these 32 patients, 20 patients (62.5%) had 2 SMN2 copies and 12 patients (37.5%) had 3 SMN2 copies. The mean age of symptom onset was similar between patients with 2 SMN2 and 3 SMN2 copies (Table 1). SMA symptoms at birth (e.g., paralytic hypotonia, apnea, or cyanosis) were noted in 33.3% of patients (37/111).

3.2. Clinical outcomes

Ventilator support was utilized for 67.6% (75/111) of patients with SMA Type I (Table 2), and was started at a mean (median) age of 5.4 (3.9) months.

As of December 2015, 95 (85.6%) patients with SMA Type I had died, 13 (11.7%) were alive (no patients achieved the motor milestone of head control), and 3 (2.7%) were lost to follow-up. Over this 36-year period, mean (SD) age at death was 31.9 (52.1) months (median [range], 8.8 [0.5–259.5] months) (Table 2). The complications experienced most frequently during
hospitalization by patients with 2, 3, an unknown number of SMN2 copies, or overall were pneumonia (75.0%, 75.0%, 72.2%, and 73.0% of patients, respectively), acute respiratory failure (55.0%, 33.3%, 29.1%, and 34.2%), upper GI bleeding (35.0%, 25.0%, 12.7%, and 18.0%) and sepsis (15.0%, 25.0%, 7.6%, and 10.8%) (Supplementary Table 1).

At the December 2015 data cutoff, the overall median survival time of patients with SMA Type I was numerically longer for the 73 patients born between 1995 and 2015 (11.1 [range: 1.4–221.9] months) compared with 35 patients born between 1979 and 1994 (5.7 [range: 0.5–259.5] months). The 240-month survival probability of patients diagnosed between 1995 and 2015 was significantly higher (p = 0.0057) compared with patients diagnosed between 1979 and 1994 (Fig. 1).

Over 240 months, the survival probability of patients with SMA Type I and 3 SMN2 copies (n = 12) was higher (p = 0.0687) than those with 2 SMN2 copies (n = 20, Fig. 2). The median (range) survival times were 60.7 (2.2–259.5) months for patients with 3 SMN2 copies, which were numerically longer versus patients with 2 SMN2 copies (9.2 [range: 1.4–221.9] months).

The median (range) survival time for patients with undocumented or unknown SMN2 copy number was 8.2 (0.5–157.2) months (Table 2).

### 3.3. Survival probability with and without supportive measures

The log-rank survival probability of patients with SMA Type I over 240 months was significantly

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**Table 1**

Demographic characteristics of Taiwanese patients with spinal muscular atrophy Type I.

| Variable                        | 2 SMN2 copies (n = 20) | 3 SMN2 copies (n = 12) | Unknown SMN2 copies (n = 79) | Overall (N = 111) | P-value |
|---------------------------------|------------------------|------------------------|-----------------------------|-------------------|---------|
| Sex, n (%)                      |                         |                        |                             |                   |         |
| Male                            | 10 (50.0)              | 7 (58.3)               | 40 (50.6)                   | 57 (51.4)         | 0.876   |
| Female                          | 10 (50.0)              | 5 (41.7)               | 39 (49.4)                   | 54 (48.7)         |         |
| SMN1 gene, n (%)*               |                        |                        |                             |                   | 0.281   |
| SMN1 deletion                   | 19 (95.0)              | 12 (100.0)             | 38 (48.1)                   | 69 (62.2)         |         |
| SMN1 mutation                   | 1 (5.0)                | 0 (0.0)                | 0 (0.0)                     | 1 (0.9)           |         |
| Age of symptom onset, n (%)     |                        |                        |                             |                   | 0.604   |
| At birth                        | 8 (40.0)               | 2 (16.7)               | 27 (34.2)                   | 37 (33.3)         |         |
| 0–1 month                       | 1 (5.0)                | 2 (16.7)               | 18 (22.8)                   | 21 (18.9)         |         |
| 1–2 months                      | 2 (10.0)               | 2 (16.7)               | 15 (18.9)                   | 19 (17.1)         |         |
| 2–3 months                      | 4 (20.0)               | 1 (8.3)                | 9 (11.4)                    | 14 (12.6)         |         |
| 3–6 months                      | 5 (25.0)               | 5 (41.7)               | 10 (12.7)                   | 20 (18.0)         |         |
| Age at symptom onset, months^# |                        |                        |                             |                   | 0.657   |
| Mean (SD)                       | 1.8 (1.9)              | 1.2 (1.8)              | 1.2 (1.4)                   | 1.3 (1.6)         |         |
| Median (range)                  | 1.5 (0.0–5.5)          | 0.3 (0.0–6.0)          | 0.5 (0.0–5.5)               | 0.8 (0.0–6.0)     |         |
| Age at confirmed diagnosis, months |                        |                        |                             |                   |         |
| Mean (SD)                       | 4.4 (2.7)              | 5.6 (3.9)              | 4.9 (3.9)                   | 4.9 (3.7)         |         |
| Median (range)                  | 4.4 (0.2–9.5)          | 4.4 (1.4–13.5)         | 4.4 (0.2–24.4)              | 4.4 (0.2–24.4)    |         |

