The Outcomes of an Individualized Physical Therapy Program in CALFAN Syndrome: A Case Report

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Purpose: This case report investigated the effectiveness of an individualized physical therapy program in CALFAN syndrome.

Case Description: A 13-year-old girl participated in physical therapy, which included trunk stabilization, balance training, and functional exercises for 12 weeks.

Assessments: The International Cooperative Ataxia Rating Scale; Trunk Impairment Scale; Pediatric Quality of Life Inventory; Functional Independence Measure for Children; Quick Disability of the Arm, Shoulder, and Hand Questionnaire; 9-Hole Peg Test; and Cobb measurement were used as outcome measures.

Results: Positive changes were observed in the International Cooperative Ataxia Rating Scale; Quick Disability of the Arm, Shoulder, and Hand Questionnaire; Pediatric Quality of Life Inventory; Trunk Impairment Scale; Functional Independence Measure; and the 9-Hole Peg Test. The Cobb angle was increased by 2° in the thoracic region and reduced by 11° in the lumbar region.

Conclusions: Physical therapy improved quality of life, functional independence, trunk control, and upper extremity performance.

What This Adds to Evidence: This case report is the first to support the effectiveness of physical therapy for a child with CALFAN syndrome. (Pediatr Phys Ther 2022;34:432–437)

Key words: ataxia, CALFAN syndrome, disabilities, osteoporosis, rehabilitation

INTRODUCTION

CALFAN (low γ-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration) syndrome is a very rare disease with onset in infancy, accompanied by hepatic involvement and various neurological manifestations.[1] Disease causing variations in the *SCYL1* gene causes the autosomal recessive cerebellar atrophy known as spinocerebellar ataxia-21 (OMIM# 616719)/CALFAN syndrome, which is characterized by ataxia, peripheral neuropathy, intellectual disability with speech disorder, and fever-induced recurrent liver failure attacks.[1,2] Furthermore, people with CALFAN syndrome may also have musculoskeletal problems such as progressive scoliosis, hip dysplasia, osteoporosis, thoracic spine anomalies, and increased lordosis.[1]

Spinocerebellar ataxia comprises a group of autosomal dominant and recessive disorders that result in progressive degeneration of the brain (specifically in the cerebellum), gait imbalance, and movement disorder. The degeneration of other sites of the nervous system causes pyramidal and extrapyramidal deficits.[3] The primary symptoms of spinocerebellar ataxia are problems with coordination and balance, mostly affecting the quality of life and independence.[4] People with spinocerebellar ataxia have deficits in motor learning. Rehabilitation represents the only form of intervention to improve ataxic dysfunctions since there are no pharmacologic treatments to reverse or reduce motor disability caused by cerebellar degeneration.[5] The dynamic regulation of balance and movements is targeted in many exercise interventions with rehabilitation. However, several studies have failed to report long-term effects or improved performance in the activities of daily living.[6]

Eleven cases with CALFAN syndrome have been reported up-to-date. Studies have sought to determine the phenotype and genotype of the disease. There is no known medical cure for CALFAN syndrome and physical therapy for management

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has not been assessed. We present clinical findings of an adolescent with CALFAN syndrome and report the effectiveness of a 12-week physical therapy program to improve motor function.

The Ethics Committee of Hasan Kalyoncu University Faculty of Health Sciences approved the study (approval number: 2020/033). Informed consent was obtained from her parents.

CASE DESCRIPTION

The adolescent was a female, right-handed, and 13 years of age. She was born at term by vaginal delivery after an uneventful pregnancy. No information was available on the birth growth measurements. Her parents were consanguineous. She gained the control of her head at 3 months, sat unsupported at 10 months, and walked independently at 26 months. She had a history of 6 cholestasis attacks accompanied by jaundice, nausea, vomiting, and fever. The first hospitalization for acute liver failure was at 6 months and then at 13, 15, and 18, months, and 10 years of age. She had undergone a liver biopsy and was diagnosed with cryptogenic cirrhosis at 18 months and confirmed at 24 months of age. Cerebellar symptoms were first noticed at 26 months of age when the adolescent displayed an ataxic gait. Her gait worsened with attacks. Her parents reported her exercise intolerance, getting tired easily, and increased gait imbalance.

