Pain in Spinal Muscular Atrophy: A Questionnaire Study

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ABSTRACT. Objective: This study aimed to reveal the chronic pain prevalence in spinal muscular atrophy (SMA) patients and identify the clinical characteristics of these patients with chronic pain. The pain status was also investigated in SMA patients with chronic pain. Methods: This cross-sectional study was conducted between July 2018 and December 2018. SMA type II and type III patients in Japan were mailed a survey questionnaire. The survey items were chronic pain prevalence, clinical characteristics, and motor function. Patients with chronic pain also answered questions on various pain status parameters: pain intensity, frequency, duration, location using body map, and factors that exacerbated and relieved pain. Results: The questionnaire recovery rate was 61.1%. Sixty-four type II (mean age 17.3 ± 11.7 years) and 22 type III (mean age 44.9 ± 21.6 years) patients were eligible for inclusion. The prevalence of chronic pain in type II and III patients was 40.6% and 40.9%, respectively. Type II patients with chronic pain were more likely to report the inability to sit without manual support than those without pain (p = 0.03). Pain intensity in SMA patients was mild, but pain usually occurred daily, for prolonged durations, most often in the neck, back, and lower extremities. Sitting and high physical activity exacerbated pain the most. Conclusion: The percentage of patients with SMA with chronic pain was high, at above 40%. Moreover, the pain experienced by patients with SMA was low in intensity but frequent and most common in the lower extremities.

Key words: Spinal muscular atrophy, Neuromuscular disease, Pain, Questionnaire survey

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Spinal muscular atrophy (SMA) is a neurogenic muscular atrophy that arises because of spinal motor neuron degeneration, primarily in the anterior horn of the spinal cord11. The morbidity rate for SMA is one per 6000–10,000 individuals15. The symptoms of SMA are progressive and manifest as weakness of muscles in the trunk and proximal upper and lower limbs, respiratory distress, contractures, and scoliosis. SMA is classified into types I through III based on severity and age of onset16. In SMA type I, motor function decreases rapidly from a few weeks after birth, with onset occurring up to 6 months postpartum. Sitting and stabilizing the head and neck are lifelong challenges due to issues with motor function, and use of mechanical ventilation is always necessary. The onset of SMA type II also occurs in infancy, at up to 18 months of age. Type II patients are able to achieve a sitting position, but it is difficult for them to stand or walk unaided. Onset of SMA type III occurs after 18 months of age. Patients are able to walk, but motor symptoms, such as a tendency to fall, appear gradually. Rehabilitation is essential for patients with SMA to maintain and improve motor function and activities of daily living (ADLs). One of the issues encountered by rehabilitation staff and SMA patients is pain.

Patients with slowly progressive neuromuscular disease (NMD), including SMA, commonly experience pain-related problems, increasing fatigue, and impaired ADLs17–19. Previous studies have presented systematic reports on the pain status of patients with Duchenne muscular dystrophy (DMD)20 and amyotrophic lateral sclerosis21. Conversely, as SMA is a rare genetic disease, there have been only few reports of large-scale investigations of pain status in SMA patients22. Patients with NMD have significantly more persistent pain than the general population23–26, but the
incidence and underlying characteristics of pain in SMA patients are not well understood.

Therefore, the primary study objective was to investigate the chronic pain prevalence and clinical characteristics of SMA type II and III patients with pain. The secondary objective was to survey the pain status of SMA patients with chronic pain. The previous study population included only few SMA patients. SMA type I patients were excluded from the subject pool due to the disease’s severity, and SMA type II and III patients were analyzed independently because motor function differs depending on the type. Systematic surveys on the pain status of patients with SMA are useful to understand specific NMDs and for appropriate selection of therapeutic interventions and rehabilitation methods.

Methods

Study design and population

This cross-sectional questionnaire survey was conducted from July 2018 to December 2018. The participants were patients with SMA type II and III and their guardians. The survey method was approved by the SMA Family Association in Japan, and we sent questionnaires to Japanese SMA patients and their guardians. The SMA Family Association comprises patients with SMA types I, II, and III; their family members; and supporting healthcare staff and volunteers. The questionnaire used in this study was self-administered and sent via post, and the responses were collected using reply envelopes. If the patients were less than 18 years old, they were given the option to respond to the questionnaire with assistance from their guardians and to clearly indicate whether their guardians helped them. Patients with SMA type I were excluded because the severity of the disease caused difficulty in accurately assessing pain using questionnaires.

