CASE REPORT OLGU SUNUMU

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The Impact of Mood Disorders on the Rehabilitation Process in a Patient Diagnosed with CADASIL

CADASIL Tanılı Hastada Duygudurum Değişikliklerinin Rehabilitasyon Sürecine Etkisi

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ABSTRACT Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease that can cause different clinical symptoms such as recurrent ischemic attacks, migraine, epileptic seizures, and dementia. In this case report, a 45-year-old female patient was diagnosed with CADASIL disease after having recurrent ischemic cerebrovascular events a year apart, after genetic evaluation performed by neurology revealed a mutation in the gene encoding the NOTCH receptor. The patient was admitted to our clinic for rehabilitation, and sudden mood changes led to disruptions in the rehabilitation program. The patient was referred to a psychiatrist, and it was concluded that the mood disorders were attributed to CADASIL disease. In this case, we reported the effects of mood changes in CADASIL on the rehabilitation program and the positive impacts of the treatment of mood changes on the clinical process. We wanted to emphasize the importance of psychiatric disorders that may accompany CADASIL patients in the rehabilitation process.

Keywords: CADASIL; mood disorders; rehabilitation

ÖZET Serebral otozomal dominant arteriyopati ile subkortikal enfarktlar ve lökoensefalopati [Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)] tekrarlayan iskemik ataklar, migren, epileptik nöbetler ve demans gibi farklı klinik tablolara neden olabilen kalıtsal serebral küçük damar hastalığıdır. Bu olgu sunumunda, 45 yaşında kadın hasta bir yıl arayla rekürren iskemik serebrovasküler olay geçirmesi üzerine nöroloji tarafından yapılan genetik incelemede NOTCH reseptörünü kodlayan gende mutasyon saptanarak CADASIL hastalığı tanısı alıyor. Kliniğimize rehabilitasyon tedavisi için kabul edilen hastada gelişen ani duygudurum değişiklikleri rehabilitasyon programında aksamalara neden oldu. Psikiyatriye danışılan hastada gelişen duygudurum bozukluklarının CADASIL hastalığına bağlı olduğu sonucuna varıldı. Bu olgu sunumunda CADASIL tanısı alan hastamızda görülen duygudurum değişikliğinin rehabilitasyon programımıza olan etkilerini ve duygudurum değişikliğinin tedavi edilmesinin klinik sürece yansıyan olumlu etkilerini raporladık. CADASIL hastalarında eşlik edebilecek psikiyatrik bozuklukların rehabilitasyon sürecindeki önemini vurgulamak istedik.

Anahtar Kelimeler: CADASIL, duygudurum bozukluğu, rehabilitasyon

Cerebral autosomal dominant arteryiopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessel disease of the brain.[1] In 1996, Joutel et al. identified the underlying genetic cause of the disease as a mutation in the NOTCH3 gene, located on the short arm of chromosome 19, which encodes the NOTCH receptor.[2] CADASIL is characterized by adult-onset recurrent ischemic stroke, cognitive decline, history of migraine with aura, and the presence of widespread white matter lesions and subcortical infarcts on brain magnetic resonance imaging (MRI). CADASIL is the most common cause of hereditary stroke and vascular dementia in adults.[3] Although the age of the first clinical stroke varies, it typically occurs between 45-50 years on average. Patients

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typically present with classic lacunar strokes, such as pure motor hemiparesis, ataxic hemiparesis, dysarthria, pure sensory stroke, or sensorimotor stroke.[4]

In addition to subcortical infarcts, the clinical features defining CADASIL include a history of migraines, cognitive impairment, and psychiatric disorders.[4,5] Although psychiatric disorders typically manifest after a diagnosis of CADASIL, they may present as the first symptom in 15% of cases, particularly in younger patients with insufficient or incorrect diagnoses. The most common mood disorders observed in CADASIL are apathy and major depression.[3] Other psychiatric conditions that may develop include anxiety disorders, adjustment disorders, agoraphobia, behavioral and personality disorders, psychotic disorders, delusions, panic disorders, substance abuse, alcoholism, hallucinations, and schizophrenia.[5] Although clinical, imaging, and pathological studies are used for diagnosis, the gold standard is the identification of a NOTCH3 mutation.[6]

In this case report, we present a patient diagnosed with CADASIL via NOTCH3 genetic analysis, who developed recurrent ischemic strokes and bilateral hemiplegia following encephalopathy associated with coronavirus (severe acute respiratory syndrome-coronavirus-2) infection. We evaluated the impact of mood changes, a component of the disease, on our rehabilitation program.

