A Case of CADASIL with *NOTCH3* Gene Mutation Presenting with Focal Epileptic Seizure: A Case of CADASIL Presenting with Focal Epileptic Seizure

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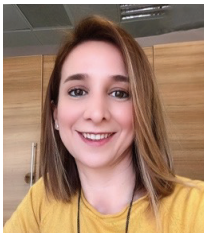

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Abstract

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disease of cerebral microvessels with autosomal dominant inheritance due to the *NOTCH3* gene mutation. Epileptic seizures were observed in 5-11% of CADASIL cases. Observation of seizures as an initial clinical observation is a rare condition in patients with CADASIL patients. In this report, we present a patient with temporal lobe seizure, whose condition was diagnosed through gene analysis as CADASIL.

Keywords: CADASIL, focal epileptic seizure, *NOTCH3* gene

INTRODUCTION

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a hereditary disease of autosomal dominant inherited cerebral microvasculature caused by *NOTCH3* gene mutation.[1,2] This condition, in previous literature, was known as "hereditary multi-infarct dementia" or "rapid-progressing Binswanger's disease". Again in 1993, it was reported that the disease gene was discovered on chromosome-19, and three years later, mutations in the *NOTCH3* gene vanished from the disease. However, the *NOTCH3* gene mutation has been shown to be responsible for the condition.[3] This disorder, with a reported prevalence of 2-4 per 100,000, is regarded to be the most prevalent form of hereditary small vessel disease of the brain and is often overlooked or misdiagnosed.[4] As a result of a mutation in the *NOTCH3* gene, the product of this gene, interleukin-1 beta converting enzyme inhibitor the r protein is eliminated, and its functional projection is Fas-mediated cell death, which is involved in intracellular signal transduction.[5] These signal abnormalities cause progressive destruction within the cell.[6] General clinical features can be summarized as recurrent stroke attacks, migraine, or migraine-like headaches, epileptic seizures, and progressive cognitive disorders. Lesions are most commonly seen clinically as migraine, stroke, transient ischemic attacks, cognitive impairment, and mood disorders. Epileptic seizures have been observed in 5-11% of CADASIL cases.[7] We shared our case, who applied to the clinic with a focal tonic seizure in which impairment of awareness and was diagnosed with CADASIL because it is very rare.[8]

CASE PRESENTATION

A 50-year-old female patient presented to the epilepsy clinic complaining of seizures. The patient's history revealed that she had experienced seizures twice. The seizure history consisted of tonic contraction on the left followed by an unpleasant odor and dizziness, lasting 1-2 min, with impairment of awareness and increased anxiety. Postictal urinary incontinence and postictal confusion were not mentioned. There was no mention of postictal urinary incontinence and postictal confusion. There were no features in the family history of the patient consisting of a history of headaches. Neurological examination was evaluated as normal. Routine biochemistry and hematological examinations were normal. Cerebral magnetic resonance imaging (MRI) scan, however, revealed multiple lesions of white matter hyperintensity on

both periventricular white matter, anterior temporal lobes, and outer capsules (Figure 1). The results of an additional planned cardiac echocardiography, carotid and vertebral computed tomography angiography, homocysteine, HIV, VDRL, anti-TPO, anti-cardiolipin, anti-nuclear and anti-beta 2 glycoprotein 1, and extractable nuclear antibody panel was also evaluated as normal. Interictal electroencephalogram was evaluated as consistent with isolated sharp wave activity, which is commonly observed in the anterior regions of the left hemisphere (Figure 2). The patient was put on 500 mg levetiracetam per day, which was increased to 1000 mg per day two weeks later. Neuropsychological test results were considered to be compatible with mild depression. Exon 11 heterozygous mutations were detected in the *NOTCH3* gene. After adding anti-aggregant therapy to her treatment regimen, our patient was been followed-up without seizures for 22 months.

DISCUSSION

Seizure is a rare clinical condition in patients diagnosed with CADASIL.[7] In patients with CADASIL, frequently occurs after a stroke and is often characterized by widespread tonic-clonic seizures.[9,10] Although the exact cause of the epileptic seizure in patients currently on CADASIL is unknown, high-signal-intensity lesions transiently located in the anterior temporal regions in these patients may be associated with epileptogenesis.[11] In the Post-mortem high-resolution 7-T MRI study, multiple cortical and subcortical lesions were also demonstrated in patients with CADASIL.[12] Recently, Gasparini et al.[13] proposed a remarkable hypothesis on the relationship between leukoaraiosis and epileptic seizures. They hypothesized that occult cortical micro-infarcts may be related to epilepsy in patients with leukoaraiosis.[14] In some previous reports, cholinergic denervation has been observed in the cerebral cortex and white matter tract in patients with CADASIL.[15] Cholinergic neurons modulate excitability in the central nervous system. Furthermore, several experimental studies have demonstrated that cholinergic denervation may induce seizures by increasing facilitation.[16] Interestingly, Keverne et al.[17] reported that nine patients with CADASIL had cholinergic neuronal damage mainly along the white matter tracts extending to the frontal cortices.