Questionnaire survey items and analysis

The questionnaire was designed by physical therapists, pediatricians, and rehabilitation doctors, referring to a previous study10. In addition, we asked two patients from the SMA Family Association in advance to confirm points that were difficult to understand and terminology when answering the questionnaire. The questionnaire survey items were designed to collect data of clinical characteristics and pain status. The clinical characteristics were sex; age; mechanical ventilation use; electric wheelchair use; presence of spinal fusion; history of tracheotomy, laryngotracheal separation, or gastrostomy; analgesic agents use; and motor function (walking, rolling over/bottom shuffling, and sitting without manual support). For the pain status-related items, we first inquired about chronic pain (pain that persists for ≥3 months) in the muscle, bone, tendons, and skin or nerves. Pain caused by headaches or psychological pain was excluded from analysis11. To understand the clinical characteristic of SMA patients with pain, SMA type II and III were divided into two groups based on the presence or absence of chronic pain, and the clinical characteristic was compared between these two groups. Next, those who answered that they had chronic pain were asked about the pain status: pain intensity, frequency, duration, location, and factors that exacerbated and relieved pain.

Questions related to pain status

A numerical rating scale (NRS)12,13 was used to determine pain intensity. The NRS evaluates pain intensity using an 11-point scale ranging from 0 to 10, wherein 0 indicates no pain and 10 indicates the maximum pain imaginable. The NRS was used to evaluate patients aged 5 years or older14, while those younger than 5 years old were excluded from the analysis. A four-scale rating was presented to describe pain frequency—always present, several times a day, several times a week, and several times a month—while a five-scale rating was presented to describe the duration of continuous pain—not continuous, within 1 hour, 1–12 hours, 13–24 hours, and ≥2 days. The locations of pain were entered as painful locations on a body map15. Multiple answers were allowed if there were multiple locations of pain. These locations were classified into four groups based on the responses: neck/back, upper extremities, lower extremities, and others. The validity and reliability of the evaluation of painful locations using the body map have been confirmed in both children and adults16. The questionnaire had 13 items to determine which factors exacerbated or relieved pain. Previous studies of patients with NMDs, including those with DMD and SMA, were used as a reference to select the items17.

Statistical methods

Chi-square test was used to compare sex; mechanical ventilation use; electric wheelchair use; presence of spinal fusion; history of tracheotomy, laryngotracheal separation, or gastrostomy; analgesic agents use; and motor function (walking, rolling over/bottom shuffling, and sitting without manual support). The unpaired t-test was used to compare the age differences between the two groups. All tests were performed using IBM SPSS Statistics for Windows, version 23 (IBM, Armonk, NY, USA). The level of significance was set at p < 0.05.

Ethics statement

This study was approved by the Ethics Committee of Tokyo Women’s Medical University (approval number: 4462). A written explanation of the study was enclosed in the envelope used to send the questionnaire survey. Only individuals who gave their informed consent to participate were included in the study. In addition, the SMA Family Association ensured that personal information was protected and that the respondents could not be identified when the questionnaires were sent and collected.

Results

Demographic and clinical characteristics

The questionnaire was sent to 221 SMA patients and 135 responded, with a response rate of 61.1%. Among them,
the type classification was 48 SMA type I patients, 64 SMA type II patients, 22 SMA type III patients, and 1 unknown. Table 1 shows the clinical characteristics and motor function of SMA type II and type III patients stratified based on the presence or absence of chronic pain. Spinal fusion was present in 14 type II patients (21.9%) but no type III patients. In terms of motor function, 1 type II patient (1.6%) and 14 type III patients (63.6%) could walk, 14 type II patients (21.9%) and 13 type III patients (59.1%) could roll over/bottom shuffle, and 25 type II patients (39.1%) and 13 type III patients (59.1%) could sit without manual support. In all, 26 type II patients (40.6%) and 9 type III patients (40.9%) reported chronic pain that persisted ≥3 months. SMA type II patients with chronic pain had limited ability to sit without manual support than those without chronic pain (p = 0.03). No other significant differences were observed between SMA type II and type III patients.

**Pain status**

We investigated the pain status of 26 SMA type II patients and 9 type III patients with chronic pain. The mean pain intensity, according to the NRS, was 3.3 ± 1.7 in type II patients and 3.6 ± 1.6 in type III patients. Pain frequencies ranging from “always present” to “several times a day” were considered to indicate high frequency, which was reported by 68.0% of the SMA type II patients and 62.5% of the type III patients. The duration of continuous pain was “within 1 hour” and “not continuous” in 36.0% and 28.0% of the SMA type II patients, respectively, accounting for two-thirds of the whole group. Long-term pain was detected in 62.5% of the SMA type III patients who responded “≥2 days.” The location of pain was most commonly in the lower extremities in both SMA type II and III patients (65.4% and 44.4% of the patients, respectively). Other responses indicated pain in the neck/back and upper extremities (Table 2).

