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Case Report / Olgu Sunumu

Results of Special Neck Exercises in a Patient with Cerebellar Ataxia and Axial Myoclonus Due to ADCK3 Mutation

Serebellar Ataksi ve Aksiyal Miyoklonusu Olan ADCK3 Mutasyonlu Bir Olguda Özel Boyun Egzersizlerinin Sonuçları

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Abstract

Cerebellar ataxia associated with the *aarF-domain-containing kinase 3 (ADCK3)* gene mutation is a hereditary type of ataxia related to autosomal recessive cerebellar ataxias. Additional symptoms, such as epileptic seizures, pyramidal signs, and myoclonus, may be seen in this progressive ataxia. This case report aimed to present the results of the physiotherapy and rehabilitation program of a 19-year-old patient with cerebellar ataxia and myoclonus, due to coenzyme Q10 deficiency, associated with the *ADCK3* gene mutation. International cooperative ataxia rating scale, mini-mental state examination, observational posture analysis, unified myoclonus rating scale, Purdue-Pegboard test, timed up and go test, functional and computerized balance tests, and Nottingham health profile were used when evaluating the patient. The patient underwent special neck exercises consisting of reeducation of neutral posture and cervical stabilization exercises for three days a week, totaling nine weeks. At the end of the treatment, improvement in the patient's posture, marked decrease in myoclonus, and significant improvements in fine hand skills, balance parameters, and quality of life were obtained. It is likely that the physiotherapy approach, consisting of special neck exercises, has improved postural control by contributing to the development of the sensory processes needed to achieve postural control. Therefore, special neck exercises have the potential to be an alternative treatment option for these patients.

Keywords: Hereditary ataxia, myoclonus, balance, physiotherapy, cervical stabilization

Öz

ADCK3 gen mutasyonu ile ilişkili serebellar ataksi, otozomal resesif geçiş gösteren serebellar ataksiler içerisinde yer alan kalıtsal bir ataksi çeşididir. Bu progresif atakside, epileptik nöbetler, piramidal bulgular ve miyoklonus gibi ek semptomlar görülebilir. Bu olgu sunumunun amacı, *ADCK3* gen mutasyonu ile ilişkili koenzim Q10 eksikliğine bağlı serebellar ataksi ve miyoklonusu bulunan 19 yaşındaki hastanın fizyoterapi ve rehabilitasyon programının sonuçlarını sunmaktır. Hastanın değerlendirmesinde uluslararası ataksi oranlama ölçeği, standardize mini-mental test, gözlemsel postür analizi, birleşik miyoklonus değerlendirme ölçeği, Purdue-Pegboard testi, zamanlı kalk yürü testi, fonksiyonel ve bilgisayarlı denge testleri ile Nottingham sağlık profili kullanıldı. Hastaya haftada 3 gün, toplam 9 hafta nötral postürün re-edükasyonu ve servikal stabilizasyon egzersizlerinden oluşan özel boyun egzersizleri uygulandı. Tedavi sonunda hastanın postüründe düzelme, miyoklonusta önemli ölçüde azalma, ince el becerileri, denge parametreleri ve yaşam kalitesinde önemli iyileşmeler elde edildi. Özel boyun egzersizlerinden oluşan fizyoterapi yaklaşımının postüral kontrolün sağlanması için ihtiyaç duyulan duyusal süreçlerin gelişimine katkıda bulunarak postüral kontrolü geliştirmiş olması muhtemeldir. Bu nedenle özel boyun egzersizleri bu hastalar için alternatif bir tedavi seçeneği olma potansiyeli taşımaktadır.

Anahtar Kelimeler: Herediter ataksi, miyoklonus, denge, fizyoterapi, servikal stabilizasyon

Introduction

Autosomal recessive cerebellar ataxias are hereditary neurological disorders, characterized by degeneration or abnormal development of the cerebellum and spinal cord. In most patients, symptoms appear before the age of 20 years. This group includes a wide variety of rare diseases, where each disease is caused by mutations in a particular gene(s). Cerebellar ataxia due to coenzyme Q10 (CoQ10) deficiency is one of the rare diseases in this group. This progressive ataxia usually begins in childhood. Symptoms such as epileptic seizures, pyramidal findings, developmental delay,

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mental retardation, and myoclonus may accompany cerebellar atrophy (1).

