

## Two Cases of Japanese CADASIL with Corpus Callosum Lesion

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IWATSUKI, K., MURAKAMI, T., MANABE, Y., NARAI, H., WARITA, H., HAYASHI, T. and ABE, K. *A CADASIL Family of Japan with Corpus Callosum Lesion.* Tohoku J. Exp. Med., 2001, **195**(2), 135–140 — Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare hereditary stroke disease. In the present study, a Japanese CADASIL family was first reported with missense mutation of Arg141Cys of *Notch3* and a unique lesion of corpus callosum. Upon neuropsychological examination, our case 1 showed only right-handed constructional apraxia associated with corpus callosum lesion. No other callosal disconnection signs were present. Sagittal T2 weighted image of case 1 showed multiple small lesions along with the pericallosal branches from the truncus to the posterior part of the splenium in the corpus callosum. Although detailed mapping of the corpus callosum for functional fractionation in humans remains incomplete, the constructional apraxia on the right may be related to callosal dysfunction from the truncus to the posterior part of the splenium in the corpus callosum. — CADASIL; corpus callosum; constructional apraxia

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebrovascular disease characterized by recurrent subcortical ischemic strokes starting in midadulthood, with stepwise progression over two decades, often leading to pseudobulbar palsy, dementia, mood disturbances, and recurrent attacks of severe migraine (Sourander and Walinder 1977; Tournier-Lasserve et al. 1991;

Hutchinson et al. 1995). However, vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia are usually absent. Brain magnetic resonance imaging (MRI) shows multiple subcortical infarcts and widespread white matter lesions. Recent genetic studies have identified missense mutations of the *Notch3* gene on chromosome 19 in CADASIL patients (Joutel et al. 1996, 1997).

In the initial reports, multiple subcortical

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infarcts and widespread white matter lesions in the cerebral hemisphere were pointed out in CADASIL patients (Skehan et al. 1995). Though a few recent reports pointed the lesion of cerebellum, brainstem, and corpus callosum (Yousry et al. 1999; Coulthard et al. 2000), subtentorial and corpus callosum lesions were considered to be rare. Symptoms of CADASIL could be variable depending on the site of lesion. However, a symptom with lesion of corpus callosum has never been reported. Here we report a Japanese family of CADASIL with corpus callosum lesion associated with a missense mutation (Arg141Cys) of the *Notch3* gene.

### CASE REPORT

#### Case 1

A 57-year-old right-handed woman began to have migraine with aura from 33 years old. Walking imbalance and slowing of speech and physical activity began at age 52. Soon after such symptoms, she developed a transient ischemic attack (TIA) with right hemiplegia and dysarthria. With MRI examination, she was diagnosed as having multiple cerebral infar-

ction in the white matter of cerebrum. Thereafter similar TIAs repeated several times, and her emotional volition decreased. She was in a depression state at age 56. She did not have hypertension, hyperlipidemia nor diabetes mellitus. In her family, her grandfather, father, aunt, and two of her siblings had the same disease. On admission at age 57, she showed normal blood pressure (130/88 mmHg) and normal general physical findings including the chest and abdomen.

On neurological examination, her consciousness was clear, but she showed slow speech and bradykinesia. Smooth pursuit eye movement was saccadic. No abnormalities were found in other cranial nerves. She showed cerebellar ataxia such as dysdiadochokinesis and impossible tandem gait. There was neither limbs muscle atrophy nor sensory impairment. Deep tendon reflexes were hyperactive. Hoffmann and Babinski reflexes were present bilaterally. Blood, urine and cerebrospinal fluid (CSF) examinations were all normal.

Gene analysis of the three patients was performed. Genomic DNA was isolated from

TABLE 1. Clinical characteristics of affected members in this CADASIL family

Case	1	2	3
Age	57	54	64
Sex	Female	Female	Male
Age at onset	33	41	34
Disease duration	24	13	31
Migraine	+	—	n.e.
Dysarthria	+	+	+
Dysphagia	—	—	+
Hemiparesis	—	+	+
Spasticity	+	+	+
Sensory deficits	—	+	+
Gait ataxia	+	—	n.e.
Depression	+	+	n.e.
Corpus callosum lesion	+	+	n.e.
Honstructional impairment rt./lt.	+/-	—/n.e.	n.e.
Cognitive deficits (Demented)	—	+	n.e.
Mini mental state examination	30	13	n.e.

n.e., not evaluated.

blood leucocytes using a standard procedure after informed consent was obtained. Exons 3 to 5 of the *Notch3* gene were amplified by polymerase chain reaction (PCR). The sense and antisense primer were 20-mer, 5'-CTGCCAACCAAGCCATCTC-3' and 5'-CTCTCGCCTGTCCAGCCATT-3', respectively. PCR was performed in a 50- $\mu$ l reaction mixture containing 1  $\mu$ g of genomic DNA, 1 U of Taq polymerase, and 10 pg of each primer. After an incubation at 95°C for 5 minutes, steps of 95°C for 60 seconds, 57°C for 60 seconds, 72°C for 120 seconds were repeated for 35 cycles, followed by an incubation at 72°C for 5 minutes. An aliquot of the PCR product was reacted with Dye Terminator Kit (Amersham Pharmacia Biotech, NJ, USA), and the reaction product was analyzed using an automated DNA sequencer (Long Read Tower, Amersham Pharmacia Biotech). Sequence analysis of the proband showed a heterozygous mutation of a normal sequence and a transition of C to T, which resulted in the substitution of Arg to Cys (R141C) in exon 4 of the *Notch3* gene.

