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Original Article

Casting Light on Mechanical Properties of Lower and Upper Extremity Muscles in Children with Spinal Muscular Atrophy and Healthy Peers

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ABSTRACT

Objective: This study aimed to compare the mechanical properties of upper and lower extremities between children with spinal muscular atrophy types 1 and 2 and healthy peers.

Methods: The study included children with spinal muscular atrophy types 1 and 2 (n = 21) and healthy controls (n = 25) aged between 1 and 4 years. Mechanical properties of the biceps brachii, triceps brachii, rectus femoris, and gastrocnemius muscles were assessed using a digital myotonometer.

Results: Muscle stiffness values of the right (d = 1.42) and left (d = 1.15) biceps brachii, right (d = 1.14) and left (d = 0.97) triceps brachii, and left rectus femoris (d = 0.85) were significantly higher in children with spinal muscular atrophy. Elasticity values of the right (d = 1.42) and left (d = 1.53) biceps brachii, right (d = 1.54) and left (d = 1.19) triceps brachii, left rectus femoris (d = 0.93), and right gastrocnemius (d = 0.92) were also significantly higher in children with SMA. No significant differences were observed between the groups in any of the evaluated resting muscle tone measurements ($P > .05$), except for the right biceps brachii muscle (d = 0.97).

Conclusion: Our study revealed that mechanical properties of the upper and lower extremity muscles in children with spinal muscular atrophy types 1 and 2 differ compared to their healthy peers. Clinicians and researchers may be able to better understand the underlying causes of spinal muscular atrophy and develop more effective treatments by having a better understanding of changes in muscle stiffness and flexibility.

Keywords: Elasticity, muscle tone, myotonometer, spinal muscular atrophy, stiffness

Introduction

Spinal muscular atrophy (SMA) is an autosomal-recessive genetic disorder characterized by degeneration of anterior horn cells, resulting in muscle atrophy and weakness due to mutations in the survival motor neuron 1 gene (SMN1).[1] The severity of SMA can be classified into 5 subtypes based on the age of the onset and motor function.[2] Type 1 SMA/Werdnig-Hoffman disease manifests in infants before 6 months of age, with hypotonia, poor head control, and absent tendon reflexes. Type 2 SMA presents as progressive proximal leg weakness, allowing unassisted sitting but not independent walking. Type 3 SMA is further divided into 3a and 3b, appearing in early childhood and enabling unassisted walking. Type 0 SMA presents symptoms before birth, while type 4 SMA is a milder form with gradually worsening weakness in adulthood.[3,4]

Although SMA is classified as a motor neuron disease, recent studies indicate that peripheral changes at the neuromuscular junction involving muscle and sensory-motor system axons occur very early, even before motor neuron loss.[5-7] It has been demonstrated that reduced proprioceptive synaptic input leads to motor neuron dysfunction in an SMA mouse model.[6] The most commonly encountered musculoskeletal problems in children with SMA type 1, which occurs frequently, include progressive symmetric and proximal muscle weakness, hypotonia, and areflexia in the extremities.[8] The introduction of new disease-modifying therapies has led to the identification of new SMA phenotypes and improved patient survival.[9] The assessment of treatment effectiveness is typically performed using clinician-rated observational developmental screening tests.[10] However, there is a requirement for dependable assessment methods that yield objective and precise outcomes, facilitating the observation of the

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physical well-being of these children, the progression of the disease, and the effectiveness of the administered treatment.

While the target center for SMA is primarily identified as the alpha motor neurons in the spinal anterior horn, the involvement of interneurons, cerebellum, neuromuscular junction, gamma-alpha motor neuron pool, descending and ascending pathways, and the reflex arc's interactive network[6,11] suggests that investigating mechanical properties such as muscle tone, stiffness, and elasticity in individuals with SMA could reveal significant insights into potential peripheral mechanisms. Conducting a myotonometer assessment to examine the muscle mechanical properties of these children and comparing them with their healthy counterparts holds promise for obtaining valuable findings. The myotonometer assessment is a non-invasive, rapid, easy, and painless technique for evaluating skeletal muscle mechanical properties. However, despite the reliability demonstrated in various studies for assessing muscle tone, stiffness, elasticity, and the severity of hyper/hypotonic conditions at the bedside,[12-16] no research has yet employed the myotonometer to evaluate the mechanical properties of postural muscles in children with SMA.

