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CASE REPORT

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CADASIL Syndrome Presenting as Obsessive-Compulsive Disorder: A Case Report

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ABSTRACT

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a small vessel disease. It is an autosomal dominant inherited disease caused by a mutation in the Notch3 gene. Clinically, it usually presents with recurrent transient ischemic attacks, strokes, vascular dementia, migraine with aura, cognitive impairments and psychiatric symptoms. Cranial MRI is the most useful imaging modality to demonstrate the characteristic radiological findings of CADASIL and gene analysis is the gold standard for diagnosis. Although the clinical manifestations are mainly neurological, CADASIL can also present with psychiatric disorders. Psychiatric disorders are one of the main clinical manifestations of the disease, with a prevalence rate ranging from 20 to 41%. Among psychiatric disorders, mood disorders are the most commonly reported, and other psychiatric diagnoses include psychotic disorders, anxiety disorders, adjustment disorder, personality disorders, behavioral disorders, substance dependence and abuse. In this case report, a paitent with CADASIL presenting with obsessive-compulsive disorder at a relatively young age will be presented.

Keywords: CADASIL, neuropsychiatry, obsessive-compulsive disorder

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INTRODUCTION

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease caused by a mutation in the neurogenic locus notch homologous protein-3 (Notch3) gene located on chromosome 19 (1). The prevalence of the disease is thought to vary between 2 and 5 per 100.000 individuals (2). The genesis of the disease can be summarized as follows: A mutation occurs in the Notch3 gene, which encodes a protein found predominantly in vascular smooth muscle cells and regulates the survival and function of these cells. The mutation in the Notch3 gene causes abnormal accumulation of this protein on the surface of smooth muscle cells. The mutant Notch3 gene cannot normally form its product, interleukin-1 beta-converting enzyme inhibitor protein (cFLIP). The functional deficiency of cFLIP affects the signaling pathway within the cell and this leads to intracellular damage and Fas ligand-mediated cell death (3). Clinically, it usually manifests with recurrent transient ischemic attacks, strokes, vascular dementia, migraine with aura, cognitive impairments, and psychiatric symptoms (4). Transient ischemic attacks and migraine with aura manifest in the relatively early stages of the disease and have been more thoroughly defined and studied. However, information on cognitive impairment and psychiatric disorders is still insufficient. The cognitive impairments observed in CADASIL are usually associated with impairment of frontal lobe function, particularly in the area of executive functions and attention. In addition, symptoms such as slowing of mental and motor skills and difficulty in concentration may also be observed.

Highlights

- **In CADASIL, psychiatric symptoms can also be observed in addition to neurologic symptoms.**
- **Mood disorders are commonly observed in patients with CADASIL.**
- **A rare case of CADASIL presenting as obsessive-compulsive disorder is presented.**

As the disease progresses, typical symptoms of subcortical vascular dementia appear.

The most useful imaging modality for demonstrating the characteristic radiological findings of CADASIL is brain Magnetic Resonance Imaging (MRI). In patients with CADASIL, brain MR imaging findings are mostly seen as diffuse areas of hyperintensity in the subcortical white matter on T2 and FLAIR weighted slices. Lacunar infarcts, microbleeds, and subcortical lacunar lesions may also be observed (5). These radiological findings can be detected even when the disease is asymptomatic. Pathologically, electron microscopic demonstration of granular osmophilic material

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(GOM) in vascular smooth muscle cells is also a pathognomic finding for CADASIL (4). However, the gold standard for the diagnosis of CADASIL is gene analysis.

Although neurological symptoms predominate, CADASIL can also present with psychiatric disorders. Psychiatric disorders are among the main clinical manifestations of the disease, with an incidence ranging from 20 to 41%. The cause of psychiatric disorders in CADASIL is not yet fully understood. However, similar to other cerebrovascular diseases, it is thought that damage to cortical-subcortical circuits may play a role in this condition (6). Among the psychiatric disorders observed in CADASIL, mood disorders are the most commonly reported with a rate of 9–41%. Other psychiatric diagnoses encountered include psychotic disorders, anxiety disorders, adjustment disorders, personality disorders, behavioral disorders, substance addiction, and abuse (7). When the literature was examined, as far as can be seen, no publication showing the association between CADASIL and obsessive-compulsive disorder was found. Therefore, our case is important both because it is a case of CADASIL at a very young age and because it is the first case presented with obsessive-compulsive disorder. In this study, we aimed to present a case of CADASIL with obsessive-compulsive disorder.

