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Pain in Spinal Muscular Atrophy Type 2 and Type 3 Patients

Spinal Musküler Atrofi Tip 2 ve Tip 3 Hastalarında Ağrı

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Abstract: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons. It is a multisystemic disease affecting non-neuronal systems and quality of life. We aimed to investigate the prevalence and characteristics of pain in children with spinal muscular atrophy. In this single-center study, by using visual analog scales, 13 patients diagnosed with SMA type 2 and type 3 accompanied by their parents filled out a questionnaire involving questions about the presence of chronic pain, pain frequency, duration, location, and intensity, causes of pain, and coping methods. All patients reported that they experienced chronic pain. Patients with type 3 experienced pain more frequently than those with type 2—multiple times each month. The terms "minutes," "mild," and "intermittent" were most commonly used to describe the length, intensity, and course of the pain in both groups. The mean pain intensity according to Visual Analogue Scale were 35.5□26.3 mm in type 2 and 25.1□10.2 mm in type 3. The localization of pain was primarily concentrated in the back and lower extremities. The most common causes of pain were stretching exercises during physical therapy and posture disorder. The most common methods of coping with pain were distraction strategy and massage. Pain is a common problem in children with SMA. Management of the pain might increase the life quality of SMA patients. A multidisciplinary approach must be considered in the treatment of these children.
Keywords: Spinal muscular atrophy, pain, child

Özet: Spinal musküler atrofi (SMA), alfa motor nöronların dejenerasyonu ile karakterize otozomal resesif geçişli bir nöromusküler hastalıktır. Nöronal olmayan sistemleri ve yaşam kalitesini etkileyen multisistemik bir hastalıktır. Spinal musküler atrofili çocuklarda ağrının prevalansını ve özelliklerini araştırmayı amaçladık. Bu tek merkezli çalışmada, SMA tip 2 ve tip 3 tanısı alan toplam 13 hastaya ebeveynler eşliğinde görsel analog ölçekler kullanılarak kronik ağrının varlığı, ağrı sıklığı, süresi, yeri, şiddeti, ağrı nedenleri ve baş etme yöntemlerinin sorgulandığı bir anket doldurduldu. Çalışma 13 hasta ile yürütüldü ve tüm hastalar kronik ağrı yaşadıklarını bildirdi. Tip 3 hastaları, tip 2 hastalarına göre her ay birkaç kez olmak üzere daha sık ağrı yaşadılar. "Dakika", "hafif" ve "aralıklı" terimleri her iki grupta da ağrının uzunluğunu, yoğunluğunu ve seyrini tanımlamak için kullanıldı. Vizüel Analog Skala'ya göre ortalama ağrı şiddeti tip 2'de 35.5□26.3 mm, tip 3'te ise 25.1□10.2 mm idi. Ağrının lokalizasyonu çoğunlukla sırt ve alt ekstremitelerde yoğunlaştı. Ağrının en sık nedenleri fizik tedavi sırasında yapılan esneme egzersizleri ve duruş bozukluklarıydı. Ağrıyla başa çıkmanın en yaygın yöntemleri dikkat dağıtma stratejisi ve masajdı. SMA'lı çocuklarda ağrı sık görülen bir sorundur. Ağrının yönetimi SMA hastalarının yaşam kalitesini artırabilir. Bu çocukların tedavisinde multidisipliner bir yaklaşım göz önünde bulundurulmalıdır.
Anahtar Kelimeler: Spinal musküler atrofi, ağrı, çocuk

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 54, Date: 16.05.2023

Informed Consent: This study did not require informed consent.

Authorship Contributions KBC conceived the idea for the study. ADYS, OU and CY contributed to the design and planning of the research. ADYS directed the individuals to study. CY made the interventions. All authors were involved in data collection. ADYS, OU, CY and KBC analyzed the data. ADYS wrote the first draft of the manuscript. All authors edited and approved the final version of the manuscript.

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1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, causing progressive proximal muscle weakness. The disease is caused by mutations in the SMN1 gene on chromosome 5, which leads to decreased expression of the Survival Motor Neuron (SMN) protein (1). Spinal muscular atrophy is classified into four subtypes according to age of onset and maximum motor development achieved (Table 1).

Table 1. Types of spinal muscular atrophy

Type	Onset	Symptoms	Maximum milestones
0	Prenatal	Respiratory failure, severe hypotonia	
1	0-6 months	Severe deficits in motor function. Difficulties in respiration and/or swallowing, and fasciculation of the tongue.	No sitting
2	<18 months	Severe deficits in motor function. Delay in motor development, weakness, scoliosis, joint contracture	Sitting, no walking
3	>18 months	Variable degrees of weakness, scoliosis, loss of ambulation	Independent walking
4	Adult	Milder weakness	Independent walking

The natural history of SMA has changed radically with the advent of improved standards of care and the availability of disease-modifying therapies. As a result of the emergence of new treatments, a significant increase in patients' quality of life was observed, as there was a dramatic change in the survival rate, the maximum motor function achieved, and the overall progression of the disease. Rehabilitation is necessary for SMA patients to maintain and improve their motor functions and activities of daily living.