Although no research has been conducted on the reliability of device use in individuals with SMA, only one study with a cross-sectional study design has examined the relationship between muscle pain and muscle strength, function, mechanical properties in patients with SMA type 3.[14] Following the observation of this reliability, it was deemed necessary to examine how the muscle mechanical properties of children diagnosed with SMA differ from those of their healthy peers. This study aims to investigate the difference in mechanical properties of upper and lower extremity muscles between individuals with SMA type 1 and type 2 and healthy controls.

Methods

This was a cross-sectional case–control study conducted with 25 healthy children and 21 patients with SMA types 1 and 2 aged 1-4 years who were routinely followed up at Medipol Mega Hospital, Pediatric Pulmonology Clinic. The research was conducted between May 2023 and July 2023. İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee approved the study (Approval no: E-10 840098-772.02-2715, Date: April 27, 2023), and we obtained written informed consent from the parents of the patients and healthy controls. All procedures were conducted according to the Declaration of Helsinki.

Participant Information

We included (i) patients with SMA types 1 and 2 with genetic confirmation (homozygous deletion of exon 7 or with compound heterozygous mutations on the SMN1 gene), (ii) aged between 1 and 4 years, along with healthy age-matched controls, (iii) child who could be removed from respiratory support during the measurements and easily tolerate the measurements, (iv) children receiving medical treatment (Nusinersen, Evrysdi, or Zolgensma), and (v) children who were living in a home environment, not in the intensive care, in this study. The exclusion criteria for patients and controls were (i) surgery and/or trauma in the muscle chosen to be studied, (ii) implant placement within the extremities, (iii) plagiocephaly, advanced scoliosis, hip dislocation, and/or other neurological and orthopedic disorders that may affect motor function, and (iv) unwillingness of families to participate in the study.

Information on age, gender, age at diagnosis, type of SMA, number of SMN2 gene copies, treatments, feeding status, and presence of tracheostomy were recorded on the demographic and clinical evaluation form (Table 1).

Table 1. Demographic and Baseline Characteristics of SMA Patients

Variables	Patients (n = 21)
Age (months), mean (SD)	32.38 (11.53)
Gender (male), n (%)	17 (81.0)
SMA type	
Type 1	16 (76.2)
Type 2	5 (23.8)
Number of patients with SMN2 gene copy, n (%)	
2	18 (85.7)
3	3 (14.3)
Age at diagnosis (days), mean (SD)	142.61 (152.34)
Treatment status, n (%)	
Spinraza	3 (14.3)
Spinraza and ZolgenSMA	15 (71.4)
Risdiplam and ZolgenSMA	2 (9.5)
Risdiplam, Spinraza, and ZolgenSMA	1 (4.8)
Feeding status, n (%)	
Oral	11 (52.4)
Nasogastric	3 (14.3)
PEG abdomen	5 (23.8)
PEG abdomen and oral	2 (9.5)
Presence of tracheostomy (yes), n (%)	4 (19.0)

SD, standard deviation; SMA, spinal muscular atrophy; PEG, percutaneous endoscopic gastrostomy.

Instrument

The MyotonPRO device (Myoton AS., Tallinn, Estonia) was used to evaluate the mechanical properties of muscles, providing a valuable tool for biomechanical analysis of muscles involved in body movement. This device measures viscoelasticity (decrement, *D*), muscle tone (frequency, *F*), and hardness of the external force, which are all important parameters in the analysis of the mechanical properties of the muscle. The device probe applies an external force that causes displacement in the tissue being examined. Oscillatory displacements are then calculated to determine the muscle mechanical properties. The device measures the oscillation frequency (Hz) and stiffness (N/m) values, which represent the resting internal intramuscular tension and resistance to external forces, respectively. Higher oscillation frequency scores indicate greater intramuscular tension, while stiffness (N/m) reflects the tissue's resistance to changes in shape due to external forces. Another mechanical property is elasticity. Elasticity is inversely proportional to the decrement. Therefore, if the decrement of a muscle decreases, the muscle elasticity increases.[16]