CASE

Twenty-five years old, male, associate degree graduate, unemployed patient living with his family was admitted to the Psychiatry outpatient clinic with complaints of handwashing, thinking that his hands were dirty, checking whether the doors were closed, checking whether the internet was turned off, and walking away from the environment with the thought that the people taking selfies would capture him in the photo frame.

In his history, it was understood that the complaints of the patient first started at the age of 17 in the form of obsession with contamination, obsession with suspicion, and compulsion to clean and check. At that time, he had a tendency to stay away from the environment where selfies were taken with the thought that the people taking selfies would capture him in the photo frame, and he was also worried that his friends would do something behind him. Due to these complaints, the patient was started on fluoxetine 20 mg/day and continued this treatment for many years, but no improvement was observed in his complaints.

Two years ago, fluoxetine treatment was discontinued and escitalopram 10 mg/day treatment was started in the Neurology outpatient clinic. When he first applied to our outpatient clinic, the patient reported that he thought that people he did not know would capture him in the photo frame while taking selfies. He did not fully believe this thought but he still felt the need to get away from the environment because he could not be sure. This thought of the patient was evaluated as an overvalued idea. The patient had no history of stroke, migraine, or seizure. There was no known or diagnosed neurologic or psychiatric disease in the family history. It was learned that his neurologic complaints started two years ago as a headache and he was diagnosed with CADASIL syndrome one year ago.

In the psychiatric examination, it was observed that his mood was euthymic, his affect was compatible with the content of thought, his judgment was intact, there was no perception disorder, and there were no delusions in the content of thought, however, he had overvalued ideas. The Yale-Brown Obsession Compulsion Scale (Y-BOCS) score was 22 and the severity of the disease was calculated as 4 in the Clinical Global Impression Scale (CGI) scores. On neurologic examination, consciousness was clear, orientation was complete, psychomotor activity was normal, cranial nerve examination was normal except for external nystagmus in the left eye, dysarthria, dysmetria, and dysdiadokinesis were absent, muscle tone in the upper and lower extremities on both sides was 5/5, tremor and increased tone were absent, Romberg test was negative, deep tendon reflexes on both sides were normal.

In laboratory tests, hematologic tests were within normal limits. In biochemical tests, all values were normal. Thyroid function tests, B12, and folic acid levels were within normal limits. In the brain MR images of the patient, hyperintense lesions involving the deep periventricular and subcortical white matter, involving the external capsule but not affecting the U fibers were found in the bilateral cerebral hemispheres in T2 and FLAIR sections (Figure 1 and 2). Genetic testing performed at an external center revealed a c1276C>T mutation in the NOTCH3 gene.

