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Potential New Cysteine Sparing Mutation in the NOTCH3 Gene in a Patient with Nonfamilial CADASIL-like Disease

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Abstract

Background—Several different mutations have been reported in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). We present a unique case with transversion not involving cysteine on neurogenic locus notch homolog protein 3 gene.

Case description—We present a case of 65-year-old woman with new ischemic stroke resulting in right hemiparesis. She has previously suffered minor strokes at age 56, 58, and 60 years and migraine headaches between age 10 and 50 years. Magnetic resonance imaging demonstrated multifocal chronic ischemic infarctions with encephalomalacia in the left posterior parietal, parieto-occipital regions and the pons. An analysis of the protein sequence of notch 3 gene did not demonstrate any alterations characteristics of CADASIL disease. There was a deoxyribonucleic acid variant with transversion of alanine with tyrosine and change of histidine with leucine on notch 3 gene. None of the family members had any clinical manifestations suggestive of CADASIL.

Conclusion—We report the first report of deoxyribonucleic acid variation in notch 3 gene associated with clinical features of CADASIL without any familial component.

Keywords

CADASIL; NOTCH3 gene; sporadic; skin biopsy; mutation

Introduction

Cereberal autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenetic cause of stroke secondary to mutations of the neurogenic locus notch homolog protein 3 (NOTCH3) gene on chromosome 19 [1]. CADASIL is characterized by a constellation of migraine with aura and subcortical strokes that lead to cognitive dysfunction [1]. The pathophysiology of CADASIL is not well understood, but at least three theories have been proposed [2]. On the basis of histopathology, the disease is characterized by degeneration of the medial smooth muscle cells and replacement with nonamyloid eosinophilic granular material within the small and medium size arteries [3]. Although several different mutations have been reported in patients with CADASIL, we present a unique case with transversion not involving cysteine on NOTCH3 gene resulting in nonfamilial or sporadic expression of a similar disease.

Case Report

A 65-year-old woman was evaluated for new ischemic stroke resulting in right hemiparesis three months ago. She had pre-existing left hemiparesis, dysphagia, memory difficulty, and gait difficulty from previous strokes. She required assistance in dressing, toilet activities, and ambulated with the help of a walker. The patient had developed classic migraines at the age of 10 years which resolved at the age of 50 years. Patient had a minor ischemic stroke at 56 years followed by two additional ischemic strokes at the age of 58 and 60 years. She then developed absence and complex seizures at the age of 62

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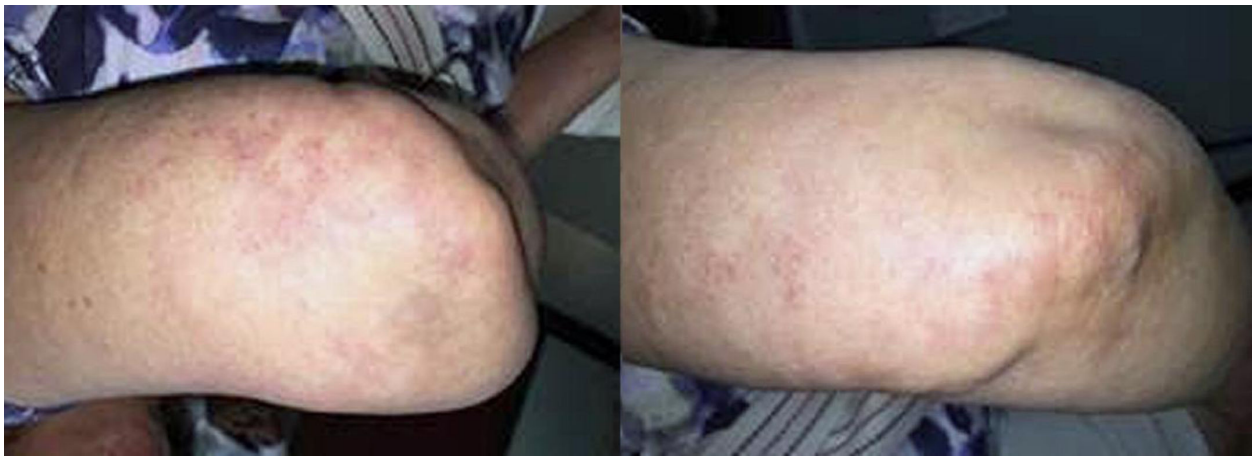

