Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2021;43(4):411- 417

Case Report / Olgu Sunumu

CADASIL: Clinic and Genetic Corelation

Cadasıl: Klinik-Genetik Korelasyon

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Abstract

CADASIL (Cerebral Autosomal Dominant Arteriopathy, Subcortical Infarcts, Leukoencephalopathy). It is an autosomal dominant familial small vessel disease caused by the mutation of the Notch3 gene in the short arm of the chromosome 19. Clinically it is characterized by recurrent stroke attacks, migraine or migraineous headaches, epileptic seizures and progressive cognitive impairment. In this article, we report four cases of CADASIL that we have clinically evaluated CADASIL and confirmed the diagnosis by moleculer analyses.

Keywords: CADASIL; headache; stroke; dementia, seizure

Özet

CADASIL (Cerebral Autosomal Dominant Arteriopati, Subcortical Infarcts, Leukoencephalopathy) 19. kromozomun kısa kolunda lokalize Notch3 gen mutasyonu sonucu gelişen otozomal dominant geçişli ailesel küçük damar hastalığıdır. Klinik olarak tekrarlayan inme atakları, migren veya migrenöz başağrıları, epileptik nöbetler ve progresif kognitif bozukluk ile karakterizedir. Bu yazıda klinik olarak CADASIL düşündüğümüz, moleküler çalışma ile CADASIL tanısını konfirme ettiğimiz dört olgu klinik ve genetik özellikleri ile sunulmuştur.

Anahtar kelimeler: CADASIL; başağrısı; inme; demans; nöbet

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Received 14.05.2020 Accepted 27.08.2020 Online published 27.08.2020

Cite this article as:
Demir T, Iscan D, Koç F, Bisgin A, CADASIL: Clinic and Genetic Corelation,Osmangazi Journal of Medicine 2021, 43(4):411 -417 Doi: 10.20515/otd.737592

1. Introduction

Cerebral small vessel diseases (CVD) are an important disease in most developed countries (1). It usually manifests as lacunar infarcts, intracerebral hemorrhage (ICH) and subcortical vascular dementia. Hypertension and diabetes mellitus are known as important risk factors for CVDs. However, many hereditary or idiopathic CVD have also been described (1). Among these, cerebral autosomal dominant arteriopathy, subcortical infarction and leukoencephalopathy (CADASIL) is the most common disease of cerebral small vessels (2). Recurrent stroke, cognitive disorders, migraine, and psychiatric disorders are the main clinical symptoms.

CADASIL was first described by Van Bogaert (1955) in two sisters with a rapidly progressing subcortical encephalopathy of the Binswanger disease type (3). Sourander and Walinder (1977) reported a Swedish family with autosomal dominant inherited cerebral ischemia (4). In this family, clinical findings were characterized by recurrent pyramidal, bulbar and cerebellar symptoms and a gradually developing severe dementia. Multiple small cystic infarctions localized in gray - white matter and pons due to obstruction of small intracerebral and leptomeningeal arteries revealed in autopsy. In the same year, Stevens et al. identified familial vascular dementia with autosomal dominant inheritance in an English family (5). Patients were admitted with temporary motor, sensory and other vascular origin symptoms. In the autopsies of these patients, many small infarct areas were detected in the basal ganglia, thalamus and cerebral white matter. Tournier-Lasserve et al. (1993) used the abbreviation CADASIL for the first time and showed that the disease was localized on the 19q12 chromosome in two French families where they performed linkage analysis (6). Later, Joutel et al. confirmed that the affected gene was Notch3 and identified several mutations related to this gene (7).

Although the prevalence of the disease is not clearly known, it is estimated to be 2-5/100,000 and is more common in men than women. It has been reported in many ethnic groups around the world (8). In this article, 4 cases, which were predicted to be CADASIL in the light of the history and neuroimaging findings accepted to the outpatient clinic with different complaints, were presented to draw attention to the disease (Table 1).