Her body weight was 36 kg (1.46th percentile) (SD: −2.89), height was 139 cm (0.08th percentile) (SD: −3.14), and occipitofrontal diameter was 48 cm (SD: −4.9). She had oculomotor apraxia, increased deep tendon reflexes, cerebellar signs (ataxia/dysarthria/dysmetria), decreased muscle strength, and hepatosplenomegaly. Dysmorphic features such as long and cylindrical fingers, bilateral hallux valgus, and thoracic kyphoscoliosis were noted. She was previously diagnosed with osteoporosis and experienced 4 bone fractures at different sites, which were attributed to ataxia-related falls. A *Z* score below 2.0 was obtained from dual-energy x-ray absorptiometry scans of the hip and the lumbar spine. Extensive investigations including serum biochemical parameters and complete blood count revealed normal values. Metabolic screening was normal. Genetic testing for Niemann-Pick type C was normal. Cranial magnetic resonance images showed wide cerebellar hemispheric sulci and gyral atrophy bilaterally. Further genetic analysis was performed, and the c.169C > T (p.Gln57Ter) homozygous disease-causing variant in the *SCYL1* gene was identified by clinical exome sequencing, which has been previously reported in 2 adolescents from Turkey with a phenotype of CALFAN syndrome.[1]

INITIAL ASSESSMENT

Curvature of the spine, balance, and coordination problems were observed on physical examination. In addition, the adolescent had dysarthria and tremor. A pes planovalgus deformity in her left foot was noted, and weakness in upper and lower extremity muscles was evident in the manual muscle strength test. The strength of biceps, deltoid, quadriceps, and hamstring muscles was grade "3+" on manual muscle tests. The range of motion of upper and lower extremities was near normal. Plain radiography and clinical evaluation revealed "S" scoliosis (Figure 1a-c). The Cobb angle results are shown in the Table. Slow walking speed decreased stride length and forward leaning and ataxic gait were observed in the gait analysis.

ASSESSMENTS

The International Cooperative Ataxia Rating Scale (ICARS) was used to determine the severity of the adolescent's ataxia, and the Trunk Impairment Scale (TIS) was used to assess static and dynamic sitting balance and trunk coordination. The Pediatric Quality of Life Inventory (PedsQL) was used to evaluate quality of life. The Functional Independence Measure (WeeFIM) for Children was used to predict functional independence. Upper limb disability was assessed using the Quick Disability of the Arm, Shoulder, and Hand Questionnaire (Q-DASH). The 9-Hole Peg Test (9-HPT) was chosen to evaluate upper extremity performance.

The International Cooperative Ataxia Rating Scale

The ICARS is a 19-item instrument, which has been developed to assess the severity of ataxia. Unlike other performance

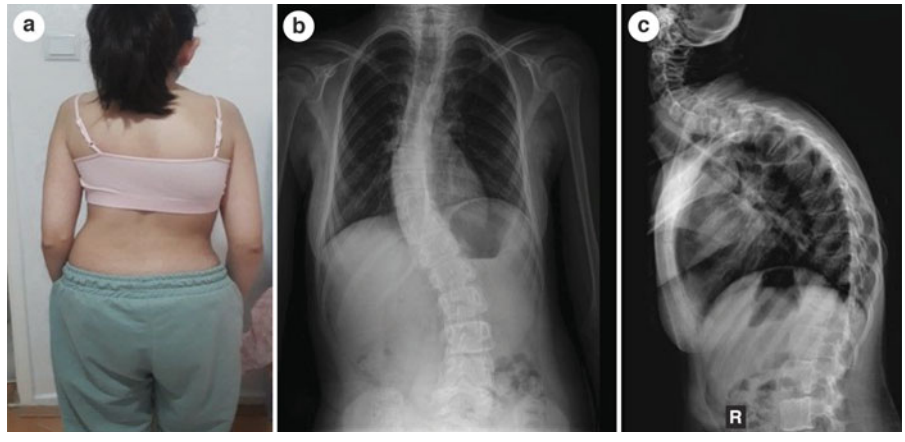

Fig. 1. Radiographic and posterior views of the adolescent. (a) Posterior postural assessment, (b) anterior-posterior view, and (c) lateral view.

