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Original Article

Genotype phenotype correlation of cadasil patients-single center experience

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Abstract

Aim: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common inherited form of cerebral small-vessel disease. The gene that causes CADASIL is the NOTCH3 gene located on the 19th chromosome. The prevalence of the disease which can present with many different neurological and psychiatric symptoms is higher than detected. We wanted to increase awareness of this disease with our publication.

Materials and Methods: Total of 20 people, 12 males and 8 females, between the ages of 26-64 were included in our study. Age of onset, initial symptoms and diagnostic processes were evaluated.

Results: The most common initial symptoms of the patients were muscle weakness. In addition, there were symptoms of sensory loss and headache. Although it was rare, there was also a history of seizures and behavioral disorders. Depending on these symptoms, patients were mostly followed up with a long-term Multiple Sclerosis pre-diagnosis.

Conclusion: CADASIL is a genetic disease that presents symptoms with very different clinical findings and is more common than expected. The genetic disorder that causes the disease can be diagnosed faster with new technologies. With family screening, asymptomatic individuals can be screened and early awareness can be created. Also the transmission of the disease to the next generations can be prevented.

Keywords: CADASIL; early diagnosis; genotype; NOTCH3; phenotype

INTRODUCTION

Cerebral small vessel disease (CSVD) is a group of diseases with various pathological and neurological causes. It is caused by structural changes of the vascular and brain parenchyma. It is a general term with a wide range of clinical symptoms and neuroimaging features (1). The pathophysiological mechanisms of CSVD have not been fully revealed to date. The most common forms of CSVD are amyloidal CSVD. It is divided into sporadic and hereditary cerebral amyloid angiopathy. Non amyloidal CSVD is age-related and vascular risk factor-related small vessel diseas (2). There are also less common forms of CSVD including Fabry disease, inflammatory and immunologically mediated CSVD, venous collagenosis, non-amyloid microvessel degeneration, and post-radiation angiopathy. There are common sporadic forms of CSVD that are mostly associated with age and hypertension. The minority of CSVD has a monogenic cause.

The most common and best known of these is Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy(CADASIL) with subcortical infarcts and leukoencephalopathy (3). Depending on this disease, clinical findings such as migraine, recurrent cerebrovascular events, psychiatric disturbances, and cognitive disorders eventually lead to dementia and disability may occur (4). Its minimum prevalence has been estimated at 2 to 5 per 100,000, but it can vary between populations (5). Thousands of CADASIL families have been diagnosed in many different ethnic groups worldwide. The disorder is often seen more than expected and misdiagnosed. The most typical pathological features of CADASIL are the accumulation of granular osmiophilic material (GOM) seen in the walls of small arteries on ultrastructural examination (6). In addition, diffuse white matter changes have often been demonstrated on Magnetic Resonance Imaging(MRI) in CADASIL patients, usually in the deep white matter, outer capsules, and anterior pole of the temporal lobes (7).

However, the gold standard diagnostic method of CADASIL is NOTHC3 mutation detection. The disease-causing mutations are found in the NOTCH3 gene that maps to

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chromosome 19p13.12, which encodes a transmembrane receptor involved in cellular differentiation and cell cycle regulation (4). NOTCH3 is a large gene of 33 exons encoding a protein with one end inside the cell, a middle section across the cell membrane, and a protruding part out of the cell surface. NOTCH3 protein is named as the receptor protein. Some other proteins called ligands bind to the extracellular loop of NOTCH3 and receptor protein. Impaired cerebrovascular autoregulation due to the inability of NOTCH3 protein to be expressed in vascular smooth muscle cells causes degeneration resulting in hypoperfusion and ischemia. This protein is thought to be essential for the regulation of blood vessels, particularly those that supply blood to the brain (4).

In this study, we evaluated clinical features and NOTHC3 gene mutations of 20 patients diagnosed with CADASIL, followed up by Department of Neurology and Medical Genetics at KTU Faculty of Medicine. In addition, we found out 7 new mutations that were not previously described in the literature.

MATERIALS and METHODS

Patient selection and genetic analysis

Twenty patients who were evaluated in the Neurology Outpatient Clinic of Karadeniz Technical University between 2015 and 2020 with the diagnosis of CADASIL and found to have NOTHC3 mutation in the sequence analysis performed by the KTU Medical Genetics laboratory were evaluated retrospectively. A total of 20 patients, 8 males and 12 females, were included in the study. All exons and exon intron junction regions of the NOTCH3 gene were screened with the next generation sequencing system (MiSeq: A Next Generation Sequencing Platform for Genomic Analysis). Results were confirmed by Sanger sequencing method. The study was carried out with the approval of the Karadeniz Technical University Faculty of Medicine Ethics Committee.