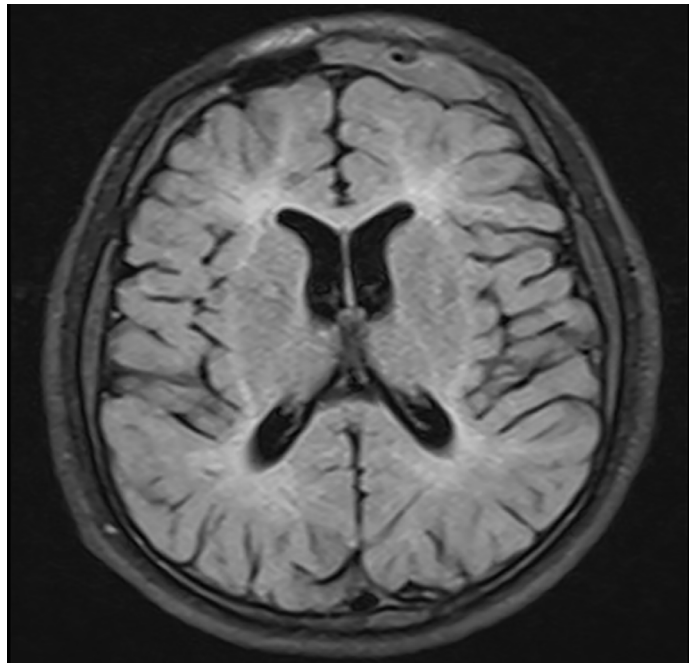

Figure 1. Subcortical hyperintense lesions in bilateral cerebral hemispheres on FLAIR sections involving the external capsule but not U fibers.

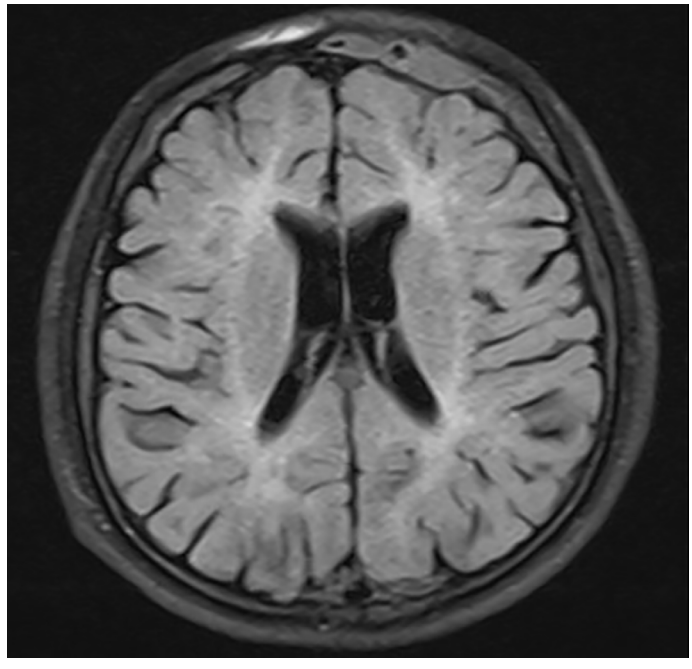

Figure 2. Subcortical hyperintense lesions in bilateral cerebral hemispheres on FLAIR sections involving the external capsule but not U fibers.

Our patient was followed up psychiatrically. In addition to escitalopram 10 mg/day treatment, olanzapine 2.5 mg/day treatment was added because of overvalued ideas. In the follow-up examination performed one month later, it was observed that the obsession with contamination and compulsions to clean up decreased, and the obsession with suspicion, control compulsions, and overvalued ideas completely recovered. The Yale-Brown Obsession Compulsion Scale (Y-BOCS) score was 10 and the severity of the disease was calculated as 3 and the improvement score was calculated as 2 in the Clinical Global Impression Scale (CGI) scores, respectively. The Montreal Cognitive Assessment Test (MoCA) score was calculated as 24. One point was lost from sentence repetition, 1 point from verbal fluency test, 1 point from pairwise similarities, and 3 points from delayed recall. In delayed recall, he was able to remember 2 out of 5 words. When semantic cues were given for the 3 words, he could not remember any of them, but when phonemic cues were given, he could remember 2 words but not one. The patient was informed about both Neurology and Psychiatry outpatient follow-up. Our patient is currently being followed up regularly in the Psychiatry outpatient clinic.

DISCUSSION

CADASIL is a syndrome clinically characterized by a series of neurological and psychiatric symptoms. The disease usually affects adults of both sexes and clinical symptoms appear between the 3rd and 6th decade (4). In this context, our case is a very young CADASIL case. The patient had no neurologic symptoms except for a headache that had been persisting for about two years and nystagmus that developed in the last year. However, although his score on the MoCA Test was normal, he lost 1 point for sentence repetition, 1 point for verbal fluency test, 1 point for pairwise similarities, and 3 points for delayed recall. In addition, it was noted that when semantic cues were given for 3 unfamiliar words, he could not remember any of them, but when phonemic cues were given, he could remember 2 words but not one. Although the result of the MoCA test performed for neuropsychiatric evaluation in our case is an indication that cognitive impairment has started in the patient, although not symptomatic, the fact that cognitive impairment was not evaluated with more detailed neuropsychiatric tests is an important limitation.