CoQ is a molecule found in all cell membranes, especially abundant in the mitochondria, and in humans, it consists of 10 units. It has cellular antioxidant properties and plays an essential role in mitochondrial energy production and electron transport in critical cellular pathways. It is involved in important biochemical reactions, such as beta-oxidation of fatty acids, biosynthesis of pyrimidines, and modulation of apoptosis. Numerous genes are involved in CoQ10 biosynthesis. According to the degree of mutation of these genes, primary CoQ10 deficiency occurs with a wide variety of clinical manifestations. Five major phenotypes are defined in primary CoQ10 deficiency: Encephalomyopathy, cerebellar ataxia, infantile multisystemic form, nephropathy, and isolated myopathy. To date, the mutation of the following eight genes is associated with CoQ10 deficiency: PDSS1, PDSS2, COQ2, COQ4, COQ6, ADCK3, ADCK4, and COQ9. Mutations of the aarF-domain-containing kinase 3 (*ADCK3*) gene, involved in the atypical kinase phosphorylation of COQ proteins, cause cerebellar ataxia due to CoQ10 deficiency (2).

Oral CoQ10 supplements are given for treating CoQ10 deficiency. While some patients respond well to this treatment, progression continues in others (1,2). Besides medical treatment, physiotherapy and rehabilitation programs should be included to reduce the symptoms as much as possible, facilitate coping, and bring the functional status to the best possible level. In this case report, considering the main complaints of a patient with cerebellar ataxia and myoclonus due to *ADCK3* gene mutation, a special neck exercise program was created, and its effect on the posture, myoclonus, fine dexterity, balance, and quality of life was investigated.

Case Report

The first complaints of a 19-year-old female patient started in 2014 with tremor in the hands and balance disorder, and over time, the tremor spread to her body. Her tremor mostly affected the neck, trunk, legs, and less often the arms. At the beginning of 2015, the patient presented for the first time due to increase in her complaints and was hospitalized in the Pediatric Neurology Service of Erciyes University (ERU) Medical Faculty Hospital. She was hospitalized for 10 days and underwent diagnostic research and drug trials. Her diagnosis could not be confirmed. The tremor was diagnosed as genetic ataxia, and medical treatment was started. However, on using a wide variety of drugs, they were ineffective, and genetic testing was requested for a differential diagnosis. An exom-sequencing analysis was performed at the Boğaziçi University in 2016, and homozygous mutations were detected in the *ADCK3* gene (c.1013C>T p.Ala338Val) (NM_020247.4). The patient's gait disorder progressed and a speech disorder started. The patient experienced a significant increase in tremor and myoclonus with stress. Cerebellar atrophy was observed on magnetic resonance imaging (MRI), and an increase in polyphasia was detected on the electromyography (EMG). The examinations were clinically compatible with CoQ10 deficiency, and in 2017, CoQ10 supplementation was started (800 mg/day). Besides CoQ10 supplementation, she was followed up with haloperidol drops (2+4), propranolol (2x1/2), clonazepam (quarter+half), and her psychiatrist prescribed her aripiprazole (5 mg/day) and sertraline (50 mg/day). The patient was referred to the physiotherapy and rehabilitation program. However, she did not participate in this program voluntarily. In the beginning of 2019, the patient was transferred to the Adult Neurology Department of ERU Medical Faculty Hospital. Spinal MRI and EMG findings were normal. In the movement analysis, activity was observed in the trunk muscles at a tremor frequency of 3-5 Hz. The use of some drugs was discontinued, and CoQ10, clonazepam (quarter + half), and sertraline (50 mg/day) were continued. In November 2019, the patient was again referred to the physiotherapy and rehabilitation program to improve her functional level. Her main complaints were gait disturbance, tremor in the upper and lower extremities, and myoclonus in the trunk.

Physiotherapy and Rehabilitation Program

Informed consent was obtained from the patient before starting the study.

The patient was included in a nine-week physiotherapy program; she attended a 45-minute session three days a week, accompanied by a physiotherapist. Considering the patient's main complaints, a special neck exercise program was created, which included cervical stabilization exercises and reeducation of the neutral spinal posture. Changes in the anatomical and physiological structure of the cervical flexor muscles, located deep in the neck, for different reasons, negatively affect postural stability by reducing proprioceptive information. The deep cervical flexors, including the longus colli and longus capitis muscles, have important roles in providing neck stability. Craniocervical flexion (CCF) is the primary function of these muscles. CCF exercises increase the coordination between anterior and posterior neck muscles and positively affect head control and postural stability (3).

