INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominantly inherited condition characterized by migraine, recurrent strokes, mood disturbance, and progressive cognitive impairment. Since the defective gene associated with CADASIL was discovered in $\text{NOTCH3}$ in 1996 (1), at least 80 CADASIL patients with $\text{NOTCH3}$ mutations have been reported in different ethnic groups (2-6). Among Asian population, to our knowledge, two Japanese families (7) and one Korean family (8) with mutations already identified in Caucasians’ have been reported. We report a Korean patient with CADASIL who carries a novel mutation in the $\text{NOTCH3}$ gene without a known family history.

CASE REPORT

We report a 52-yr-old Korean woman with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) whose diagnosis was confirmed by skin biopsy and the presence of a novel mutation in the $\text{NOTCH3}$ gene. The patient’s clinical features were rather unusual in that 1) clinical presentations were only two episodes of stroke and mild dementia unaccompanied by mood disturbances or migraine, and 2) there was no family history. Brain MRI showed T2 hyperintensities in both temporal pole areas in line with the recent suggestion by O’Sullivan et al. that the abnormality could be a radiologic marker of CADASIL. FDG-PET also showed a hypometabolism in the temporal pole areas with an abnormal finding on MRI in addition to the hypometabolism in cortical and subcortical regions. We could learn from this case that CADASIL may be included in the differential diagnoses in patients with vascular dementia associated with a small vessel disease, even in the absence of a family history, especially when there are no known stroke risk factors and when the MRI shows T2 hyperintensity in the temporal pole regions.

Key Words : CADASIL; Dementia, Multi-infarct; Tomography, Emission-Computed; The NOTCH3 Gene; Polymorphism (Genetics)
antithrombin III, protein C and S, homocysteine, and lipoprotein(a). Electrocardiogram, transthoracic echocardiogram, and ultrasonographic evaluation for intra- and extra-cerebral vessels were normal. T2-weighted brain magnetic resonance (MR) images showed diffuse confluent ischemic changes in periventricular and subcortical white matter or lacunes in the basal ganglia, thalamus, and brainstem (Fig. 1). On diffusion-weighted images, a high signal intensity suggestive of recent infarction was observed in the right corona radiata (Fig. 1E). Gradient echo images did not show any evidence of large or small hemorrhages. MR angiography was normal. FDG-PET showed an abnormally decreased uptake bilaterally in the fronto-parieto-temporal cortices, basal ganglia, and thalamus, more markedly in the right hemisphere than in the left.

Ultrastructural examination of the skin biopsy, with special attention to the dermal arteries, revealed vascular smooth muscle cells with a thickened basal lamina distorted by irregular deposits of granular osmiophilic material, a finding consistent with CADASIL (Fig. 2).

With an informed consent, mutational analysis of the NOTCH3 gene was performed as previously described (2). Genomic DNA was extracted from peripheral blood leukocytes of the patient and both exon 3 and 4 regions of the NOTCH3 gene was amplified by polymerase chain reaction (PCR) (primer sequences were by courtesy of Dr. E. Tournier-Lasserve, Genetique des Maladies Vasculaires, Inserm, Paris, France) and directly sequenced on an ABI Prism 377 Genetic Analyzer (Applied Biosystems, Foster City, CA, U.S.A.) using the ABI Prism BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems). We found a heterozygous G-to-A transition of the third nucleotide in exon 3 of the NOTCH3 gene, resulting in a Cys67Tyr substitution within the fourth epidermal growth factor-like repeat domain of the Notch3 receptor (Fig. 3A). The G-to-A transition creates a novel RsaI
recognition site, which was confirmed by the PCR-RFLP method (Fig. 3B). The mutation was not observed in 60 healthy Koreans.

Since the patient’s parents were all dead and her siblings (one stepbrother, one stepsister, and one brother) refused to be tested, we could not confirm whether the mutation is de novo or not.

