A Case Report About CADASIL: Mutation in the NOTCH 3 Receptor

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Abstract- CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a rare autosomal dominant genetic disease characterized with recurrent stroke, migrainous headache, cognitive deficits, and psychiatric symptoms associated with mutations in the NOTCH 3 gene on chromosome 19. Here, we report a case of CADASIL who presented with migrainous headache, behavioral disorder, and familial history of stroke and the diagnosis was established by the findings of head magnetic resonance images revealing characteristic white matter lesions and a mutation in the NOTCH 3 gene.

Key Words: CADASIL, Migraine, Magnetic resonance image, Notch 3

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INTRODUCTION

CADASIL is an autosomal dominant arteriopathy associated with mutations in the NOTCH 3 gene on chromosome 19[1-12]. Clinical manifestations include recurrent cerebral ischaemic episodes, progressive cognitive deficit, migraine with aura, dementia, and psychiatric symptoms[2-12]. The neurological symptoms often develop between the 3rd and 6th decades. Head magnetic resonance image (MRI) often discloses diffuse white matter lesions, small subcortical lacunar infarcts, and cerebral microhemorrhages[1,3-5,8,9,13]. Electron microscopy evaluations of skin or smooth muscle biopsy specimens may show the characteristics of CADASIL, that are specific accumulation of granular osmophilic material (GOM) in the basal lamina[5,6,9,10]. The diagnosis of CADASIL is established by the detection of mutations in the NOTCH 3 gene. This report aimed to discuss neurological and radiological characteristics of CADASIL through evaluation of a patient diagnosed with this rare disease.

CASE REPORT

A 43-year-old female patient presented with the complaints of headache for 7 years with the frequency of 1 to 2 episodes a year. The headache was severe and throbbing in nature, generally located in the vertex, and accompanied with nausea and vomiting. She had sustained progressive mental deterioration since 10 years ago and became more severe in the recent 2 years. The patient also suffered from intermittent occasional numb-

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ness of the left arm and leg, lasting shorter than 15 minutes.

According to the history obtained from her spouse, the patient had suffered from behavioral changes, such as extreme irritability and crying and laughing episodes, in the last few years. Her personal history was non-specific otherwise, except smoking habit. She did not experience problem during pregnancy. Her family history revealed that her father died at the age of 56 years and her uncle died in his 50s from ischemic cerebrovascular disease, and her brother had been bed-ridden after an ischemic cerebrovascular attack in his 40s.

There was unremarkable for blood pressure and physical examination, nor pathological focal neurological deficit. Head computer tomography (CT) showed hypodense lesions with undefined margins in bilateral periventricular white matters, external capsules, centrum semiovales, and left temporal lobe (Fig.). Head MRI showed widespread lesions in bilateral periventricular and subcortical white matters, external capsules, and the white matter of both temporal lobes. Lesions close to the temporal poles were more marked. The lesions were iso-hypodense in the pons on T1-weighted sections and hyperintense on T2-weighted and FLAIR sections. The lesions did not have edematous changes and contrast involvement. Head MRI of her brother, who also had cerebrovascular disease, revealed hyperintense lesions in the periventricular white matter on T2- weighted sections (Figs.).

The results of routine hematological, biochemical, hormonal, coagulopathy and vascularity studies were normal. The levels of lysosomal enzymes, serum B12, lactic acid, and pyruvic acid were also normal. Brucellosis agglutination test and lyme screening results