RESULTS

We detected previously identified mutations in 12 out of 20 patients and mutations not previously identified in the literature in 8 patients (same in 2 patients). While there were different clinical symptoms and features in different mutations, there were differences in the first symptoms even in individuals with the same mutation.

The initial symptoms, pre-diagnosis and time until patients diagnosed were evaluated. The patients mean age of onset the symptoms was average at 43.65 ± 10.80 years. The mean time to diagnosis was approximately at 5.2 ± 2.91 years. 12 of the patients applied with complaints of loss of muscle strength or sensation in different parts of the body. 4th of them had complaints of headache or dizziness. The first symptom was forgetfulness in 1 patient, seizure in 1 patient, and behavioral change in 1 patient. Only 1 patient was admitted to the hospital unconscious (Table1).

Table 1. Demographic, clinical and genetic characteristics of CADASIL patients

Patient No	Sex/Age	Nucleotide change	Amino acid change	Early Symptom	Early Symptom Age	Prediagnosis	Time to Diagnosis of CADASIL
Patient 1	M/53	c.163T>G	p.C55G	Loss of muscle strength	45	Multiple sclerosis	5 years
Patient 2	M/61	c.505C>T	p.R169C	Loss of muscle strength	49	Multiple sclerosis	8 years
Patient 3	F/48	c.1774C>A*	p.R592S*	Headache	46	Migraine	2 years
Patient 4	F/48	c.6092G>A*	p.R2031H*	Burning on the right side of the face	39	Multiple sclerosis	7 years
Patient 5	F/52	c.3016C>T	p.R1006C	Loss of sensation	38	Multiple sclerosis	10 years
Patient 6	F/52	c.319C>T	p.R107W	Dizziness	47	Acute stroke	3 years
Patient 7	M/51	c.268C>T	p.R90C	Loss of muscle strength	57	Acute stroke	2 years
Patient 8	F/50	c.3412G>A*	p.V1141M*	Amnesia	57	Demantia	4 years
Patient 9	M/46	c.163T>G	p.C55G	Ptosis	38	Vasculitis	7 years
Patient 10	M/67	c.261T>G*	p.C87W*	Loss of balance while walking	57	Acute stroke	2 years
Patient 11	M/58	c.6092G>T*	p.R2031L*	Headache	51	Migraine	6 years
Patient 12	M/38	c.163T>G	p.C55G	Loss of muscle strength	28	Multiple sclerosis	8 years
Patient 13	F/43	c.163T>G	p.C55G	Loss of muscle strength	30	Multiple sclerosis	8 years
Patient 14	F/55	c.4660A>T*	p.M1554V*	Loss of consciousness	51	Acute stroke	3 years
Patient 15	M/64	c.272G>T*	p.G91V*	changes in mood	57	Mood disorders	4 years
Patient 16	F/34	c.451C>G	p.Q151E	Seizures	23	Multiple sclerosis	10 years
Patient 17	F/26	c.163T>G	p.C55G	Headache	25	CADASIL	-
Patient 18	F/57	c.6092G>A*	p.R2031H*	Loss of balance while walking	40	Metabolic Disorders	8 years
Patient 19	F/55	c.1672C>T	p.R558C	Burning on the right side of the face	50	Vasculitis	3 years
Patient 20	F/50	c.1672C>T	p.R558C	Loss of muscle strength	45	Multiple sclerosis	4 years

DISCUSSION

In this study, we presented the genotype phenotype differences in CADASIL patients to the literature together with the mutations we recently identified. Studies on CADASIL disease in our country and in the world are still not sufficient to explain many different characteristics in the disease clinic. In the most comprehensive study in our country conducted in 2014 with 48 patients with CADASIL pre-diagnosis; only exon 2 to exon 6 and exon 11 was sequenced in the NOTCH3 gene (33 exons in total) (7). Similarly, not all coding exons belonging to the NOTCH3 gene were sequenced in studies conducted in Japan in 2015 and 2020 (8). In our study, we sequenced all exonic regions and intron-exon junctions.