Although the nervous system is the main target of SMA, it is a multisystemic disease that affects the quality of life (QOL) of cases. Pain is one factor contributing to patients' QOL (2). Pain is defined as "an unpleasant sensory and emotional experience linked to or characterized by actual or potential tissue damage." The causes of pain in SMA are multifactorial, including excessive muscle use, vertebral fractures and/or orthopedic problems, and respiratory reasons. The expression of pain complaints may also be affected by various psychological factors. Perceived pain associated with SMA or therapeutic procedures may be dismissed or viewed as fate by both patient and caregiver. Therefore, there are difficulties in its recognition and evaluation.

Information about pain in children with SMA is limited. This topic is essential for understanding treatment options, the effect of pain on patient compliance, and the outcomes of other rehabilitation interventions. We aimed to investigate pain characteristics in SMA patients.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional survey research was conducted from July 2023 to November 2023. Patients with a confirmed diagnosis of SMA, younger than 18 years of age, who agreed to participate in the survey, and who had no cognitive problems were included in the study. Participants consisted of SMA type II and III patients and their parents.9 SMA type 2 and 4 SMA type 3 patients participated in the study. The questionnaire used in this study was applied during routine outpatient clinic controls. Since the patients were under the age of 18, they answered the questionnaire with the help of their parents. SMA type I patients were excluded from the study due to the different severity of the disease. Patients and their caregivers both signed the informed consent.

2.2. Questionnaire Items and Questions on Pain

The questionnaire items were designed to collect demographic and clinical characteristics and pain status data. The patients were asked whether they had experienced any pain other than occasional headache, abdominal pain, and toothache in the last three months. The questionnaire included questions about the location of pain, frequency of pain, duration of pain, severity of pain, pain affecting activities of daily living, and factors that aggravate and alleviate pain. This study defined pain, under the International Association for the research of Pain (IASP), as an unpleasant sensory and emotional experience linked to or characterized by actual or probable tissue damage (3). Chronic pain was

defined as persistent or recurrent pain lasting longer than three months. Pain caused by headache, dental pain, abdominal pain, or psychological pain was excluded from the analysis. The location of pain was assessed using a body map where the location of pain could be marked. The severity of pain was evaluated using the Visual Analogue Scale (VAS).

VAS has been used since the 1920s to evaluate abstract quantities such as pain, quality of life, and anxiety. In VAS, pain sections consist of a line, usually 100 mm long, with descriptions such as "no pain" and "worst pain imaginable." The patient places a mark reflecting his pain, and the distance from the left endpoint to the mark is measured in mm. VAS was first used in psychology to measure mood disorders and, since the mid-1960s, to measure pain. The scale can be horizontal or vertical. VAS is used in daily clinical practice both as a research tool and for repeated measurements to manage chronic pain (4).

2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 21 was used for the statistical analysis. Descriptive statistics provided numerical data and percentages regarding demographic and clinical characteristics, prevalence, frequency, duration, and location. The frequency of factors that aggravate or alleviate pain was also evaluated. Age was represented using mean values and standard deviations. The severity of pain and the discomfort it induces were assessed, and the median and range of the VAS and numerical rating scales were determined to evaluate pain interference.

2.4. Ethics Notification

The study was conducted in compliance with the principles of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The study was approved by the Local Ethical Committee.

3. Results

The study was conducted with thirteen SMA patients. The mean age of cases was calculated as 128.4±50.5 months of age. The majority of patients were non-ambulatory. Tracheostomy and gastrostomy were present in two cases. One type 2 SMA case had scoliosis surgery previously. Demographic data and motor functions of the patients were shown in Table 2.

Table 2. Demographic and clinical characteristics study group.

	SMA Type 2	SMA Type 3	Total
Sex			
Female	7	2	9
Male	2	2	4
Mean age (months)	118.7± 49.9	150.2± 51.7	128.4± 50.5
Ambulation status			
Non-ambulatory	8	0	8
Ambulatory	1	4	5

All patients reported that they had experienced pain. Among SMA patients, the course of pain was mostly intermittent in both groups. The two patients who described constant pain were non-ambulatory patients with SMA type 2 and tracheostomy and gastrostomy. Pain experienced several times a month was more frequent in patients with type 3 than in patients with type 2. Duration of pain was most frequently reported as 'minutes' in both groups. The mean pain intensity according to VAS was 35.5±26.3 mm in type 2 patients and 25.1±10.2 mm in type 3 patients. In both groups, the severity of pain was most frequently rated as 'mild' by the patients. The localization of pain was primarily concentrated in the back and lower extremities. The most common causes of pain were stretching exercises during physical therapy and posture disorder. The most common methods of coping with pain were distraction strategy and massage. The features of pain status were presented in Table 3.