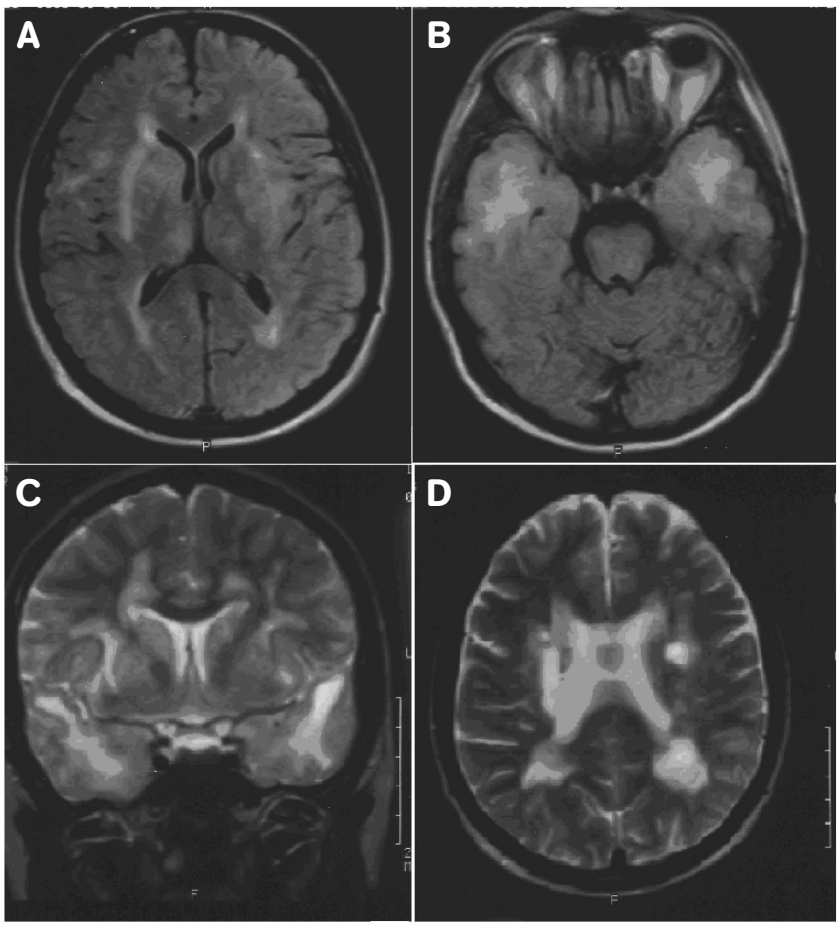

Figure. (A) hyperintensity lesions in the external capsule, the anterior and posterior horns of the lateral ventricules, and the white matter of the subcortical right frontoparietal lobe on the FLAIR axial images; (B) subcortical widespread hyperintensity lesions in bilateral anterior temporal lobes on the FLAIR axial images; (C) widespread hyperintensity lesions in the subcortex of the bilateral temporal lobes and periventriculary area on the T2 coronal images; and (D) hyperintensity lesions in bilateral periventriculary and deep white matter areas on the T2 axial images.

were negative. No abnormality was detected in visual evoked potential, electroencephalopathy, and electroneuromyography. Due to mental and behavioral changes in the patient, cognitive and psychometric measurements were performed. Short-term memory functions test (SMFT), mini-mental state examination (MMSE) and Benton tests showed the scores were at the lower threshold of normal levels. The test results generally showed deficiency in attention. Through the clinical observations and neuropsychiatric inventory (NPI) studies, unmarked behavioral changes of agitation, irritability, and disinhibition in particular were detected. The genetic analysis of the patient and her brother revealed a heterozygote R153C mutation in the exon 4 of the NOTCH 3 gene. The diagnosis of CADASIL was based on the presence of family history of stroke, clinical and head MRI findings, and the detection of NOTCH 3 gene mutation.

DISCUSSION

CADASIL is a hereditary vasculopathy affecting the small arteries and arterioles of the brain and other tissues[1]. It was first described in 1977 in a case with hereditary multiinfarct dementia syndrome, followed by several reports of cases with autosomal dominant genetic stroke and dementia[1-21]. CADASIL syndrome is the first detected form of vascular dementia with a genetic-origin[10]. It is also one of the common hereditary forms of stroke[4]. The incidence of CADASIL in general population is thought to be higher than estimated[4,10].