TABLE

Initial and Follow-up Assessments

Assessments (Minimum-Maximum)	Initial	Follow-up
ICARS score (0-100)	47	42
Posture and gait disturbance (0-34)	12	11
Kinetic function (0-52)	26	22
Speech disorders (0-8)	6	6
Oculomotor disorders (0-6)	3	3
TIS score (0-23)	9	13
Static sitting balance (0-7)	6	7
Dynamic sitting balance (0-10)	2	4
Coordination (0-6)	1	2
WeeFIM score (0-126)	79	83
Self-care (0-42)	15	18
Sphincter control (0-14)	8	8
Transfers (0-21)	21	21
Locomotion (0-14)	4	5
Communication (0-14)	14	14
Social cognition (0-21)	17	17
PedsQL score (0-100)	47.11	52.17
Physical health-related quality of life score (0-100)	21.8	28.1
Psychosocial health-related quality of life score (0-100)	70	65
Q-DASH score (0-100)	59	56
9-Hole Peg Test (right), s	48.8	42.9
9-Hole Peg Test (left), s	66.1	56.4
Thoracic Cobb (angle)	34	36
Lumbar Cobb (angle)	32	21

Abbreviations: ICARS, International Cooperative Ataxia Rating Scale; PedsQL, Pediatric Quality of Life Inventory; Q-DASH, Quick Disabilities of the Arm, Shoulder, and Hand; TIS, Trunk Impairment Scale; WeeFIM, Functional Independence Measure for Children.

tests, kinetic function, speech disorder, and oculomotor disorders are also rated in addition to posture and gait disturbance. Maximum score is 100 and higher scores indicate greater ataxia severity.[7]

Trunk Impairment Scale

The TIS consists of 17 items, including 3 items for static balance, 10 items for dynamic balance, and 4 items for the coordination ability of the trunk stabilizer muscles. The total TIS scores were between 0 for a minimal performance and 23 for perfect performance.[8]

The Pediatric Quality of Life Inventory

The PedsQL measures health-related quality of life in children and adolescents aged 2 to 18 years. It consists of 23 items that are suitable for use with school and clinical pediatric populations as well as in children who are healthy and with health conditions. Higher total PedsQL scores indicate better health-related quality of life.[9]

Functional Independence Measure for Children

The WeeFIM is a measure of functional ability, which consists of a total of 18 items and 6 subdomains including self-care, sphincter control, transfers, locomotion, communication, and social cognition. Each item is scored between 1 and 7 points based on the level of assistance required to perform the task, in which 1 denotes total assistance and 7 indicates complete independence.[10]

Disabilities of the Arm, Shoulder, and Hand—Short Form

The Q-DASH is a questionnaire used to assess limitations in activity and participation in common upper extremity problems. Reliability and validity of the Turkish version of the tool were demonstrated by Düger et al in 2006.[11] From the item scores, scale scores are calculated, which range from 0 (no disability) to 100 (most severe disability).[11]

9-Hole Peg Test

The 9-HPT is a test that assesses manual dexterity using a wooden board with 9 holes and 9 wooden pegs. For the test, the adolescent was first asked to place the pegs into the holes and then remove them as quickly as possible, and the total time to complete the test was recorded using a stopwatch. For each hand, the test was repeated 3 times and the average of 3 trials was recorded.[12]

Cobb Angle

The intervertebral spaces are narrower on the concave side of the curvature. The levels at which the intervertebral spaces begin to expand are the end vertebrae. The angle between lines drawn on end plates of the end vertebrae, measured from the superior end plate of upper end vertebra to the inferior end plate of a lower end vertebra, is the Cobb (c) angle.[13]

INTERVENTION

The primary goal of the physical therapy program was to increase stability of the core muscles and, accordingly, to achieve improved upper limb function. After initial assessments, the adolescent continued to participate in the physical therapy program for 12 weeks (sessions: 45 min/3 d/wk). Her final measurements were taken at the end of the physical therapy program. Functional training exercises were conducted with the aim to improve motor learning skills and trunk stabilization, and scoliosis brace was used to improve Cobb's angles. Sit-ups, crunches (forward crunch and oblique crunch) at different directions, and hip flexion, extension, and abduction exercises were applied to strengthen abdominal and gluteal muscles. These exercises were performed on a mat in the supine position for the abdominal region and in the side-lying and prone positions for the hip region. During the bridge exercise, the adolescent was asked to lie on her back with the knees bent at 90° and raise her hips and maintain this position for 10 seconds. Forward plank, contralateral arm, and leg extension exercises were conducted for trunk stabilization. For the plank exercise, she was asked to stay in the prone position for 10 seconds with the elbows bent at 90° (3 repetitions per session). Arm and leg extension exercises were performed in the cross-crawl position. For trunk control exercises, she was asked to