CASE REPORT

Our patient, a 45-year-old married woman with one child, was pursuing a doctoral degree at a university. She was diagnosed with viral pneumonia secondary to coronavirus infection after presenting with symptoms of cough and shortness of breath and was started on symptomatic treatment. One day later, she returned to the hospital with complaints of speech loss. Diffusion MRI revealed acute ischemic diffusion restriction, leading to hospitalization and a 45-day stay in the intensive care unit. During her hospital stay, the patient developed subcortical encephalopathy. One year after being discharged, she experienced an ischemic attack that resulted in left hemiplegia, followed by a second ischemic attack a year later, leading to right hemiplegia. Extensive laboratory testing conducted to evaluate the etiology of the strokes revealed no abnormalities. Genetic analysis was performed due to characteristic MRI findings and recurrent strokes, confirming a NOTCH3 gene mutation and leading to a diagnosis of CADASIL. During the patient's' second ischemic attack, MRI revealed acute ischemia in the posterior limb of the left internal capsule. In addition, there were widespread ischemic-gliotic foci in the bilateral cerebral hemispheres, basal ganglia, pons, frontoparietal region, and periventricular white matter, consistent with Fazekas grade 3. The MRI also showed multiple lacunar infarcts, some of which were new. The patient's brain MR findings are shown in Figure 1.

The patient was referred to us for rehabilitation because of cerebrovascular events and was admitted to our service. The patient reported a history of multiple neurology clinic visits for chronic headaches since childhood. No vascular risk factors or other significant medical history were identified.

The patient was evaluated in the Physical Medicine and Rehabilitation outpatient clinic and was subsequently hospitalized for rehabilitation. On physical examination, the joint range of motion was

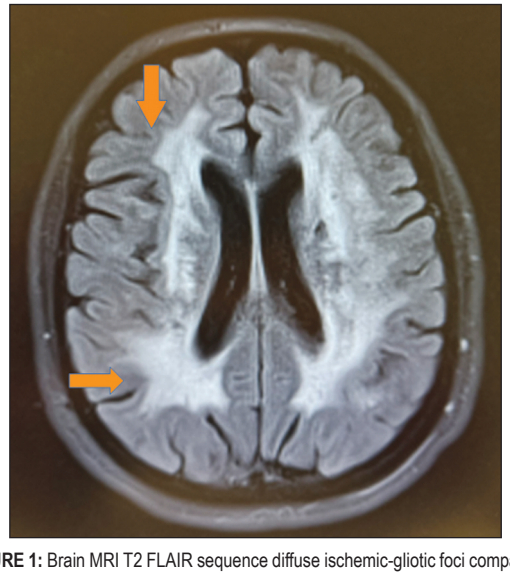

FIGURE 1: Brain MRI T2 FLAIR sequence diffuse ischemic-gliotic foci compatible with Fazekas grade 3 (areas indicated by orange arrows)
MRI: Magnetic resonance imaging

normal in the upper extremities, while dorsiflexion was limited in both ankles. The Brunnstrom recovery stage was 6 for both the upper extremities and hands and 5 for the lower extremities. According to the Modified Ashworth Scale, spasticity was graded as stage 2 in the bilateral gastrocnemius muscles. The cranial nerve examination was normal. Deep tendon reflexes were hyperactive in the bilateral upper and lower extremities. Hoffman's and Babinski reflexes were bilaterally positive, and clonus was present in both lower extremities. The patient exhibited full long and short sitting balance and could ambulate with a walker. The patient had neither bladder sensation nor control and exhibited dysarthria with slurred speech.

The patient was enrolled in a neurological rehabilitation program consisting of 30 sessions of neurophysiological exercises, upper and lower extremity active assisted range of motion exercises, strengthening exercises, functional electrical stimulation of the lower extremities, gait, posture, and balance-coordination exercises, and occupational therapy. Virtual reality-assisted walking and assistive device use training were conducted. The patient was admitted to the speech and language therapy program for dysarthria by a speech and language therapist. Swallowing function was evaluated, revealing adequate laryngeal elevation and timely reflex initiation although the oral phase was prolonged. The patient laughed during feeding, which led to delayed bolus transfer and aspiration. Although no swallowing dysfunction was detected, aspiration occurred due to laughing fits. The patient was evaluated cognitively, and the Montreal Cognitive Assessment score was 11, indicating deficits in memory and executive function, necessitating cognitive therapy.