In our study, we evaluated a total of 20 patients. p.C55G changes were detected in 5 of these 20 patients. In 3 of our 5 patients with the same mutation, the disease clinic started as muscle weakness, while 1 of them had ptosis. Patients who presented with muscle weakness were followed up with a pre-diagnosis of Multiple Sclerosis(MS) for a long time. Their first magnetic resonance imaging(MRI) reports were same as non-contrast enhancing lesions in the corpus callosum, cerebral white matter, bilateral thalamus and basal ganglia, brain stem (chronic MS plaques). After years the MRI report changed as multiple chronic lacunar infarcts, nonspecific hyperintense lesions, compatible with CADASIL. Patient with ptosis was followed up with a pre-diagnosis of vasculitis for about 7 years. The last patient was immediately evaluated with a headache symptom because it was detected during family screening. The p.C55G modification was previously defined. However, detailed data on clinical information have not yet been presented clearly. The p.R2031H change was a new mutation not previously described. We had 2 patients with this mutation. Despite having the same mutation, they applied with very different clinical pre-diagnoses and were followed up with different clinics. The first finding of one of our patients was loss of balance while walking, and he was followed up with a pre-diagnosis of metabolic disease for a long time. In the other, burning on the right side of the face was the first symptom of the other patient and was followed up with MS for a long time. When we looked at all the patients we evaluated, the most common early symptom was muscle weakness (6/20), while headache was the other common symptom (3/20). Eight of the patients were followed up for an average of 6-7 years with a diagnosis of MS. The number of patients followed up with acute infarction was four. Two patients were followed with migraine and vasculitis diagnoses. One patient was followed up with pre-diagnoses of Demantia, Mood disorders and Metabolic Disorder. CADASIL was considered at the prediagnosis, but only two patients were.

Clinical characteristics and age of onset vary in individuals with different mutations. Depending on the genetic variations of the individuals, clinical differences can be seen even if they have the same mutation. CADASIL patients have a broad spectrum of clinical features at first admission. Dizziness, slow muscle weakness, personality changes, headache, forgetfulness are some of these (9). Although migraine is generally less common in Asian populations, it is the earliest feature of the disease, reported in approximately 55–75% of cases in the Caucasian race (10). Although the age of onset varies, usually around 30 years (11). In a study conducted on 378 CADASIL patients, 54.5% of the patients had a history of migraine, while 84% of them had migraine with aura (MA) (12). Transient ischemic attacks and stroke are reported in approximately 85% of symptomatic individuals and this is associated with cerebral small vessel pathology (13).

There is a risk of ischemic attack in patients between the ages of 30 and 80, the average age is 45-50 (14). Patients typically have ischemic attacks that cause clinical conditions such as pure motor stroke, ataxic hemiparesis, dysarthria, pure sensory stroke, and sensorimotor stroke. In patients, depending on these conditions, gait disturbance, urinary incontinence, pseudo bulbar palsy and cognitive impairment and even serious disability may occur. Approximately 10% of CADASIL patients can present with an acute encephalopathy (15). The average age at presentation in these patients is 42 year (16). These patients are often misdiagnosed as encephalitis. In CADASIL patients primarily processing speed and executive functions are impaired. Episodic memory is relatively preserved (17, 18). Psychiatric disorders are also seen in CADASIL patients, although the incidence in different studies varies (20–41%) (19). The most common forms are apathy and depression. Also, bipolar disorder and emotional incontinence can be seen. Due to common symptoms, many of the patients are followed up with different diagnosis such as migraine, dementia, and multiple sclerosis for a long time. In another study, it was revealed that the time for patients to be diagnosed with CADASIL was approximately 12 years and this patients unnecessarily received immune modulatory therapies with a diagnosis of MS for an average of 3.5 years (20).

The average time to diagnosis of our patients evaluated in our study was 5.5 years. We believe that especially the development of new generation sequencing systems and so the sequencing of all exons of the gene at the same time will shorten the diagnosis times in the new period. In our study, a patient in a family with a previously defined mutation was directly diagnosed with CADASIL when he was 26 years old with headache. When new cases with a family history of CADASIL start to show symptoms, the time to diagnose CADASIL differs significantly from other cases. These patients are not exposed to inappropriate treatment protocols due to misdiagnosis for a long time. In addition, all family members of the patients we diagnosed are screened and possible patients are determined. There is no effective treatment for CADASIL (21). Given the evidence of a more serious course of disease in individuals with vascular risk factors, particularly smoking and hypertension, control of vascular risk factors is an important part of CADASIL management.

CONCLUSION

Although the disease is more common than predicted, the diagnosis rates are still at lower levels. With the detection of the disease, family screening should be done and individuals should be informed in advance and followed up accordingly. CADASIL, which causes severe clinical situations, can be prevented from being transferred to future generations. Thus, unnecessary hospital expenses are prevented by increasing the living standards of new generations. With developing technology, personalized treatment protocols and gene therapies will soon be offered to humanity. Accordingly, determining the diagnosis of individuals will be a guide for their future treatments.

Conflict of interest : The authors declare that they have no competing interest.

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