The onset of the disease is usually between the ages of 30 and 60 years[8]. Eighty-five per cent of the patients experience recurrent strokes and transient ischemic attacks[8]. The first stroke usually occurs in the ages of 35-45 years[6]. Recurrent strokes may result in motor disability, pseudobulbar palsy, and urinary incontinence[2,5,8]. The patient may become bed-ridden in time and has a mean life expectancy of 65 years[9]. Cognitive changes may develop after 35 years of age. However, in 70-80% of the patients, marked cognitive deficit develops parallel to the increased burden of lesions at about 60 years of age and is followed by dementia[3,13,15]. Cognitive decline may be progressive as well as stepwise with acute episodes[2]. In 30-50% of the patients, migraine attacks occur and are usually with aura[2-11]. Migraine attacks generally present a few years before the first vascular event[11]. Patients with CADASIL may also show behavioral anomalies and psychiatric disorders[2-5,7-10]. Psychiatric symptoms vary from mild personality disorders to severe depression and mania[2-4]. The onset of migraine and psychiatric symptoms is usually in the early phases of the disease[6,9] and in some families, they are the dominant clinical findings[9]. Ten per cent of CADASIL patients suffer epileptic attacks, and in some, subclinical polyneuroptahy has been reported[8-11,15,16]. In a series of 45 patients, the incidence rate for subcortical events was 84%; for progressive or stepwise subcortical dementia accompanied by pseudobulbar palsy, 31%; for migraine with aura, 22%; and mood disorders accompanied by severe depression attacks, 20%[20]. Subclinical retinal lesions[8] and rarely, hearing loss have been reported in some cases[1]. Our patient suffered from occasional migraine attacks without aura. Occasional short-term and transient numbness on her left side could not be explained; however, it was attributed to the ischemic attacks associated with the lesions detected on the head MRI. The psychiatric evaluation of our patient revealed impaired executive and concentration functions as well as findings of increased agitation, irritability, and disinhibition.

Hyperintense areas are observed in the subcortical white matter of CADASIL patients on T2-weighted sections of cranial magnetic resonance images[1,3-5,8,9,13]. In addition, 2/3 of the subcortical lacunar infarcts and rarely microhemoorahges in the thalamus may be observed[1-5,8,9,13,18,19]. On head MRI, involvement of the white matter of the anterior temporal lobe and external capsule are characteristic[5,6,8,10,11]. Hyperintensities in the white matter of the anterior lobe have been reported to provide high sensitivity (90%) and specificity (100%) rates for the diagnosis of the disease[21]. External capsule involvement is less specific and may be observed in the early phase of the disease[5]. In some patients, the corpus callosum was also involved[5]. The frontal lobes have the highest burden of lesions in the white matter, followed by the temporal and parietal lobes[17]. Characteristic MRI

findings may be observed in asymptomatic individuals with mutations in the NOTCH 3 gene[3,9], and in just about all of the mutant gene carriers, pathologic MRI findings are observed in the 3rd decade[1]. Cerebral angiography results are normal because of the small size of the involved arteries, the images of which cannot be obtained[11]. Angiography has not been recommended for CADASIL patients because of increased risk of complications[11]. Similarly, in our patient, involvement of the periventricular and subcortical white matter as well as the temporal poles and bilateral external capsule was observed. The head MRI findings of her brother were compatible with CADASIL findings; however, they were in the form of atypical widespread hyperintensities in the periventricular white matter.

Because the disease systemically affects the vascular structure, the result of the peripheric biopsy evaluation is often positive. In the electron microscopy evaluation of the smooth muscles and skin specimens, GOM may be detected[5,6,9,10]. Although evaluation of the skin biopsy is a common procedure, the results of almost half of the studies are false negative[11]. Muscle biopsy studies, however, have a higher sensitivity[11]. The disease develops due to the mutations in the NOTCH 3 gene on chromosome 19. This gene codes a large transmembrane receptor that is expressed in the arterial smooth muscle cells and has a role in the arterial development[4,5,10,11]. In our patient and her brother, a heterozygote R153C mutation in the exon 4 of the NOTCH 3 gene was detected. NOTCH 3 gene is a long one and may have multiple mutations. However, most of these mutations are seen in exon 3 or exon 4[5,9,10]. In Turkey Utku and his friends found out R90C mutation in 12 individuals in four generations in the same family[22]. Uyguner and his coworkers presented 3 families with mutation in the Notch 3 receptor: two in the exon 3, and the one in the exon 4[23]. Although mutations in NOTCH 3 have commonly been reported in patients with familial history of CADASIL, there have also been recent reports of novo mutations[4]. This indicates that CADASIL is more common than thought and suggests that even when there is no familial history, investigations for possible NOTCH 3 gene mutations may prove useful in patients with clinical findings of CADASIL[4].

Lesions observed on the MRI of CADASIL patients mimic lesions in sparodic arteriopathies, including Binswanger disease. However, in such conditions, deep perforating arteries are affected, while the external capsule, corpus callosum, and anterior temporal lobes are intact[11]. Sparodic arteriopathies were ruled out in our patient based on the absence of vascular risk factors except smoking habit, presence of familial history for stroke, specific lesions observed on MRI and detection of the mutation in the NOTCH 3 gene. Multiple sclerosis, primary angitis of the central nervous system, mitochondrial cytopathies (MELAS), Fabry disease, leukodystrophies, and CARASIL should be considered in differential diagnosis[10]. These diseases were ruled out in the light of clinical findings, hereditary transmission and its form as well as the results of the laboratory studies and imaging.