**Discussion**

In this study, we describe the results of a questionnaire survey on pain administered to Japanese SMA type II and III patients and their families. Our results show that almost 40%...
of the SMA type II and III patients experience chronic pain lasting at least 3 months. These findings are in agreement with those of previous reports that many patients with NMD have chronic pain\(^\text{19}\). In particular, Lager et al.\(^\text{19}\) performed a pain survey of patients with NMD, including 17 SMA type II and III patients each, and reported frequent onset of low-intensity pain in the lower extremities and neck. However, the previous study included only few SMA patients\(^\text{19}\). To our best knowledge, this is the first study to survey the characteristics of chronic pain and pain status in SMA patients. We analyzed the survey results of 64 SMA type II patients and 22 type III patients who reported experiencing chronic pain. We observed that only 6 (23.1%) SMA type II patients and 2 (9.1%) type III patients had pain that could sit without manual support, while 19 (50.0%) type II patients without pain were able to do the same (p = 0.03). Patients with NMDs and pain have lower motor function and fewer ADLs\(^\text{10}\). The highest functional attainment of SMA type II patients is usually sitting\(^\text{16}\), and it is reasonable to assume that patients who experience difficulty sitting without manual support have a lower motor function.

Respondents to the questionnaire reported pain intensities ranging from mild to severe pain. An NRS score ranging from 1 to 3 is considered to represent mild pain, and scores ≥4 points are considered to represent pain that can restrict physical function\(^\text{10}\). The results of the NRS, which was used to evaluate SMA patients above 5 years old, suggest that chronic pain occurring in SMA is usually mild. However, the frequency of pain appears to be high for both SMA type II and III patients. Further, when the duration is continuous, SMA type II patients appear to experience short, intermittent periods of pain, whereas type III patients continuously experience chronic pain. Pain that is persistent and high in frequency can negatively affect patients’ quality of life, despite low pain intensity\(^\text{10}\). For both SMA type II and type III patients, the most commonly reported location of pain was the lower extremities. It is presumed that the pain worsened due to decreased opportunities for muscle contraction in the lower extremities and deterioration of blood circulation\(^\text{20}\).

The most commonly reported factors that exacerbated pain in SMA type II and type III patients were “sitting” and...
“high physical activity.” This result was consistent with that reported for other NMDS. In contrast, the most commonly reported factors for pain relief were “changing position” and “massage” in SMA type II patients and “resting” in SMA type III patients. The pathophysiology of pain might be different between these SMA types II and III patients. Many SMA type II patients had low physical activity and experienced difficulty sitting straight without manual support. Low physical activity is likely to cause immobilization pain, which is a cause of pain and a risk factor for exacerbations.

The mechanism underlying the pathogenesis of pain is thought to be affected by the attenuation and disappearance of sensory stimulus input due to inactivity and joint contracture, which causes sensitization and plastic changes in the nervous system, including in the spinal cord and brain. It is believed that prolonged immobilization can cause changes in the nervous system, leading to chronic pain.

In addition, SMA type II patients include those who have undergone spinal fusion due to scoliosis. Spinal fusion improves sitting balance and endurance in the sitting position, but there is a risk of immobilization associated with spinal fusion. On the other hand, many SMA type III patients have high physical activity. Patients with SMA have a weaker trunk than healthy controls, requiring excessive muscle contraction for various movements. These patients have an increased risk of exercise-induced muscle injury and can easily experience fatigue from overwork, even when performing simple ADLs. Therefore, it was considered that “changing position” and “massage” were effective for SMA type II patients, and that “resting” was effective for SMA type III patients.

This study had a few limitations. Pain reported by young SMA patients was based on their guardian’s judgment and not direct observation. Previous studies have noted that guardians’ judgments of pain tend to be valid, although parents may underestimate their child’s pain. Additionally, pain is frequently affected by physiological, psychological, and social factors; unfortunately, these were not investigated. Moreover, since the ages differ greatly between type II and type III, the effects of aging and contracture may differ. Finally, because the number of patients with chronic pain was small, it was not possible to analyze pain according to motor function for each type. In the future, it is necessary to increase the number of cases and verify the relationship between motor function and chronic pain.

**Conclusion**

In this study, the percentage of patients with SMA with chronic pain was high, at above 40%. Moreover, the pain experienced by patients with SMA was low in intensity but frequent and most common in the lower extremities. We believe our results can facilitate pain treatment for SMA patients in clinical practice and aid future studies to better evaluate the results of various therapeutic interventions.

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**Conflict of Interest:** The authors declare that there is no conflict of interest regarding the publication of this paper.

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