A pressure biofeedback device (Stabilizer, Chattanooga, USA) was used for CCF exercises. The pressure biofeedback device was placed between the earlobe and chin projection, while the patient was in the supine hook lying position, and inflated to 20 mmHg pressure. In the first week of the treatment, the patient was taught how to perform the correct CCF movement without activating the superficial muscles. An increase in the activation of the superficial muscles was undesired, so the patient was told that this movement did not require force. She was asked to relax the tongue and palate muscles to reduce the activity of the superficial muscles. To achieve this, the patient was told to separate the tongue from the palate, if her tongue was on the palate, and slightly open her teeth. The patient was asked to look slightly toward the chest with her eyes. Starting at 20 mmHg, she was asked to maintain the movement at that level for 10 seconds. When successful 10 repetitions were performed with three-to-five-second rest intervals, the pressure was increased by 2 mmHg. The patient reached the level of 26 mmHg in the sixth week, and unilateral upper extremity movements were added to the program with CCF movement, to increase the dynamic stabilization by maintaining this level. In the eighth week, bilateral upper extremity movements were added to the program.

Regarding the reeducation of the upright neutral spinal posture, the patient was taught the proper sitting position. The training started from the lumbopelvic region. Scapular adduction and depression were taught for thoracic stability after achieving lumbopelvic alignment with awareness of normal lordosis (4). As a final step, the patient was asked to perform a gentle occipital lift. The same training was given in the standing position. Initially, the

trainings were run in front of a mirror to provide visual feedback for the patient. From the second week onwards, the patient was asked to practice the alignment training in front of the mirror at home. In each session, whether the patient did the exercises correctly or not was checked, and corrections were made if necessary. After the patient's postural awareness increased, she was asked to practice this posture during the day and keep it as much as possible in her daily activities.

Evaluations

The patient's demographic and clinical information were recorded. The severity of ataxia was evaluated with the international cooperative ataxia rating scale (ICARS) (5) and the cognitive level with the mini-mental state examination (MMSE) (6). Before and after the physiotherapy program, the posture was evaluated using observational posture analysis (7); myoclonus, unified myoclonus rating scale (UMRS) (8); fine dexterity, Purdue Pegboard test (9); balance, functional tests [Berg balance scale (BBS) and timed up and go (TUG) test] (10,11) and computerized devices (HUR Labs Balance Software Suite device) (12); quality of life with the Nottingham health profile (NHP) (13).

The ICARS is a scale developed to evaluate ataxia symptoms. It consists of four subscales, including posture and gait disturbances, kinetic functions, speech disorders, and oculomotor disorders. The total score of the subscales ranges from 0 to 100, and as the score increases, the severity of ataxia increases (5).

The MMSE is a test used to assess the cognitive function and consists of orientation, recall, attention and calculation, registration, and language headings. It consists of 11 questions, and a maximum of 30 points can be obtained. Scores between 24 and 30 points are considered normal, those between 18 and 23 indicate mild cognitive impairment, and those below 17 indicate severe cognitive impairment (6).

The head and trunk posture of the patient was examined from the anterior, posterior, and lateral aspects with observational posture analysis (7).

To assess myoclonus, the subscales of the UMRS, namely, myoclonus at rest, stimulus sensitivity, myoclonus with action, and functional tests, were used. Video recording was taken according to the standard protocol for scoring this scale (8). The same person scored the scale before and after the treatment. A high score indicates an increase in myoclonus severity.

The Purdue Pegboard test is used to assess fine dexterity. The testing board consists of two vertical rows side by side and has 25 small holes in each row. In this test, the person is asked to do certain tasks on the board for 30 to 60 seconds. The board includes small pins, washers, and collars. The test consists of five substeps, including an evaluation using the right hand, evaluation using the left hand, evaluation using both hands, the sum of the first three evaluations, and assembly. The patient is asked to place as many pins as possible into the holes using the tested hand within 30 seconds for each of the right hand, left hand, and both hands assessment. The score at the end of the time is recorded. In the fourth step, no evaluation is made, and the sum of the first three evaluation results is calculated. In the assembly step, pins, washers, and collars are placed on top of each other using both hands in coordination within 60 seconds. The score is obtained by multiplying the number of pins, washers, and collars, placed at the end of the time, by four and is recorded (9).

Balance assessment was done using the functional balance tests and computerized balance device. The functional balance tests included BBS and TUG test, which had Turkish validity and reliability (10,11). The BBS consists of 14 items that assess balance during activities, frequently performed in daily functions, and static sitting and standing balance. Each item is scored between 0 and 4. A low score is associated with an increased risk of falling (10).