Table 1. Distribution of clinical features of cases

Case	G	A	Complaint	Diagnosis	PH	FH	Notch3 gen mutation
1	F	53	headache	migraine with aura	hypothyroidism	no feature	(C.1903C>T(p.R635C) (p.Arg635Cys)
2	F	24	headache	migraine with aura	no feature	CADASIL	(exon 3- C. 268 C>T/ R90C CM971055)
3	M	46	headache	migraine with aura	aphthae in the mouth	no feature	(p. N944Tfs*328 (c.2829_2829delG)
4	M	41	headache, numbness in the hands and feet	migraine without aura	no feature	no feature	(exon 4 - C.535 C >T/ R153C)

G: gender F: female M: male A: age PH: past history FH: family history

Case 1

A 53-years-old female patient has been suffering from migraine-related headache for the last two years. It was referred to our clinic due to the lesions detected in cerebral Magnetic Resonance Imaging (MRI) performed in an external center where she was evaluated with this complaint. She did not take any other medication except levothyroxine sodium due to Hashimoto's thyroiditis. Her family history was

unremarkable. She did not use alcohol, cigarettes.The physical examination, including the detailed neurological examination, was normal. On laboratory examination; the complete blood cell count, biochemistry panel including lipid profile, kidney, liver and thyroid function tests, collagen tissue tests (including antinuclear antibody, anticardiolipin and antiphospholipid antibodies, anti ds-DNA), and thrombophilia panel were negative. Both Electrocardiography (ECG) and Echocardiogram were normal. Cerebral MRI showed periventricular hyperintense lesions while cerebral MR angiography examination was normal (Image 1a-b). In the light of headache and neuroimaging findings, genetic analysis was requested from the patient who was predicted to be CADASIL, and (C.1903C> T (p.R635C) (p.Arg635Cys) (Heterozygous) mutation was detected in the Notch3 gene. The patient was recognized as CADASIL, genetic counseling provided and family screening recommended (Table1).

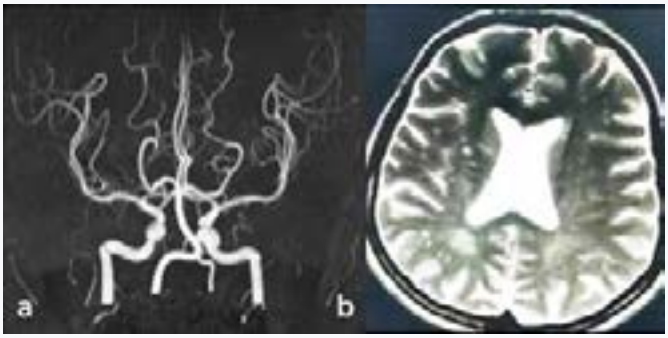

Image : a. *Normal MR angiography* ***b.*** *Hyperintense signal pathologies in the deep white matter adjacent to the posterior horn of the bilateral lateral ventricles prominent on the right in the axial T2 sequence*

Case 2

A 24-years-old female patient had migrainous headaches accompanied by the aura for the last 5 years. For this reason, she was diagnosed migraine with aura. Her parents were 3rd degree relatives, her brother and an older sister were diagnosed as CADASIL previously.

On laboratory examination; the complete blood cell count, biochemistry panel including

lipid profile, kidney, liver and thyroid function tests, collagen tissue (romatolojik test desek?) tests (including antinuclear antibody, anticardiolipin and antiphospholipid antibodies, anti ds-DNA), and thrombophilia panel were negative. ECG and Echocardiography were normal. Cerebral MR angiography examination was normal with periventricular hyperintense lesions on cerebral MRI (Image1c-d). Considering her family and past history and findings on neuroimaging, molecular analaysis was performed and detected (exon 3- C. 268 C> T / R90C CM971055) (Heterozygous) mutation in Notch3 gene. Patient was recognized as CADASIL (Table 1).

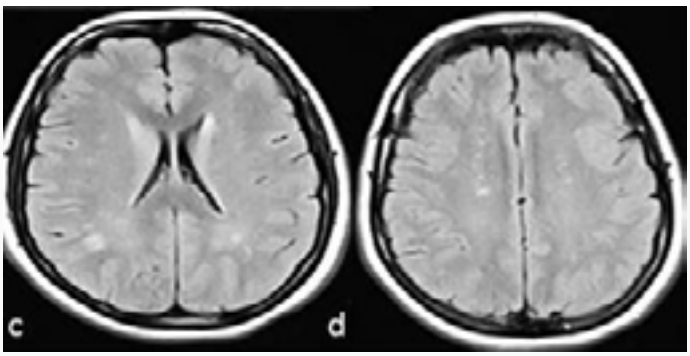

Image : c. *Signal pathologies of bilateral parietal subcortical white matter in T1 sequence* ***d.*** *Hyperintense signal pathologies located in the bilateral sentrum semiovale in the T1 sequence*

Case 3

A 46 years-old male patient has had migrainous headaches for the last 10 years. He was admitted to the clinic due to the increase in the frequency and severity of his headache in recent days. Over the past 15 years, he has had recurrent aphthous ulcers in his mouth. There is no feature in the family history.