During myotonometer measurements, the examiner holds the device and applies pressure to the muscle in a perpendicular direction. The device's probe then administers a brief mechanical impulse of 0.18 N for 15 ms on the skin to measure various oscillation parameters of the muscle response. This predetermined force (0.4 N) mechanical impulse results in dampened natural muscle oscillations following a rapid release.[17,18] The inner probe is inserted into the muscle by applying pressure until the plexiglass frame is immobilized on the skin's surface. Once the estimated motor point is marked, pressure application is terminated when the red light on the device probe's plexiglass frame changes to green, and the probe is held steady until 5 pulses are completed. Each pulse lasts for 15 ms, and the interval between pulses is 8 ms. The device records these oscillations as an acceleration graph and calculates parameters using values obtained from the graph. Detailed information can be found in the user guide of the device.[19]

Procedures

Bilateral measurements were performed from the rectus femoris, triceps brachii, biceps brachii, and gastrocnemius muscles in all patients

and controls. Demographic information of the children was recorded on the data entry platform of the MyotonPRO software program prior to commencing the assessment. The system was preloaded with pattern entries specifying that all measurements would be taken from the estimated motor point of the relaxed muscles in the resting position. The measurements were conducted in a calm, well-lit room with a neutral temperature, 2 hours after feeding. The children were mostly undressed and in a relaxed state during the assessment. For the MyotonPRO measurement, the estimated motor point was determined with reference to the SENIAM sensor location guideline.[20]

The assessment positions for different muscle groups are described below.

In the rectus femoris measurement, the children were seated in a chair with their knees slightly flexed and upper body leaning back. The midpoint (50%) of the line extending from the anterior spina iliac superior to the patella superior was marked as the evaluation point.

In the biceps brachii measurement, the children were seated with their elbow joint flexed at 90° and forearm in supination. The reference line was determined in the direction of the line between the acromion and cubital fossa, and the estimated reference motor point was accepted at a distance of 1/3 of this length from the fossa cubiti reference.

In the triceps brachii measurement, the children were seated with their shoulder joint abducted at 90°, elbow flexed at 90°, and forearm supinated. The line between the posterior cristae of the acromion and the olecranon was used as the reference line, and the midpoint (50%) of this line was marked as the predicted motor point.

In the gastrocnemius measurement, the children were placed in a prone position, and the most prominent protrusion of the muscle was marked as the estimated motor point with the dorsum of the foot supported at the table corner. The same measurements were made with the children in a side-lying position if they had a tracheostomy.

An experienced physiotherapist (SKY) performed and recorded all measurements according to procedures for all patients and controls. After standard positioning was achieved, the measurement was taken by placing the device probe at a right angle to the estimated motor points. The measurement results were exported to the computer after being removed from the device.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA). The normal distribution of the data was examined using visual (histogram and probability plots) and analytical (Shapiro–Wilk test) methods. The descriptive statistics are presented as median and interquartile range or mean and standard deviation for the quantitative variables, and frequency and percentage values for qualitative variables. Group differences were investigated using Mann–Whitney *U*- or independent *t*-test for continuous variables. Cohen's *d* effect sizes were calculated, and 0.2-0.49 was considered as a small effect, 0.5-0.79 as a moderate effect, and > 0.8 as a large effect.[21] An α level of 0.05 was used throughout the analysis.

Results

In this study, we compared a total of 21 children with SMA (16 with type 1 and 5 with type 2) to 25 healthy controls. The mean age of the healthy children was 31.52 ± 16.29 months, and there were no statistically significant differences between the groups ($P = .84$). The demographic and clinical characteristics of the SMA patients were analyzed and presented in Table 1.

Regarding muscle tone measurements, no significant differences were found between the groups, except for the right biceps brachii muscle ($P < .05$), as shown in Table 2.

Our results revealed that children with SMA exhibited significantly higher stiffness and elasticity values compared to the control group, except for the stiffness values of the gastrocnemius muscle ($P < .05$), as presented in Tables 3 and 4.

Specifically, stiffness values for the right and left biceps brachii, right and left triceps brachii, and left rectus femoris were significantly higher in the SMA group compared to the healthy controls ($P < .05$). Table 3 demonstrates a large effect size of stiffness values for the biceps brachii (right and left), triceps brachii (right and left), and rectus femoris (left). Furthermore, we observed significantly higher decrement values for the right and left biceps brachii, right and left triceps brachii, left rectus femoris, and right gastrocnemius in the SMA group compared to the healthy control group ($P < .05$). Table 4 demonstrates a large effect size of decrement values for these muscles.