Ultrastructural analysis of skin vessels disclosed granular osmiophilic material within the vascular smooth muscle basal lamina.

In higher cerebral function, her intelligent quotient was 80 (verbal scale, 92; performance scale, 66) on Wechsler adult intelligence scale-revised, but her mini mental state examination (MMSE) scale was 30/30. Test for brick was poor on the right hand but good on the left hand. Upon neuropsychological examination,

the model cube was copied fairly well by the left hand but not by the right hand (Fig. 1). She showed right-handed constructional apraxia. However, no other callosal disconnection signs including the left-limb apraxia were present. Neither aphasia, ideomotor apraxia nor anosognosia were observed. No unilateral spatial neglect was found.

Brain MRI showed multiple hyperintense lesions with T2-weighted image in the anterior portions of the temporal lobe and cerebellum, and basal ganglia, subcortical cerebral hemispheres bilaterally (Figs. 2A and 2B). The multiple lesions of the corpus callosum are along with the pericallosal branches of the anterior cerebral artery from the truncus to the posterior part of the splenium (Fig. 2C, arrowheads). A little decrease in cerebral blood flow in bilateral frontal and temporal lobes and the right parietal lobe was detected by  $^{99m}$ Tc-HMPAO single photon emission computed tomography.

#### Case 2

A 54-year-old right-handed woman is a sister of case 1. She first noticed sensory disturbance of temperature in left body at age 41, and was diagnosed as having multiple cerebral infarction in the white matter of cerebrum and rostral part of pons on MRI examination. She did not have hypertension, hyperlipidemia nor diabetes mellitus. Thereafter, she sometimes had dysarthria and dysphasia as symptoms of a TIA. She then had a permanent left hemi-

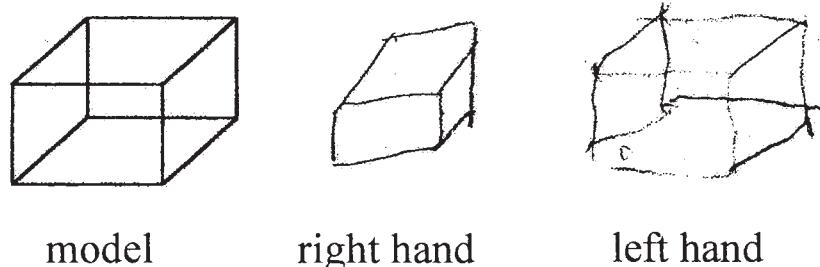


Fig. 1. Showing right-handed constructional apraxia of case 1. The model cube was copied fairly well by the left hand but not by the right hand.