The TUG test is a widely used test to evaluate functional mobility and dynamic balance. After the patient was taught the test, she was asked to stand up, walk 3 m (10 ft), turn back, and sit down again. After each test, the patient rested. The test was repeated three times. The completion time of each test was recorded, and the average value was calculated. A high duration is associated with an increased risk of falling (11).

For the computerized balance assessment, the HUR Labs Balance Software Suite device was used (12). The evaluation was made according to the Romberg test and limits of stability test protocol included in the device. The Romberg test protocol evaluates the static balance and includes measurements made under four conditions, each lasting 30 seconds (eyes open/stable platform, eyes closed/stable platform, eyes open/unstable platform, and eyes closed/unstable platform). At the end of the test, the static balance score, proprioception disturbance score, visual dependency score, and vestibular dominant score are recorded. A decrease in the proprioception disturbance score indicates an increase in the patient's proprioceptive input, a decrease in the visual dependence score indicates a decrease in visual information dependency, and a decrease in the vestibular dominant score indicates a decrease in the dominance of the vestibular system in maintaining balance. The changes indicated in these parameters are an indication that the static balance has improved. The limits of stability test evaluates the dynamic balance and consists of four phases, including forward, backward, rightward, and leftward. After each test, a rest break was given and the patient was asked to bend as much as possible in each direction for eight seconds without taking a step in the normal posture. The mean score of the bending angle was obtained for each direction. An increase in score is associated with increased balance.

The NHP, a general health questionnaire, was used to assess the quality of life. This questionnaire consists of 38 items and six subscales, namely, emotional reactions, sleep, social isolation, physical mobility, energy, and pain. The total score of the questionnaire ranges from 0 to 600, and an increase in scores reflects a lower quality of life (13).

Results

Our patient is a 19-year-old woman, who is 161 cm tall and has a body weight of 60.1 kg and body mass index of 23.19 kg/m^2. Her education level is high school. Her MMSE score indicates a cognitive level of 27, and the ICARS score indicates that the severity of ataxia is 20.

The observational posture analysis, performed before the treatment, revealed forward head posture, significant height difference between the shoulders (the left shoulder is higher) and protraction, increased thoracic kyphosis, and right lateral flexion of the trunk. After the treatment, all problems were significantly

reduced. It was observed that the head and shoulders approached the neutral position, the thoracic kyphosis was reduced, and the trunk was in the neutral position, instead of lateral flexion.

Table 1. UMRS and Purdue Pegboard test results before and after the treatment

	Before treatment	After treatment
UMRS		
Myoclonus at rest	31	2
Stimulus sensitivity	0	0
Myoclonus with action	33	14
Functional tests	13	9
Purdue Pegboard test		
Right hand	7	8
Left hand	5	5
Both hands	5	5
Right + left + both hands	17	18
Assembly	0	16

UMRS: Unified myoclonus rating scale

According to the UMRS, the scores of the subscales, myoclonus at rest, myoclonus with action, and functional tests, decreased after treatment compared with before treatment (Table 1).

In the Purdue Pegboard test, before the treatment, the patient could not score in the assembly task performed within 60 seconds, while, after the treatment, she achieved 16 points. Moreover, while the right hand pin insertion score increased from seven to eight, other parameters remained unchanged (Table 1).

The patient's balance and gait test results are shown in Table 2. It was observed that the patient's static balance score increased, while the scores of proprioception disturbance, visual dependency, and vestibular dominant decreased. An increase was detected in all parameters of the limits of stability test. A decrease was detected in the time of the TUG test. There was no change in the BBS score of the patient, which was high before the treatment.

On examining the quality of life findings, it was observed that the quality of life increased with the decrease in the scores of all subparameters, except social isolation, and the total NHP score decreased from 305.62 to 197.97 (Table 3).

Discussion

The functional results of special neck exercises were investigated in a patient with cerebellar ataxia and myoclonus associated with

Table 2. Changes in balance parameters after physiotherapy

	Before treatment	After treatment
Romberg test		
Static balance score	75	78
Proprioception disturbance score	95	72
Visual dependency score	87	58
Vestibular dominant score	97	86
Limits of stability test		
Forward	0.47	2.85
Backward	1.17	6.74
Rightward	0.28	7.96
Leftward	1.25	6.88
TUG test (sec)	8.82	7.95
BBS	54	54

TUG: Timed up and go, BBS: Berg balance scale

Table 3. Results of the quality of life after physiotherapy

	Before treatment	After treatment
NHP		
Emotional reactions	66.92	19.78
Sleep	12.57	0
Social isolation	84.03	84.03
Physical mobility	21.99	20.09
Energy	100	60.8
Pain	20.18	13.22
Total	305.62	197.97

NHP: Nottingham health profile

CoQ10 deficiency, which is one of the rare autosomal recessive cerebellar ataxias. Significant improvements were achieved in the patient's posture, fine dexterity, myoclonus, balance, and quality of life parameters.