On laboratory examination; the complete blood cell count, biochemistry panel were normal except homocysteine level. Homocysteine level was slightly high (15 µmol / L; reference range: 5-12). collagen tissue tests and pathergy test were negative. ECG, transthoracic and transesophageal Echocardiography were all normal. Serebral MRI showed periventricular cortical, subcortical hyperintense lesions (Image 1e-f). Moleculer analysis was performed and detected (p. N944Tfs*328 (c.2829_2829delG) (Heterozygous) mutation in Notch3 gene. Thus, he was evaluated as CADASIL (Table1).

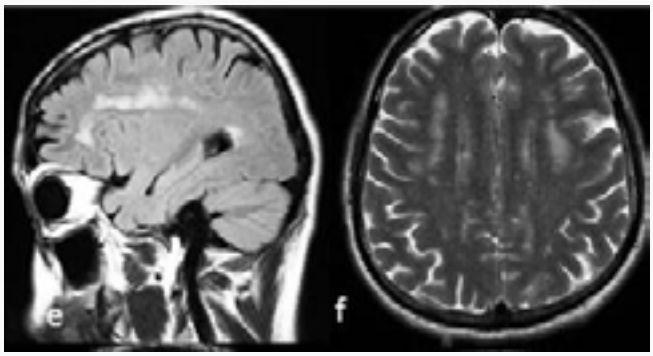

Image : e. *Signal pathologies in periventricular location and tendency to merge in the sagittal section FLAIR sequence* ***f.*** *Signal pathologies in bilateral frontoparietal subcortical location in axial T2 sequence at vertex level*

Case 4

A 41 years-old male patient presented with the complaint of headache and numbness in the hands and feet. He reported that had migrainous headaches for the last 5 years and numbness in his hands and feet since the last 1 year.

Neurological examination of the patient, who has no features in his past and family history, was normal. Biochemistry analysis including hemogram, fasting blood sugar, HbA1C, insulin, C-peptide, B12/folate vitamin levels, thrombophilia panel, collagen tissue tests, sugar loading test were normal. ECG was in sinus rhythm and transthoracic and transesophageal Echocardiography were normal. In Electroneuromyography; motor

and sensory nerve conduction velocities and amplitudes were normal.

There was significant periventricular hyperintense lesions in the posterior horns on cerebral MRI. Cerebral MR angiography was normal (Image 1g-h). In the molecular studies, mutation in the Notch3 gene (exon 4 - C.535 C> T / R153C) was detected and the patient was recognized as CADASIL.

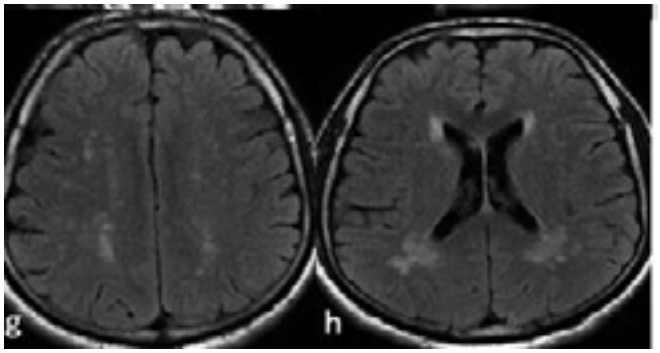

Image: g. *Signal pathologies in bilateral parietal localization at the vertex level in FLAIR sequence* ***h.*** *Hyperintense signal pathologies in the deep white matter adjacent to the posterior horn of the bilateral lateral ventricles in FLAIR sequence*

2. Discussion

CADASIL characterized by different neurological symptoms such as ischemic stroke, dementia, migraine, psychiatric complaints and epileptic seizures. Ischemic stroke is the most common clinical manifestation of CADASIL and occurs in approximately 60-84% of patients. (3,9). Stroke is usually presented with lacunar syndromes such as pure motor, pure sensory, dysarthria or clumsy hand syndrome, and ataxic hemiparesis and occurs at a young age (mean 41-49 years). It is sometimes progressive and large cerebral artery involvement is detected in 20-30% of patients. But symptomatic arterial stenosis are rare (10). Some cases may be asymptomatic and the presence of cerebral ischemic lesions detected incidentally on cerebral MRI should suggest CADASIL (11). Lesions that are presented with nonspecific or periventricular ischemia in the early period, spread to the external capsule, the anterior of the temporal lobe and subcortical regions, which are characteristic for the disease in a few years (12). In addition to ischemic stroke, spontaneous intracerebral hemorrhages (ICH) due to increased vascular fragility may also be seen. Hemorrhages are often localized to the thalamus, basal ganglion, cerebellum and cerebral lobes. In studies conducted on the subject in Korea and Taiwan, ICH have been reported in 25% of symptomatic cases (13,14). In approximately 70% of patients who have had a stroke, recurrent strokes cause subcortical infarcts, resulting in vascular parkinsonism and pseudobulbar palsy (14). In our series, the strongest evidence suggesting CADASIL in all four cases was the presence of subcortical ischemia in the cerebral MRI examination.