In our preliminary study, we examined the reliability of the myotonometer in evaluating the mechanical properties of postural muscles in children diagnosed with SMA. The preliminary results of our study, which is currently in the evaluation phase, conducted at our clinic, showed high intra-rater and inter-rater reliability of the myotonometer in assessing all the mechanical properties of postural muscles (m. gastrocnemius, m. rectus femoris, m. biceps brachii, and m. triceps brachii) in individuals diagnosed with SMA types I and II. Except for the stiffness value of the left gastrocnemius muscle, which presented good reliability (ICC = 0.71), the ICCs for the inter-rater reliability analysis were above 0.75 and showed excellent reliability.

Table 2. Comparison of Frequency (Hz) Values between Patients with SMA and Healthy Controls

Variable	Patients (n = 21)	Controls (n = 25)	Mean Difference (95 % CI)	Effect Size (*d*)	*P*
Right biceps brachii	14.60 (13.45-16.55)	13.50 (12.95-14.40)	1.44 (0.47-2.41)	0.97	**.010**[a]
Left biceps brachii	14.00 (12.95-16.30)	13.50 (13.00-14.35)	1.06 (0.05-2.07)	0.67	.112[a]
Right triceps brachii	13.48 (2.09)	12.61 (1.17)	0.86 (−0.20 to 1.93)	0.52	.108[b]
Left triceps brachii	13.80 (11.12-12.37)	12.60 (12.10-13.25)	1.35 (0.08-2.62)	0.69	.142[a]
Right rectus femoris	11.60 (11.12-12.37)	12.20 (11.65-12.60)	−0.41 (−1.01 to 0.19)	0.41	.221[a]
Left rectus femoris	12.28 (1.16)	12.29 (0.82)	−0.11 (−0.63 to 0.61)	0.01	.971[b]
Right gastrocnemius	12.80 (11.75-13.95)	12.70 (12.40-13.75)	−0.20 (−1.06 to 0.64)	0.14	.651[a]
Left gastrocnemius	12.69 (1.16)	12.80 (0.80)	−0.11 (−0.70 to 0.47)	0.11	.702[b]

Bold values indicate significant difference.
CI, confidence interval; *d*, effect size.
[a]Mann–Whitney *U*-test.
[b]Independent *t*-test.

Table 3. Comparison of Stiffness (N/m) Values between Patients with SMA and Healthy Controls

Variable	Patients (n = 21)	Controls (n = 25)	Mean Difference (95 % CI)	Effect Size (d)	*P*
Right biceps brachii	266 (221.5-311.5)	206 (190-224.5)	62.23 (34.24-90.22)	1.42	**.001**[a]
Left biceps brachii	252 (204.5-292)	206 (186-225)	51.71 (23.34-80.08)	1.15	**.002**[a]
Right triceps brachii	321 (214-443.5)	209 (182.5-275.5)	118.08 (50.76-185.40)	1.14	**.005** [a]
Left triceps brachii	300.5 (189.75-430.5)	221 (183.5-252.5)	95.48 (29.44-161.51)	0.97	**.024** [a]
Right rectus femoris	194.90 (34.42)	182.52 (29.22)	12.38 (−6.75 to 31.51)	0.39	.199[b]
Left rectus femoris	218 (188.5-254)	190 (174-204.5)	31.64 (8.33-54.96)	0.85	**.014**[a]
Right gastrocnemius	209 (184.5-254)	200 (191.5-226)	10.22 (−16.74 to 37.19)	0.22	.791[a]
Left gastrocnemius	209 (182-234.75)	198 (181.5-213)	15.34 (−9.24 to 39.92)	0.37	.326[a]

Bold values indicate significant difference.
CI, confidence interval; *d*, effect size.
[a]Mann–Whitney *U*-test.
[b]Independent *t*-test.

Table 4. Comparison of Decrement Values between Patients with SMA and Healthy Controls