**Table 2**

Clinical characteristics of Taiwanese patients with spinal muscular atrophy Type I.

| Variable                           | 2 SMN2 copies (n = 20) | 3 SMN2 copies (n = 12) | Unknown SMN2 copies (n = 79) | Overall (N = 111) |
|------------------------------------|------------------------|------------------------|-----------------------------|-------------------|
| Ventilation use (any), n (%)*      | 17 (85.0)              | 10 (83.3)              | 48 (60.8)                   | 75 (67.6)         |
| Age at initial ventilation (any), months |                         |                        |                             |                   |
| Mean (SD) age                      | 5.9 (4.8)              | 10.9 (14.7)            | 4.1 (3.2)                   | 5.4 (6.5)         |
| Median (range) age                 | 3.5 (1.0–15.0)         | 5.0 (1.0–48.0)         | 3.5 (0.0–11.5)              | 3.9 (0.0–48.0)    |
| Deaths, n (%)                      | 15 (75.0)              | 5 (41.7)               | 75 (94.9)                   | 95 (85.6)         |
| Survival, months                   |                         |                        |                             |                   |
| Mean (SD)                          | 32.4 (59.4)            | 84.0 (87.8)            | 23.6 (36.7)                 | 31.9 (52.1)^#     |
| Median (range)                     | 9.2 (1.4–221.9)        | 60.7 (2.2–259.5)       | 8.2 (0.5–157.2)             | 8.8 (0.5–259.5)   |

SD, standard deviation; SMN, survival motor neuron.

* N = 70.

^ The small sample size and large variability should be taken into account when interpreting these data.

# 3 patients were lost to follow-up.

Over 240 months, the survival probability of patients with SMA Type I and 3 SMN2 copies (n = 12) was higher (p = 0.0687) than those with 2 SMN2 copies (n = 20, Fig. 2). The median (range) survival times were 60.7 (2.2–259.5) months for patients with 3 SMN2 copies, which were numerically longer versus patients with 2 SMN2 copies (9.2 [range: 1.4–221.9] months). The median (range) survival time for patients with undocumented or unknown SMN2 copy number was 8.2 (0.5–157.2) months (Table 2).
improved in those who received tracheostomy intervention versus those who did not receive tracheostomy intervention (p < 0.0001) (Supplementary Fig. 1). As of December 2015, the mean survival time of patients who received tracheostomy (p < 0.0001) or gastrostomy (p = 0.0145) was significantly improved versus patients who did not receive these interventions (Supplementary Table 2). The use of a mechanical insufflation-exsufflation device, endotracheal intubation, or nasogastric feeding showed no significant difference in survival between those patients who did or did not receive them (Supplementary Table 2). Among 8 patients with SMA Type I undergoing continued follow-up, all received ventilator care, 3 received tracheostomy, 6 received ventilation for >18 h per day, and 2 used a ventilator during sleep. Three of these patients received nutritional care with nasogastric feeding, and 2 received gastrostomy. None of these patients were able to achieve head control, active limb movement, or active palmar grasp.

4. Discussion

At 36 years, the Cooperative Study of the natural history of SMA Type I in Taiwan has one of the longest observational periods for a study of SMA. Our results show greater survival of patients diagnosed between 1995 and 2015 compared with those diagnosed between 1979 and 1994. Our findings also demonstrate survival-related benefits of supportive measures, such as respiratory and nutritional support. Although these results are consistent with those of other previously published studies [15,28], this is the first time these findings have been demonstrated in the Taiwanese population.

SMA survival data from before and after the incorporation of supportive care into national policy were compared and, to our knowledge, have not been reported previously. We found that patients with SMA Type I diagnosed between 1995 and 2015 had improved survival compared with those diagnosed between 1979...
and 1994, and there was no significant difference in survival probability of patients who did not receive ventilators or respiratory support between 1995 and 2015 (n = 8), and between 1979 and 1994 (n = 10) (data not shown). This agrees with previous reports and is largely expected, given the beginning of full reimbursement following the 1995 introduction of national health insurance in Taiwan not only for the expenses of critical care and ventilator and nutritional support in hospital, but also for long-term respiratory care at home. With sufficient care at an affordable cost, the survival probability of patients with SMA Type I in our study has improved after the implementation of national health insurance. The improved survival of patients with SMA Type I over the last decade also indicates that data should be carefully chosen for use in clinical trials of SMA as a natural history control group, only including recent data with similar supportive care measures, as the interventions allowed in the clinical trials.