Table 1. Results of neuropsychological tests in the patient

| Cognitive domain/neuropsychologic tests | Results |
|----------------------------------------|---------|
| Attention                              |         |
| Digit span: forward/backward           | 6/3     |
| Language and related functions         |         |
| Fluency                                | NL      |
| Auditory comprehension                 | NL      |
| Repetition                             | NL      |
| Naming (K-BNT)                         | 45/60 (48%ile) |
| Reading                                | NL      |
| Writing                                | NL      |
| Calculation                            | NL      |
| Right-left orientation                 | NL      |
| Body part identification               | NL      |
| Limb praxis                            | NL      |
| Visuospatial functions                 |         |
| Interlocking pentagon                  | NL      |
| Rey-Osterrieth Complex Figure Test (Rey CFT) | 18/36 (<1%ile) |
| Memory                                 |         |
| HVLT: Free recall (1st; 2nd; 3rd; total) | 3/12; 8/12; 7/12; 18/36 (1.5%ile) |
| 20-min delayed recall                  | 3/12    |
| Recognition (true positive-false positive) | 8-1=7 |
| Rey CFT:                               |         |
| Immediate recall; 20-min delayed recall| 4/36 (<1%ile); 4/36 (<1%ile) |
| Recognition (true positive-false positive) | 6-1=5 (2%ile) |
| Frontal/Executive Function             |         |
| Contrasting program                    | NL      |
| Go-no-go test                          | AB      |
| Fist-edge-palm                         | AB      |
| Alternating hand movement              | AB      |
| Alternating square and triangle         | NL      |
| Luria loop                             | NL      |
| Semantic word fluency: animal; supermarket items | 9; 8 (6%ile) |
| Phonemic word fluency (sum of three consonants) | 9 (9%ile) |
| Stroop test: word reading: correct/incorrect | 98/0 |
| color naming: correct/incorrect        | 47/0    |
| General Index                          |         |
| MMSE                                   | 23/30   |

K-BNT: The Korean version of the Boston Naming Test, HVLT: Hopkins Verbal Learning Test (Korean version), MMSE: Mini-Mental State Examination (Korean version), NL= within normal limit, AB= abnormal.
DISCUSSION

The diagnosis of CADASIL in our patient was confirmed by skin biopsy and the presence of the NOTCH3 gene mutation. However, our patient may differ from "typical" CADASIL patients in that 1) there was no family history, although the patient’s parents lived up to 60 and 65 yr of age, respectively, and her 4 siblings were alive and aged more than 55 yr and 2) our patient had no history of mood disorders or attacks of migraine which have been reported to be the frequent early symptoms in the Caucasian CADASIL patients (4). Rather, our patient presented only with two episodes of strokes and mild dementia. Despite severe leukoaraiosis on MRI, absence of known risk factors for stroke in detailed laboratory tests motivated us to consider CADASIL. A similar case without a family history has been reported, but the patient had a history of migraine (6).

Regarding the neuroimaging findings of CADASIL, MRI abnormalities have not been specific for the disease and therefore are not sufficient to establish the diagnosis. Recently, however, MRI of genetically confirmed CADASIL patients showed an abnormally increased signal on T2-weighted images in both temporal poles, which was never observed in non-CADASIL stroke patients (9). T2-weighted and FLAIR MRI of our patient showed the same finding (Fig. 1D), thereby supporting the notion that a temporal pole hyperintensity may be a radiologic marker of CADASIL. To our knowledge, little has been reported about FDG-PET findings of CADASIL (10). In our patient cerebral glucose metabolism was decreased not only in the subcortical regions (basal ganglia and thalamus) but also in the cortex, more markedly on the right side. These findings were consistent with neuropsychological findings that showed a left hemispatial neglect and visuospatial dysfunction in the presence of general cognitive decline. The FDG-PET also showed a hypometabolism in both temporal pole areas that corresponded to the regions with an MRI abnormality.

Our patient had a Cys67Tyr substitution within the NOTCH3 gene, a mutation that has not been identified in the previous patients with CADASIL. Considering the absence of a family history, it may be a de novo mutation, although genetic studies of the family were not performed. Among the Asian population, two families with CADASIL from Japan have been reported so far. However, given that the incidence of subcortical vascular dementia is higher than that of Alzheimer’s disease in Asian countries compared to Europe and United States (11), and that, as a cause of stroke, intracranial arteriopathy is more frequent than extracranial arteriopathy (12), it is possible that cases of CADASIL might have been overlooked.

In conclusion, we could learn from this case that CADASIL may be included in the differential diagnoses in patients with vascular dementia associated with a small vessel disease, even in the absence of a family history, especially when there are no known stroke risk factors and when the MRI shows a T2 hyperintensity in the temporal pole regions.

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