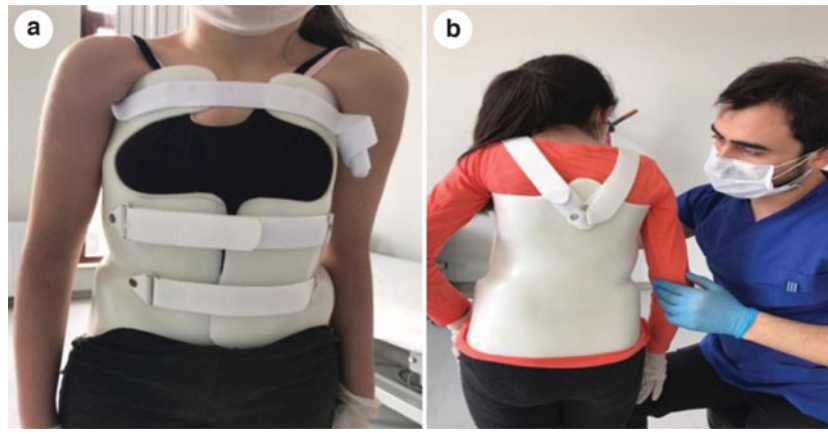

Fig. 2. Anterior and posterior views of the scoliosis orthosis. (a) Anterior view and (b) posterior view.

hold the exercise ball (45 cm) with both hands and try to keep her balance in different positions. Functional activities were also performed including throwing a ball into a bucket and ring toss in the prone position on a Swiss ball (65 cm). The adolescent was then turned on her back on the Swiss ball to mobilize the thoracic region. Perturbation-based balance training with hands tied and extended forward, low-intensity push-pulls, and functional reaches with trunk elongation were performed while she was in the sitting position. The same exercises were repeated in standing position.

Scoliosis was managed with the thoracic expansion and diaphragmatic breathing during trunk stabilization exercises. Also, a custom-made scoliosis brace was used (Figure 2a and b). The corrective pressures of the brace were not applied because of the osteoporosis to prevent complications and used for 12 hours a day.

FOLLOW-UP ASSESSMENTS

The ICARS and Q-DASH scores decreased and PedsQL, TIS, and WeeFIM scores increased. The completion time of the 9-HPT was improved in both upper extremities. Thoracic and lumbar Cobb angles increased by 2° and decreased by 11°, respectively (Table).

DISCUSSION

This is the first study to report the outcomes of physical therapy program for CALFAN syndrome. Physical therapy studies in individuals with hereditary degenerative ataxia have used balance and coordination training, cycling regime, balance exercises with technology-assisted biofeedback, treadmill, and respiratory muscle training.[14] The assessments used in those studies are similar to those used in our study. The medical problems addressed by the physical therapy treatment in our study are not specific for CALFAN syndrome but could be found in many other neurodegenerative disorders. However, the current study differs from previous studies in that it examined the effect of trunk stabilization on both upper extremity functioning and spinal curvatures on the outcomes of an adolescent with CALFAN syndrome by using a tailored physical therapy program. There is no study available in the literature that involved exercise training in combination with the use of orthosis in children with rare hereditary ataxias.