Variable	Patients (n = 21)	Controls (n = 25)	Mean Difference (95 % CI)	Effect Size (*d*)	*P*
Right biceps brachii	1.17 (0.18)	0.97 (0.11)	0.19 (0.10-0.29)	1.42	**.001**[b]
Left biceps brachii	1.11 (1.02- 1.33)	0.95 (0.88-1.00)	0.22 (0.12-0.33)	1.53	**.001**[a]
Right triceps brachii	1.66 (0.28)	1.29 (0.21)	0.36 (0.21-0.51)	1.54	**.001**[b]
Left triceps brachii	1.62 (0.32)	1.31 (0.21)	0.30 (0.14-0.46)	1.19	**.001**[b]
Right rectus femoris	1.12 (0.23)	1.02 (0.20)	0.10 (−0.02 to 0.23)	0.47	.127[b]
Left rectus femoris	1.16 (0.14)	1.01 (0.19)	0.14 (0.04-0.25)	0.93	**.005**[b]
Right gastrocnemius	1.08 (0.96- 1.33)	0.95 (0.93-1.03)	0.13 (0.04-0.23)	0.92	**.013**[a]
Left gastrocnemius	1.05 (0.94- 1.24)	0.97 (0.92-1.09)	0.09 (−0.01 to 0.20)	0.57	.115[a]

Bold values indicate significant difference.
CI, confidence interval; *d,* effect size.
[a]Mann–Whitney *U*-test.
[b]Independent *t*-test.

Discussion

In this study, we assessed mechanical properties of lower and upper extremity muscles, comparing differences between children with SMA (types 1 and 2) and healthy peers. Our study findings revealed that the mechanical properties of upper and lower extremity muscles in children diagnosed with SMA types 1 and 2 differ compared to their healthy peers. Skeletal muscle stiffness was significantly higher in children with SMA, while elasticity was lower. These results indicate the need for a more detailed examination of muscle mechanical properties in children with SMA.

Recent experiments utilizing SMA mouse models have revealed that not all motor neurons are equally susceptible to the disease.[11,22-25] Immunohistochemical analyses of late symptomatic SMA mouse spinal cords, in comparative evaluations of the pools of alpha motor neurons (α-MNs) and gamma motor neurons (γ-MNs), demonstrated a significant reduction in the number of α-MNs at all levels of the spinal cord compared to controls, while the number of γ-MNs remained constant. Similarly, the average size of α-MN cell bodies decreased in mice with SMA without any changes observed in γ-MNs. In the evaluation of other spinal cord cholinergic neuron pools, preganglionic sympathetic neurons, spinal interneurons, and preganglionic autonomic dorsal commissural nucleus neurons were unaffected in SMA mice. These findings indicate that α-MNs are uniquely vulnerable among the cholinergic neuron populations in the SMA mouse spinal cord, while γ-MNs and other cholinergic neuronal populations are largely preserved.[11] Consistent with these results, it was found that the resting skeletal muscle tone controlled by gamma motor neurons[26-28] in children diagnosed with SMA types 1 and 2 did not show significant differentiation from healthy children. In contrast to the mechanical properties of other skeletal muscles evaluated (stiffness and elasticity), only increased responses in muscle tone were observed in the right biceps brachii muscle compared to healthy controls, suggesting that the reason may be the small number of children included in the study. Considering the selective loss in the neuron pool observed in SMA, it is possible that the change in postural extremity muscle resting tone occurs as a complication of progressive deformity or other alterations in viscoelastic mechanical properties rather than as a direct result of the disease etiology.

In the study of Lidström et al., the reliability of myotonometry measurements was investigated by evaluating rectus femoris muscle tone in children with cerebral palsy and nondisabled children. A total of 15 children with cerebral palsy and 15 nondisabled children participated in the study, and differences in muscle tone were investigated between groups and between contracted or relaxed muscle conditions. When comparing tissue displacement under isometric contraction, the study reported no statistically significant differences between children with cerebral palsy and healthy peers.[17] In contrast, the current study findings showed that muscle stiffness values of the biceps brachii (right and left), triceps brachii (right and left), and rectus femoris (left) were significantly higher in children with SMA compared to healthy children. Additionally, muscle elasticity values of the biceps brachii (right and left), triceps brachii (right and left), rectus femoris (left), and gastrocnemius (right) were also significantly lower in children with SMA compared to healthy peers. Unlike the pathogenesis of SMA, the mechanism of change in muscle mechanical properties may differ in cerebral palsy due to the central nervous system being affected. Tharaneetharan et al.[29] investigated the functional changes in brain regions in the mouse model of SMA and demonstrated impairments in motor control outputs from both the motor cortex and the cerebellum. They reported functional neuronal defects in these areas, specifically noting significantly lower spontaneous firing and network activity in the cerebellum, while no such change was observed in the motor cortex. Furthermore, differences