The treatment of CADASIL is symptomatic. Literature presents no specific studies on the use of acetilacidic acid in CADASIL patients. Nevertheless, it has been recommended for the treatment of CADASIL because it is a general antiaggregant agent used in cerebrovascular disease prophylaxis[8]. In addition, recommendations have been made for CADASIL patients to avoid risk factors for ischemic cerebrovascular diseases[8].

In conclusion, particularly in young adult patients with no vascular risk factors, mild clinical findings, but a familial history of stroke and characteristic lesions on MRI, CADASIL should be suspected, and mutations in NOTCH 3 gene should be investigated.

REFERENCES

1. Scheid R, Preul C, Lincke T, et al. Correlation of cognitive status, MRI and SPECT imaging in CADASIL patients. Eur J Neurol 2006;13:363-70.
2. Buffon F, Porcher R, Hernandez K, et al. Cognitive profile in CADASIL. J Neurol Neurosurg Psychiatry 2006;77:175-80.
3. Liem MK, van der Grond J, Haan J, et al. Lacunar infarcts are the main correlate with cognitive dysfunction in

CADASIL. Stroke 2007;38:923-8.
4. Coto E, Menedez M, Navarro R, et al. A new de novo Notch3 mutation causing CADASIL. Eur J Neurol 2006;13:628-31.
5. Gurumukhani JK, Ursekar M, Singhal BS. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): a case report with review of the literature. Neurol India 2004;52:99-101.
6. Tuominen S, Juvonen V, Amberla K, et al. Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch 3 mutation. Stroke 2001;32:1767-74.
7. Tang SC, Lee MJ, Jeng JS, et al. Arg332Cys mutation of NOTCH3 gene in the first known Taiwanese family with CADASIL. J Neurol Sci 2005;228:125-8.
8. Opherk C, Peters N, Herzog J, et al. Long term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. Brain 2004;127:2533-9.
9. Hassan A, Markus HS. Genetics and ischemic stroke. Brain 2000;123:1784-812.
10. Dichgans M. Genetics of ischemic stroke. Lancet Neurol 2007;6:149-61.
11. Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg. Psychiatry 2005;76:35-44.
12. Caeiro L, Ferro JM. Cognitive profile in CADASIL patients. J Neurol Neurosurg. Psychiatry 2006;77:144-5.
13. Charlton RA, Morris RG, Nitkunan A, et al. The cognitive profiles of CADASIL and sporadic small vessel disease. Neurology 2006;66:1523-6.
14. Orlacchio A, Bernardi G. Research actuality in the genetics of stroke. Clin Exp Hypertens 2006;28:191-7.
15. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 1998;44:731-9.
16. Schroder JM, Züchner S, Dichgans M, et al. Peripheral nerve and skeletal muscle involvement in CADASIL. Acta Neuropathol 2005;110:587-99.
17. Chabriat H, Pappata S, Poupon C, et al. Clinical severity in CADASIL related to ultrastructural damage in white matter: in vivo study with diffusion tensor MRI. Stroke 1999; 30:2637-43.
18. van Den Boom R, Lesnik Oberstein SA, Van Duinen SG, et al. Subcortical lacunar lesions: an MR imaging finding in patients with CADASIL. Radiology 2002;224:791-6.
19. Lesnik Oberstein SA, van den Boom R, van Buchem MA, et al. Cerebral microbleeds in CADASIL. Neurology 2001; 57:1066-70.
20. Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of seven families. Lancet 1995; 346:934-9.
21. O'Sullivan M, Jarosz J, Martin RJ, et al. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology 2001;56:628-34.
22. Utku U, Celik Y, Uyguner O, et al. CADASIL syndrome in a large Turkish kindred caused by the R90C mutation in the Notch 3 receptor. Eur J Neurol 2002;9:23-8.
23. Uyguner ZO, Siva A, Kayserili H, et al. The R110C mutation in Notch 3 causes variable clinical features in two Turkish families with CADASIL syndrome. J Neurol Sci 2006;246:23-30.