In the study of Dichgans et al.,[18] 102 patients with CADASIL were evaluated, 10 of them had seizures, nine of the patients with seizures were in the generalized tonic-clonic seizure clinic, and one presented as focal onset seizures. In Another data analysis consisting of CADASIL cases, 6 of 105 patients showed that.[9] Two cases that presented with non-convulsive status epilepticus and recurrent status epilepticus and were diagnosed with CADASIL were reported in the literature. A 30-year-old female patient presenting with focal seizures and diagnosed with CADASIL was reported by Velizarova et al.[7] In our case, our patient had bilateral generalized tonic-clonic seizures with focal onset. In these two cases, seizure clinic and electrophysiological findings were consistent with temporal lobe seizures. Co-occurrence of focal seizures and CADASIL is very rare, and three cases have been reported in the literature together with our case.

Although seizures are more likely to occur following a stroke in patients with CADASIL, seizures may rarely happen in these patients. CADASIL should be suspected when encountering patients with new-onset of seizures with unexplained white matter lesions on a brain MRI scan. Furthermore, the precise mechanism of seizure development remains unclear. This necessitates additional research with more patients with CADASIL, to investigate the association of CADASIL with seizure types.

MAIN POINTS

- Seizure is a rare clinical condition in patients diagnosed with CADASIL. It is hypothesized that occult cortical microinfarctions in patients with leukoaraiosis may be associated with epilepsy. In some previous reports, cholinergic denervation has been observed in the cerebral cortex and white matter tract in patients with CADASIL.
- Focal seizures and CADASIL are very rare, and three cases have been reported in the literature together with our case. CADASIL should be suspected when encountering patients with new-onset of seizures with unexplained white matter lesions on a brain MRI scan.

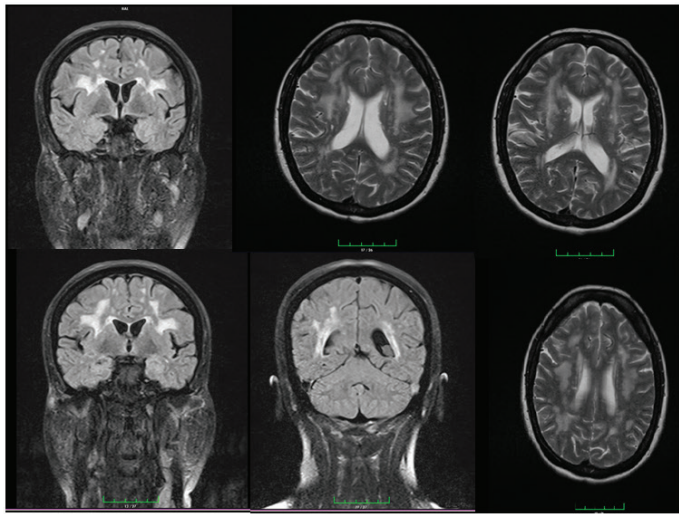

Figure 1. Cerebral magnetic resonance imaging: multiple lesions of white matter hyperintensity on both periventricular white matter, anterior temporal lobes, and outer capsules

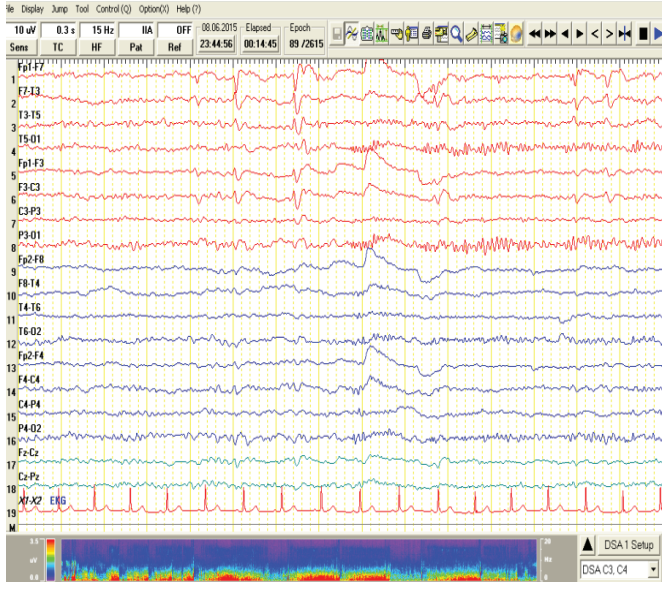

Figure 2. Electroencephalogram: isolated sharp wave activity, which is commonly observed in the anterior regions of the left hemisphere

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.İ.A., O.O.E., D.Ö.A., Concept: D.İ.A., O.O.E., D.Ö.A., Design: D.İ.A., O.O.E., D.Ö.A., Data Collection or Processing: G.U., D.İ.A., Analysis or Interpretation: G.U., D.İ.A., Literature Search: G.U., D.İ.A., Writing: G.U., D.İ.A.

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