During rehabilitation, the patient experienced mood fluctuations. Sudden laughter outbursts and occasional crying episodes negatively impacted the rehabilitation process, also leading to aspiration during swallowing. The patient was consulted with psychiatry, and it was revealed that she had been diagnosed with a mood disorder four years prior, following a stressful event. She had been prescribed quetiapine (Seraquel,AstraZeneca,USA) 25 mg/day, chlorpromazine (Largactil,AventisPharma,FRA) 50 mg/day, and sertraline (Lustral,Pfizer,USA) 150 mg/day, from which she had partially benefited. However, she discontinued her medication and psychiatric follow-ups. The psychiatric evaluation revealed good self-care, complete orientation, and clear consciousness, with a labile effect characterized by bouts of laughter and crying. Thought processes were organized and goal-directed. Sleep and appetite were regular, and the patient denied suicidal or homicidal thoughts. Her treatment was adjusted to sertraline 200 mg/day, quetiapine 50 mg/day, and chlorpromazine 50 mg/day, and she was enrolled in psychotherapy. Due to increased sleepiness, quetiapine was reduced to 25 mg/day. At the 2-week follow-up, mood improvements and reduced laughing and crying episodes were observed, with subsequent increased participation in the rehabilitation program and reduced aspiration episodes during swallowing.

At the end of the 6-week rehabilitation program, the patient's laughter and crying episodes had significantly decreased, leading to increased participation in the rehabilitation program and improvements in walking distance and quality. Written and verbal consent was obtained from the patient for the case presentation.

DISCUSSION

CADASIL is a rare, hereditary, autosomal dominant disease caused by a mutation in the NOTCH3 gene, which leads to dementia and disability in adults over 40 years of age.[7] The onset and clinical manifestations of CADASIL vary significantly among patients. The most common symptoms include typical migraines with aura, subcortical ischemic stroke, mood disorders, psychiatric disorders, and cognitive impairment.[8] In addition to these classic symptoms, rarer clinical findings such as incontinence, epilepsy, brain hemorrhage, pseudobulbar palsy, and gait abnormalities have also been reported in the literature.[9] In our case, the patient developed encephalopathy during a corona virus disease-2019 infection, followed by recurrent strokes occurring at 1-year intervals. The diagnosis of CADASIL was confirmed through the identification

of a NOTCH3 gene mutation. Coronavirus infection, through endothelial damage and procoagulant effects, can lead to ischemic and hemorrhagic strokes as well as various neurological symptoms. However, encephalopathy is a rare manifestation. In a case report by Giménez et al., similar to our case, a NOTCH3 gene mutation was identified in a patient who developed encephalopathy due to acute coronavirus infection, leading to a diagnosis of CADASIL.[10]

Progressive cognitive impairment, gait disturbances, and depression are the major clinical features of CADASIL. In a meta-analysis by Xie et al., which included 77 studies, it was found that white matter damage in specific areas was strongly associated with impairments in various cognitive domains. White matter lesions or microbleeds affecting the pathways connecting the cortical and subcortical regions lead to frontal-subcortical damage, causing cognitive impairments in executive function and attention. The corpus callosum, which contains commissural fibers connecting the frontal lobe to other cortical areas, is believed to be damaged early during CADASIL.[11] In our patient, widespread ischemic-gliotic foci and lacunar infarcts consistent with Fazekas grade 3 were observed in the pons, frontoparietal, and periventricular white matter, which aligns with these findings. Mood disorders are frequently observed during CADASIL. In a study analyzing 13 cohorts, the prevalence of mood disorders in CADASIL patients was found to range from 7% to 50%. Mood disorders may manifest not only as depressive symptoms but also as irritability, a tendency toward anger, and excessive or inappropriate laughing or crying. Depression has an independent impact on the quality of life of patients.[12] Behavioral changes in CADASIL can occur at any stage of the disease but are often associated with the onset of cognitive changes. Initially, patients or their relatives frequently notice personality changes, such as increased irritability, although these changes are rarely self-reported and need to be actively inquired about. A decrease in interest and activity is also frequently observed, which typically progresses to apathy, one of the most common behavioral symptoms of the disease. Apathy, defined as a significant reduction in goal-directed behavior, has been reported in more than one-third of symptomatic individuals.[13] In this case, the patient's cognitive and mood disorders were consistent with those observed in CADASIL and had a negative impact on the rehabilitation process. Initially, participation in the rehabilitation program was limited; however, following treatment for these conditions, the patient's engagement improved, leading to positive rehabilitation progress.

CADASIL is a disease that negatively affects a patient's cognitive, motor, and behavioral functions as well as their overall quality of life. As demonstrated in our case, mood disorders and cognitive impairments negatively affect the rehabilitation process of patients. This case report highlights the impact of mood disorders on the rehabilitation of patients with CADASIL and emphasizes the need to recognize these conditions as essential considerations in disease management.

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