Psychiatrically, he had obsessive-compulsive disorder symptoms for about six years. CADASIL is known to be associated with psychiatric disorders. In the literature, it has been reported that 10% of patients with CADASIL have major depression and 23% have adjustment disorder (8). Again, apathy independent of depression has been reported as a major clinical manifestation in 40% of patients (9). In addition, cases of bipolar disorder (10) and psychotic disorder (11) in association with CADASIL have also been reported in the literature.

Our case is a case of obsessive-compulsive disorder with obsessions of contamination and suspicion and compulsions of cleaning and control. He also had overvalued ideas that did not cross the border of psychosis. Obsessive-compulsive disorder is a disorder characterized by recurrent obsessions and/or compulsions, usually with a chronic course, which significantly affects the functionality of the individual. Studies on the neurobiology of obsessive-compulsive disorder have suggested structural and functional abnormalities in frontal-striatal-thalamic-cortical circuits (12). These cortical and subcortical circuits are interconnected through white matter. It is thought that disruptions in white matter microstructure may play a role in the pathophysiology of obsessive-compulsive disorder. Studies have shown white matter abnormalities in patients with obsessive-compulsive disorder (13). When the literature is examined, it is observed that there are no publications reporting the association between CADASIL and obsessive-compulsive disorder, but there are case reports of obsessive-compulsive disorder after cerebrovascular events (14,15). In these case reports, it was stated that the most important brain region responsible for the development of obsessive-compulsive disorder following a cerebrovascular event was the basal ganglia and the frontal lobe and basal ganglia were held responsible for the symptoms. In another case report, it was reported that only compulsions without obsessions were observed in the subcortical region after stroke and it was suggested that the observation of compulsions without obsessions might occur through the dysfunction of a network including external globus pallidus and dorso-lateral prefrontal regions (16). In another case report in which obsessive-compulsive symptoms were reported after chronic cerebral ischemia, it was stated that lesions in the basal ganglia and fronto-occipito-parietal dysfunction could explain the relationship between the two conditions (17). Apart from these findings indicating that obsessive-compulsive disorder develops after cerebrovascular events, it has also been reported that the risk of stroke increases in patients with obsessive-compulsive disorder (18).

The exact mechanism of obsessive-compulsive disorder in our case is unknown. There may be a possible common dysfunction for both obsessive-compulsive disorder and CADASIL. Considering the data suggesting that white matter abnormalities may play a role in the pathophysiology of obsessive-compulsive disorder, the subcortical white matter hyperintensities observed in our case and the neuropsychological test findings suggesting the onset of cognitive impairment, as well as the occurrence of obsessive-compulsive symptoms in conditions such as stroke and cognitive impairment in which white matter lesions are thought to play a role, suggest that there may be a cause-effect relationship between these two conditions. However, since it was understood that obsessive-compulsive disorder symptoms in our patient started long before neurologic symptoms and signs, these two conditions were evaluated as comorbidity rather than a cause-and-effect relationship.

In conclusion, although the incidence of CADASIL in clinical practice seems to be low, the number of case reports related to the disease is increasing day by day. When neurologic manifestations such as stroke or transient ischemic attack occur, more imaging is usually performed, whereas in the presence of psychiatric symptoms, the diagnosis of CADASIL may be missed or diagnosed late because imaging is less frequently ordered (19). Therefore, CADASIL, a hereditary cerebrovascular disease, should be considered as a potential differential diagnosis in patients with different neurologic and psychiatric complaints and these patients should be evaluated in detail in terms of psychiatric findings.

Informed Consent: The patient was informed before the study and written informed consent was obtained.

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