The physical therapy program was tailored according to the clinical symptoms and focused on trunk control and spinal deformities. We used exercises because of the fracture risk, especially perturbation-based balance training. Aquatic therapy could be included in physical therapy programs since it helps improve postural control and creates resistance in all directions. Clinics with aquatic therapy facility may consider using this approach in appropriate adolescents. Beneficial effects of aquatic therapy have been reported in pediatric adolescents with neurodegenerative disorders such as Waardenburg syndrome, spinal muscular atrophy (type I), and Rett syndrome.[15]

Trunk stabilization exercises were reported to improve upper extremity functions,[16] which is consistent with our findings. Moreover, our physical therapy program improved ICARS, TIS, and PedsQL scores. The trunk has a vital role in creating dynamic stabilization for postural reactions and limb movements. Trunk stabilization is critical to support the upper and lower extremity movements, share loads, and protect the spinal cord. Close relationships among upper extremity function, trunk stabilization, and the activities of daily living have been observed. The role of trunk control is also important in other activities such as climbing stairs, bathing, and toileting.[17] The improvements in functional independence in the activities of daily living and upper extremity performance supported the effectiveness of our stabilization exercise and resulted in improved trunk control.

In adolescents with ataxia, deficiencies in postural control are associated with reduced functional independence and impairment in activities of daily living.[18] We think that improvement in self-care activities (eg, eating and washing hands) is related to improved trunk control. In adolescents with Friedreich's ataxia, a physical therapy program led to an improvement of 2 points, on average, in the functional independence score.[19] In addition, the importance of postural control and selective voluntary motor movements for self-care skills has been demonstrated in children with upper motor lesions.[20]

Adolescents with cerebellar ataxia have lower quality of life than individuals with chronic diseases. Although psychosocial

health-related quality of life is affected to a lesser extent, physical health-related quality of life is affected.[21] In our study, an increase was observed in physical health-related quality of life along with a reduction in psychosocial health-related quality of life. We think that reduced psychosocial health-related quality of life may be related to COVID-19 pandemic. Our physical therapy program provided improvements in postural control and upper limb functioning, which was reflected by better quality of life. In a child with ataxia telangiectasia, postural stability and dynamic balance exercises and Wii Fit balance–based video training led to improvements in postural control and balance, which were associated with improved quality of life.[22] In future studies, long-term follow-up may be useful to detect changes in quality of life in adolescents with multisystem involvement such as CALFAN syndrome.

Stabilization exercises are regarded as an effective treatment method in scoliosis. These exercises improve quality of life and functional capacity in adolescents with scoliosis. Improvement in postural parameters positively affects self-confidence and personal satisfaction. The improvements in functional independence and quality of life that we achieved in our case are consistent with the literature.[23] Moreover, stabilization exercises reduce the asymmetric loading of the spine by improving motor control in the lumbar multifidus and deep paraspinal muscles. They reduce the asymmetrical loading and prevent the abnormal growth of the vertebral body.[23] This kind of exercise reduces the progression of scoliosis associated with pelvic tilt. Postexercise findings demonstrated that lumbar curvature was reduced and thoracic curve was increased. The main reason for this discrepancy may be related to lumbar multifidus and core muscles that largely affect the lumbopelvic area. Furthermore, it might be better to follow the scoliosis at least every 6 months to see improvements as recommended by the guidelines.[24] The custom-made orthosis was designed in such a way that it did not exert corrective pressure for scoliosis. Therefore, our aim to use the brace was just to support trunk stability and alter sensorimotor feedback. This kind of orthotic design without corrective pressure may be beneficial in the rehabilitation. Direct pressures over the bones in the subcostal and spinal areas can cause complications (eg, fracture, bone bruise), rather than correcting spinal curves.

The CALFAN syndrome is a multisystemic neurologic disease associated with a plethora of symptoms. A case of recurrent lung infections and restrictive lung capacity has been reported previously.[25] However, our case did not have respiratory symptoms and showed no respiratory insufficiency during the rehabilitation program. Nonetheless, we preferred to use thoracic expansion and diaphragmatic breathing exercises due to her scoliosis in order to maintain the normal lung capacity.

In neurodegenerative disorders, the needs of affected adolescents change as their medical condition deteriorates over time. Therefore, physical therapy programs should be adjusted over time according to changing needs of the adolescents on a continuous basis. In addition, it is crucial to improve current functional status of the adolescents and at least maintain function for some time despite progression of the disease.

In the present study, trunk muscle strength and endurance were not evaluated and this is one of the limitations of our study. The questionnaires used in the study represent a potential source of bias, since they are subjective, self-report tools. Another limitation is that the interventions and assessments were performed by the same investigator. More definitive results could be obtained if the treatment and evaluations were conducted by different persons.

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