Table 3. The features of pain in the study group.

	SMA Type 2	SMA Type 3	Total
Pain in the last 3 months	9	4	13
Course of pain			
Intermittent	7	4	11
Continuous	2	0	2
Pain frequency			
Several times a day	3	0	3
Several times a week	3	1	4
Several times a month	3	3	6
Duration of pain			
Seconds	1	0	1
Minutes	6	4	10
An hour	1	0	1
Several hours	1	0	1
VAS* (mm)	35.5±26.3	25.1±10.2	32.3±22.4
Severity of pain			
Mild	5	3	8
Moderate	2	1	3
Severe	2	0	2
Localization of pain			
Neck	0	0	0
Arms	0	0	0
Legs	2	3	5
Back	4	0	4
Feet	3	1	4
When the pain occurs			
Overstrain	0	1	1
Stretching during physical therapy	3	2	5
Intensive exercise			
Posture disorder	1	1	2
Prosthesis use	4	0	4
	1	0	1
Methods to cope with pain			
Analgesic use	1	0	1
Distraction strategy	4	2	6
Continuation of daily activities	0	1	1
Massage	4	1	5

*SMA: Spinal muscular atrophy, *VAS: Visual Analogue Scale (0-100 mm)*

4. Discussion

Evaluating children with SMA in terms of pain is essential in terms of adequately recognizing pain and providing treatment options for the causes of pain. Valid and reliable pain assessment parameters are available for children. In this study, we described the results of a questionnaire study on pain administered to SMA type 2 and type 3 patients and their families treated at the child neurology clinic of a tertiary university hospital. Chronic pain lasting at least 3 months was described in all patients with SMA type 2 and type 3. Similarly, there are reports in the literature indicating that children with neuromuscular diseases may have chronic pain (5). Uchio et al. conducted a pain questionnaire study in 2018 that included a total of 86 patients with SMA type 2 and type 3. They reported that 40.6% of patients with type 2 and 40.9% of patients with type 3 had chronic pain (6). In a study on the prevalence of pain in neuromuscular diseases, chronic pain was reported in more than two thirds of patients (7). The reason for the higher prevalence of chronic pain in our study may be the fact that the study was conducted in children younger than 18 years of age, the subjective and complex nature of pain, and the administration of the questionnaire with families.

In this study, patients stated that the pain course was primarily intermittent. The patients who described constant pain in the study may describe continuous pain because they were nonambutary, tracheostomized, and gastrostomized. The quality of life of these patients should also be examined (8). In a study investigating the prevalence of pain in children with neuromuscular diseases, the rate of patients with persistent pain was reported as be 4% (9). Inadequate physical activities may affect the

course of pain. Although acute exercises increase pain sensitivity, it was observed that the development of chronic pain was prevented after regular physical activity (10).

In our study, the characteristics of the pain were mainly mild, resolved within minutes, and localized primarily on the lower extremities. Pain concentrated in the lower extremity may worsen due to hypotonicity, increased fatigue, and deterioration of posture (11). In a study conducted with 115 children with a history of neuromuscular disease, the mean VAS was 31.5±24.3 mm(12). In our study, similar to the literature, the mean VAS was 32.3±22.4 mm. Different studies have found that pain rates differ according to the diagnosis of neuromuscular disease (13). Little is known about the details of the nature and impact of chronic pain in patients with neuromuscular disease, but there are studies suggesting that chronic pain is associated with poor quality of life (14).

In our study, stretching exercises and posture disorders during physical therapy were the most common time periods for the pain occurance. This may be due to severe scoliosis and less physical activity in SMA patients (15). The probability of being unable to walk increases with the clinical course of SMA disease and the progression of scoliosis. Pain due to immobility is a common complaint in such patients (16).

The most common methods of coping with pain were distraction strategy and massage. In the literature, studies are show that distraction strategy reduces anxiety (17). Similarly, massage has been reported to be effective in improving pain and function in patients with chronic pain (18).

This study had several limitations. Clinical differences may be observed between SMA types. The small number of cases in this single-center study is also one of its limitations. In the future, the relationship between SMA and chronic pain should be investigated in larger number of patients.

5. Conclusion

SMA is a multisystemic disease affecting quality of life (QOL). Pain is one of the factors contributing to patients' QOL. A multidisciplinary evaluation of pain in children with SMA must be considered.

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