Cognitive impairment is the second most common symptom. It occurs in approximately 60% of cases and causes dementia in almost a quarter or half of cases (15). In these cases, frontal lobe dysfunction is remarkable and it is characterized by findings such as executive function, working memory and impaired verbal fluency. Patients with episodic memory impairment have difficulty recalling rather than coding. As the disease progresses, typical signs of subcortical vascular dementia develop. Cognitive dysfunction is closely related to the number of lacunar infarcts in the brain MRI (16).

Migraine is one of the common symptoms (22-77%) in CADASIL patients. Migrainous headaches usually begin around the age of 20. 80% of migraine has aura. The mechanism of migraine is not fully known in patients with

CADASIL. In terms of clinical features, there is no difference between patients with and without migraine (17). In all of our cases, the symptom of admission was headache, and three of them described the aura.

Psychiatric complaints such as conversion, anxiety, behavior and personality disorders, psychosis and delusion, drug addiction and alcoholism occur in 20-41% of patients. These complaints rarely occur at the beginning of the disease, most of them are temporary. Most patients with psychotic symptoms have an underlying dementia. Apathy is one of the remarkable findings and it occurs in approximately 41% of cases with cognitive impairment (9). A detailed psychiatric history was taken from our cases and no symptoms suggesting any disease were detected.

In 5-10% of patients, epileptic seizures occur in the late period, and most of these cases have a history of stroke and dementia. Seizures are generalized tonic-clonic features rather than focal. A few patients may have acute reversible encephalopathy, which lasts for several days, accompanied by fever, confusion, coma, and seizures. In approximately half of these cases, right-to-left shunt was detected in the Transcranial Doppler. However, the clinical significance of this condition is uncertain because there was no difference in clinical or MRI findings between patients with and without shunting (18). No seizures were detected in any of our cases.

The clinical course of the disease is quite variable, even among family members; The age of onset of stroke, dementia and migraine can cover a fairly long time, such as 20 years, among family members (9). This suggests a weak correlation between genotype and phenotype.

Diagnosis of CADASIL is important for several reasons. First, the clinical course and prognosis are different in CADASIL and other stroke patients. Second; proven treatments for ischemic stroke, including thrombolytic, antithrombotic, antihypertensive agents, and statins have not been validated for CADASIL patients. Migraine, recurrent subcortical stroke, psychiatric complaints and family history associated with these diseases are more common in CADASIL, contributing to its differentiation from other cerebrovascular diseases (19). The diagnosis is made by the presence of subcortical multiple lacunar infarcts in cerebral MRI, presence of NOTCH 3 gene mutation, as well as granular osmophilic material (GOM) accumulation in the skin and muscle vessels. There is no specific treatment in CADASIL. Genetic counseling includes supportive care, depression, and symptomatic treatments for comorbid diseases such as migraine, as well as treatment for secondary prevention from ischemic stroke. Some studies have shown that acetazolamide is effective in migrainous headaches (20). Although the risk of ICH is higher from the society, acetylsalicylic acid can be given to patients who have an ischemic stroke, there are opinions suggesting the use of donepezil to reduce cognitive destruction. Life expectancy is lower than the normal population. The most common causes of death are pneumonia, cardiac arrhythmia and myocardial infarction.

Consequently, due to the limitations in clinical, neuroradiological and genetic diagnosis in day conditions, CADASIL seems to be low in incidence and prevalence, but the number of notifications about the disease is increasing day by day. CADASIL, which is the most common hereditary cerebrovascular disease, should be considered in the differential diagnosis in patients who present to the neurology outpatient clinics with different complaints and findings in favor of ischemia in neuroimaging.

• *Çalışma, 2019 yılında Adana'da düzenlenen "5. Adana Genetik Günleri Nörogenetik Sempozyumu"nda sözel bildiri olarak sunulmuştur.*

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