in excitability and synaptic transmission of output neurons were observed in both the cerebellum and motor cortex. These findings suggest that neuronal dysfunction in these brain regions may contribute to the pathology of SMA. The study emphasized the importance of considering motor regions beyond the spinal cord in developing comprehensive treatment strategies. These central system changes reported by Tharaneetharan et al.[29] align with our research results, which revealed increased stiffness and decreased elasticity in skeletal muscle mechanical properties in children with SMA, highlighting the interconnected nature of peripheral and central components in SMA. These findings suggest that stiffness and elasticity values could serve as potential indicators of muscle function in children with SMA. The significant differences in muscle stiffness and elasticity observed between the 2 groups could be attributed to the underlying pathology of SMA. In children with SMA, muscle stiffness can be increased due to the loss of muscle fibers and the replacement of muscle tissue with fibrotic tissue.[29] This fibrosis can cause the muscle to become stiff and less pliable, which can limit the range of motion and contribute to contractures.[30]

Elasticity, on the other hand, is a measure of a muscle's ability to return to its original shape after being stretched. In healthy individuals, muscles are highly elastic and can absorb energy during movement, reducing the risk of injury.[31] However, in children with SMA, the elasticity of muscles can be reduced due to muscle wasting and fibrosis. This can result in decreased muscle function and increased susceptibility to injury. Measuring muscle stiffness and elasticity in children with SMA can be valuable in assessing disease progression and monitoring the effects of interventions. Additionally, understanding changes in muscle stiffness and elasticity can help clinicians and researchers better understand the underlying mechanisms of SMA and develop more effective treatments. For instance, one study found that the motor skills of children with SMA depend on muscle strength, range of motion, spine, and chest deformities. In this study, the functional relationships between selected neck, upper and lower extremity ranges of motion, neck and trunk muscle strength, postural parameters, and motor functions of 27 children diagnosed with SMA type 1 and SMA type 2 between the ages of 6 months and 15 years were investigated.[32] Another study explored the relationship of nociceptive muscle pain to changes in muscle strength, function, stiffness, frequency, decrement, relaxation, or creep in patients living with SMA type 3 and reported that muscle elasticity, as a measure of the ability of the muscle to regain its original shape after deformation. It was concluded that the lower elasticity of knee extensor muscle, lower pain threshold, and muscle pain in SMA type 3 are mainly caused by changes in the dysbalanced musculoskeletal system.[14] These studies further support the notion that SMA leads to significant muscle dysfunction and highlight the potential utility of measures such as stiffness and decrement values in assessing muscle function in children with SMA. This muscle weakness and wasting could explain the observed differences in stiffness and elasticity values between the 2 groups.

There are some limitations to our study that must be acknowledged. First, the small sample size of the study may limit the generalizability of our findings to a larger population. Second, the study design was cross-sectional, which makes it difficult to establish a causality. Third, differences in medical treatment received can be considered another limitation of the study.

Conclusion

Our study provides evidence about the mechanical properties of upper and lower extremity muscles in children diagnosed with SMA types I and II by displaying notable differences compared to their healthy peers. Specifically, we observed significantly higher skeletal muscle stiffness and lower elasticity in children with SMA. These findings highlight the impact of SMA on muscle biomechanics and suggest potential implications for motor function and mobility in affected individuals. Future studies could adopt a longitudinal design to understand better the relationship between muscle function and disease progression in children with SMA. Besides that, further research is warranted to elucidate the underlying mechanisms contributing to these alterations in muscle mechanical properties and explore their relationship with disease progression and therapeutic interventions. Understanding the specific changes in muscle biomechanics associated with SMA can aid in the development of targeted interventions to improve motor function and quality of life for affected children.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee approved the study (Approval no: E-10840098-772 .02-2715, Date: April 27, 2023)

Informed Consent: Written informed consent was obtained from all the parents of the patients in the study.

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Author Contributions: Concept – S.K.Y., T.Ç.S.; Design – S.K.Y., T.Ç.S.; Data Collection and/or Processing – S.K.Y., S.Ö.; Analysis and/or Interpretation – S.K.Y., T.Ç.S., Ö.Ö., S.Ö.; Literature Search – S.K.Y., T.Ç.S., Ö.Ö., S.Ö.; Writing Manuscript – S.K.Y., T.Ç.S., Ö.Ö., S.Ö.; Critical Review – S.K.Y., T.Ç.S., Ö.Ö., S.Ö.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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