In ataxias that occur as a phenotype associated with CoQ10 deficiency, atrophy occurs in the cerebellum, and the cerebellar ataxia manifests itself as the main problem. Although the type and severity of the findings in cerebellar ataxias vary according to the affected area of the cerebellum, the most common disorders are postural control disorders, coordination problems, hypotonia, tremor, dysarthria, and gait disturbances. The dependence on visual information increases in these patients. Myoclonus may also accompany this picture (14). Although CoQ10 supplements given in this disease group are beneficial in some patients, drug treatments are insufficient in many types of autosomal recessive cerebellar ataxias (1,14). In patients where drug treatments are insufficient, it is crucial that they participate in physiotherapy and rehabilitation to cope with these symptoms, by identifying the problems that bother the patients the most and affect functionality. The physiotherapy program aims to determine the main complaints of the patient and bring the functional status to the best possible level.

In this patient, considering the main complaints, the somatosensory information was increased to improve the functional level. The somatosensory information is essential for postural control. Particularly, proprioception is the primary source of postural responses. Since the neck region is where the proprioceptive receptors, such as muscle spindles, are densely located, it provides afferent input in stability. Studies have shown that many receptors related to the sense of position are located on the deep cervical flexor muscles, such as the longus capitis and longus colli muscles (3). Atrophy and fat infiltration in these muscles decrease the proprioceptive sensation. Altered afferent somatosensory information causes altered efferent input from the cervical muscles. The altered efferent information leads to dynamic instability of the cervical region or inhibition of voluntary movements, causing decreased or inhibited spinal reflexes. Due to these changes, a decrease in the functional ability and motor control patterns of the cervical region occurs, and postural stability is adversely affected (3). Cervical stabilization exercises were developed to increase the motor control of the cervical spine. In this program, the muscles in focus are the longus capitis and longus colli muscles. The first phase of the exercise program is to activate and train these muscles. In line with its functional support role, low-load endurance exercises are applied to train the deep muscles. Low-level endurance training of the deep neck flexors begins as soon as the patient performs the CCF movement correctly. Spinal and pelvic posture control training is also included in this program. Maintaining a neutral upright spinal posture at regular intervals throughout the day has many benefits. Mechanically, the upright neutral posture increases the activation of the deep flexor muscles by reducing the passive load on the cervical structures (4).

With special neck exercises, the balance disturbance and myoclonus in the trunk, the main complaints of the patient, decreased. Moreover, postural awareness improved and fine hand skills increased. It is thought that the motor control of the cervical region improves with this exercise program, and accordingly, correct proprioceptive information positively affects postural stability. Simultaneously, stability in the proximal joints is needed for quality movement in the distal joints. Depending on the increase in the motor control of the cervical region, the dexterity of the patient was positively affected. The decrease in basic complaints and the increase in functional status increased the patient's quality of life.

Physiotherapy programs based on static and dynamic balance and coordination exercises are recommended for patients with cerebellar ataxia. There is moderate evidence in the literature that these programs improve postural capacity. Therefore, there is a need to investigate the effectiveness of different treatment programs in this patient group (15). Based on the fact that the cervical region is rich in proprioceptive receptors, the aim is to improve postural control. The training is performed in the supine position. We think that these programs can be used as an option in the clinic to improve postural control in patients with poor balance. Simultaneously, a decrease in the severity of myoclonus was achieved in our patient. A physiotherapy protocol that reduces myoclonus has not been found in the literature for this patient group.

The only limitation of our study was that we did not examine the long-term results in our patient. Knowing the duration of the effects will be important in evaluating the effectiveness of this special program we have implemented. Long-term randomized controlled studies with a large number of patients are needed to obtain clear results on the effectiveness of the program.

Ethics

Informed Consent: Informed consent was obtained from the patient before starting the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., Concept: Ö.M., S.B., Design: Ö.M., S.B., M.G., Data Collection or Processing: Ö.M., Analysis or Interpretation: Ö.M., S.B., Literature Search: Ö.M., Writing: Ö.M., S.B.

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