When the data were analyzed according to SMN2 copy number, the mean age of symptom onset was similar for patients with 2 or 3 SMN2 copies; however, the probability of survival for patients with 3 SMN2 copies was longer over the 240-month follow-up period, which may be due to high complications of acute respiratory failure and gastroesophageal reflux in patients with SMA Type I with 2 SMN2 copies (Supplementary Table 1). These results are consistent with previous studies that demonstrated an inverse correlation between SMN2 gene copy number and disease severity [12,29].

Our analysis also demonstrated positive impact of supportive measures on survival, with significantly improved survival observed in patients with SMA Type I who received tracheostomy or gastrostomy support, which is again consistent with previous observations [15]. Current guidelines recommend proactive airway clearance and ventilation support early in the disease process in infants with SMA Type I, or gastrostomy if insufficient calorific intake or oral feeding is of concern [6,7]. Findings from this current study support the benefit of these interventions in patients with SMA Type I. The probability of survival for patients who received invasive ventilation support was numerically higher than for those who did not receive this intervention. Oskoui et al. reported significant improvements in the survival of patients with SMA Type I in relation to the growing trend toward more proactive respiratory support (ventilation for more than 16 h per day, use of a mechanical insufflation-exsufflation device), and nutritional care (gastrostomy tube feeding) [15]. The relatively high percentage of patients who received ventilation support in our study (75/111 [67.6%]) highlights the severity of symptoms experienced by patients with SMA Type I.

Strengths of this study include the large sample size, long duration of retrospective data collection, and high quality of data extracted from medical records into case report forms to collect data. The population frequency and severity of SMA Type I, however, may be underestimated due to (1) the ongoing evolution of SMA cases and subtype definitions, and (2) the high case fatality rate of SMA, which may have prevented patients from being observed in secondary or tertiary care centers.

Furthermore, prior to 2005, genetic testing for the identification of the SMN gene was not common in Taiwan; newborn screening is now recognized as essential for early diagnosis and treatment of SMA in the new therapeutic era [23,30]. Among potential limitations of this study is the fact that the analyses of survival by SMN2 gene copy number include only part of the study cohort.

Moreover, selection bias may exist in the recruitment of patients from hospitals, secondary centers, and tertiary centers, as parents of children with SMA Type I who travel to hospitals and care centers may be more proactive, and may obtain earlier treatment than patients with SMA who either die very early in their disease course or are diagnosed at a later stage of the disease. In this study, most patients were recruited from tertiary centers. In addition, when mean age of disease onset (1.3 months) is compared with age at confirmed SMA diagnosis (4.9 months), results indicate that referrals from primary clinics to tertiary centers were relatively delayed.

5. Conclusions

Despite earlier improvements in palliative care in Taiwan, these natural history data demonstrate the high mortality rate, short survival, and delayed diagnosis of SMA Type I, highlighting the need for SMA newborn screening. These results also show improved survival of patients with SMA Type I in Taiwan since 1995, when ventilator and nutritional support were made widely available following the commencement of national health insurance. This study also found an association between increased SMN2 copy number and reduced disease severity in Taiwanese patients with SMA Type I. Given the relatively young age at disease onset and death observed in this cohort of patients with SMA Type I, natural history data show a high need for effective therapies in this area. It is our hope that these data on the natural history of SMA in patients from Taiwan will lead to a better understanding of SMA Type I and serve as a basis for understanding therapeutic impact in future clinical and translational studies.

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Conceived and designed the study: SFO, CSH, WTL, KLL, CCJ, YJJ. Oversaw the study: SFO, CSH, WTL, KLL, CCJ, YJJ. Collected data: SFO, CSH, WTL, KLL, YJJ. SMA Study Group. Analyzed data: SFO, CSH, YJJ. Primary contributors toward development of the manuscript: SFO, CSH, WTL, KLL, CCJ, YJJ.

Competing interests

SFO, CSH, WTL, and KLL: co-principal investigators of the study; nothing to disclose. CCJ: full-time employee of and holds stock/stock options in Biogen. YJJ: principal investigator of the study; personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities for Biogen; research grants and clinical trials funding from Biogen for the ENDPEAR and NURTURE studies; president of non-profit organization Taiwan SMA Families.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2020.07.012.

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