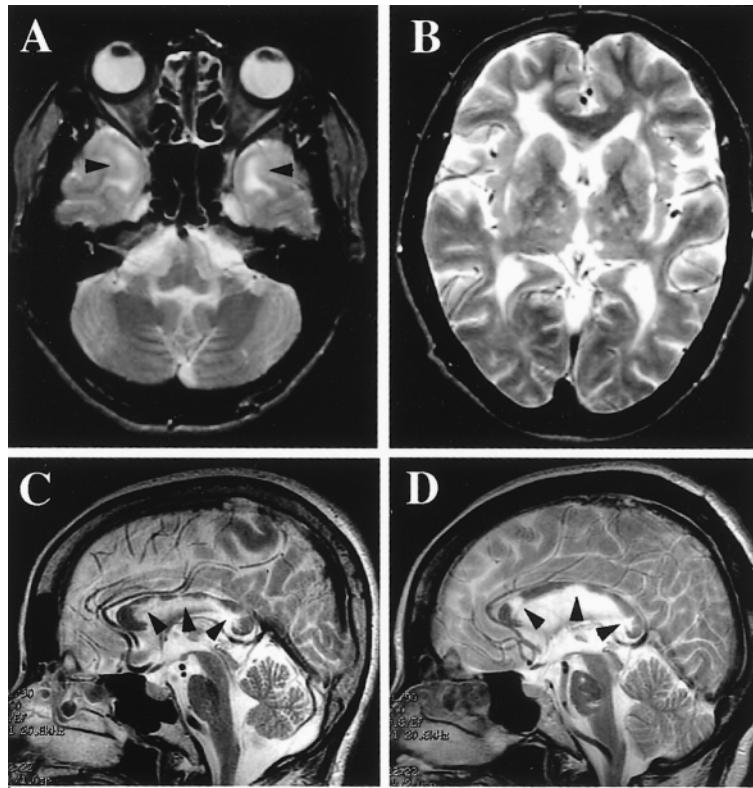


Fig. 2. A: Axial T2 weighted image of case 1 at the level of the thalamus shows confluent, bilateral and symmetrical subcortical hyperintensities. B: Axial T2 weighted image of the same patient at the level of the centrum semiovale shows hyperintensity multiple small lesions, confluent, bilateral and symmetrical subcortical hyperintensities. C: Sagittal T2 weighted image of case 1 shows multiple small lesions along with the pericallosal branches of the anterior cerebral artery from the truncus to the anterior part of the splenium (arrowheads). The similar lesion is also found in case 2 (D, arrowheads).

plegia and became depressed at age 43 and demented at age 50.

On medical examination at age 54, she showed normal findings of the chest and abdomen with normal blood pressure (120/74 mmHg). Neurologically, her speech was dysarthric, and smooth pursuit eye movement was saccadic. No abnormalities were found in other cranial nerves, and muscle volume or power in the extremities. Sensory disturbance was unidentified due to dementia. Deep tendon reflexes were hyperactive. Snout and Babinski reflexes were present. She did not show cerebellar dysfunction. Blood, urine and CSF examinations were all normal. Case 2 had the same missense mutation as case 1 in the *Notch3* gene. The skin biopsy was not perfor-

med. In higher cerebral function, she had dementia with MMSE scale of 13/30. She did not obviously show right-handed constructional apraxia. The left-handed constructional apraxia and callosal disconnection signs containing the left-limb apraxia was not evaluated due to her left hemiplegia. Neuropsychological examination including aphasia, ideomotor apraxia, anosognosia, and unilateral spatial neglect was not also evaluated due to dementia.

Brain MRI showed multiple hyperintense lesions with T2-weighted image in the bilateral brainstem, basal ganglia, and subcortical cerebral hemispheres predominantly in right side. The lesion of the corpus callosum (Fig. 2D, arrowheads) was similar to case 1 (Fig. 2C).

Such lesion was smaller than case 1.

### Case 3

A 64-year-old right-handed man is an elder brother of case 1. He had frequent dysarthria as TIA from age 34. He developed left hemiplegia at age 37, then right hemiplegia at age 41. These cerebrovascular events resulted in akinetic mutism at age 50. He is bed-ridden now. Brain MRI was not performed. He did not have hypertension, hyperlipidemia nor diabetes mellitus. He also has a missense mutation of Arg141Cys in the *Notch3* gene. Neuropsychological examination and the skin biopsy were not performed. Clinical characteristics of cases 1-3 are summarized in the Table 1.

## DISCUSSION

In the present study, a Japanese CADASIL family was reported with missense mutation of Arg141Cys and a unique lesion of corpus callosum. The missense mutation is located within the extracellular domain coded in exon 4, which forms epidermal growth factor-like repeats of the *Notch3* protein. This missense mutation of Arg141Cys was reported in 6 patients with CADASIL in France (Joutel et al. 1997), but is the first from Japan (Kotorii et al. 2001).

The main lesion in CADASIL has been recognised in the white matter of immediate periventricular or subcortical regions, the basal ganglia, thalamus, and external capsule. Recent reports pointed out that lesions are also present in brainstem, cerebellum, and corpus callosum (Yousry et al. 1999; Coulthard et al. 2000). Neuropathologically the lesion in corpus callosum was demyelinated, and that was radiologically hypointense on T1-weighted and hyperintense on T2-weighted images, and multiple thick lesions with the atrophic corpus callosum on sagittal T2 weighted images (Gazzaniga et al. 1965; Coulthard et al. 2000). Our cases also showed similar MRI findings (Fig. 2). However, signs associated with lesion

of corpus callosum have never been reported in CADASIL. Upon neuropsychological examination, our case 1 showed only right-handed constructional apraxia associated with corpus callosum lesion. No other callosal disconnection signs were present. Sagittal T2 weighted image of case 1 showed multiple small lesions along with the pericallosal branches from the truncus to the anterior part of the splenium (Fig. 2C, arrowheads). Previous studies have indicated that constructional apraxia on the right was present in patients with complete commissurotomy (Gazzaniga et al. 1965; Bogen 1969; Zaidel and Sperry 1977). Although detailed mapping of the corpus callosum for functional fractionation in humans remains incomplete (Graff-Radford et al. 1987; Suzuki et al. 1998), the constructional apraxia on the right may be related to callosal dysfunction from the truncus to the posterior part of the splenium. This case of limited callosal disconnection sign due to multiple lesions from the truncus to the posterior of the splenium indicates the presence of callosal channels responsible for the constructional apraxia on the right. Further study of similar cases of callosal lesion will help to clarify the nature of modality and function in the corpus callosum.

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