Figure 1. Erythematous skin lesions on extensor surface of elbows

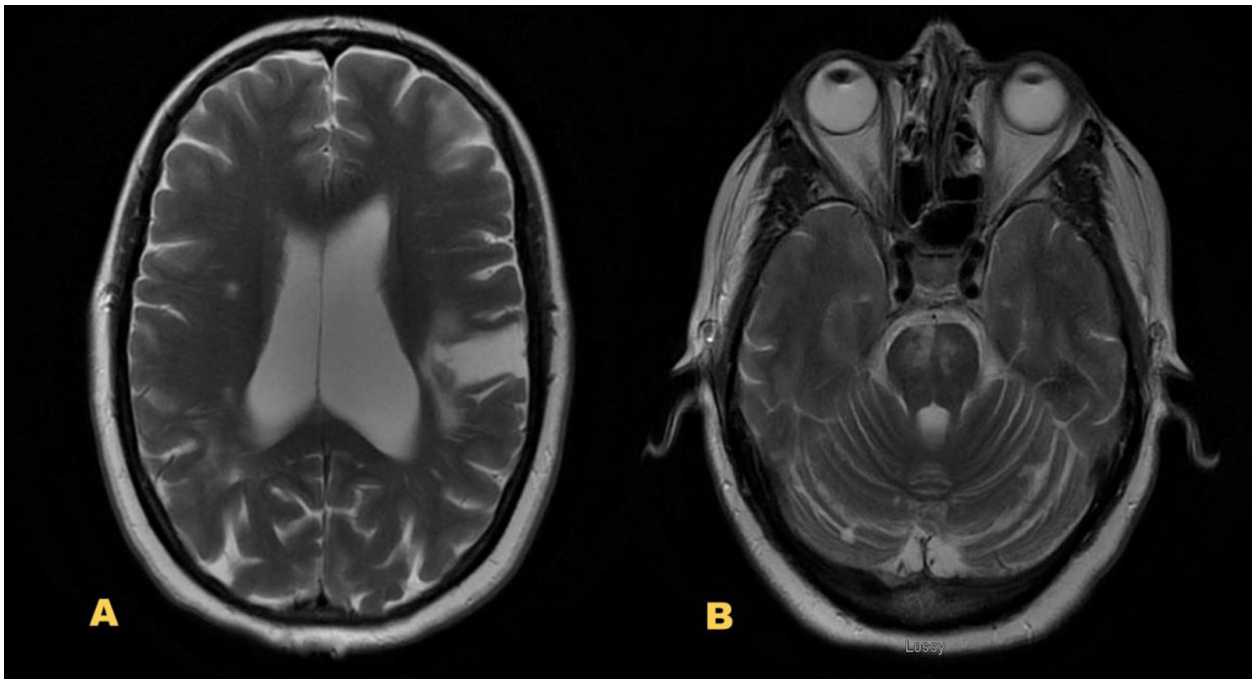

Figure 2. (A) T2 weighted images showing left parietal encephalomalacia. (B) T2 weighted images showing hyperintensities in pontine region

years. Patient suffered another stroke at the age of 64 years followed by the current episode. Her father died from a stroke at the age of 75 years. Patient's mother was alive at the age of 75 years without any stroke. She also had a brother and sister without any history of stroke. Patient had three sons aged 21, 28, and 34 years of age out of which the middle son had a history of migraines.

On examination, patient had mild dysarthria and left hemiparesis. Montreal cognitive test score was 21 out of 30. Patient had skin macular erythematous lesions more extensive at elbow joints (see Figure 1). Magnetic resonance imaging (MRI) demonstrated multifocal chronic ischemic infarctions with encephalomalacia in the left posterior parietal, parieto-occipital regions, and the pons (see Figures 2 and 3). Magnetic resonance angiography demonstrated attenuated and irregular signal in both ver-

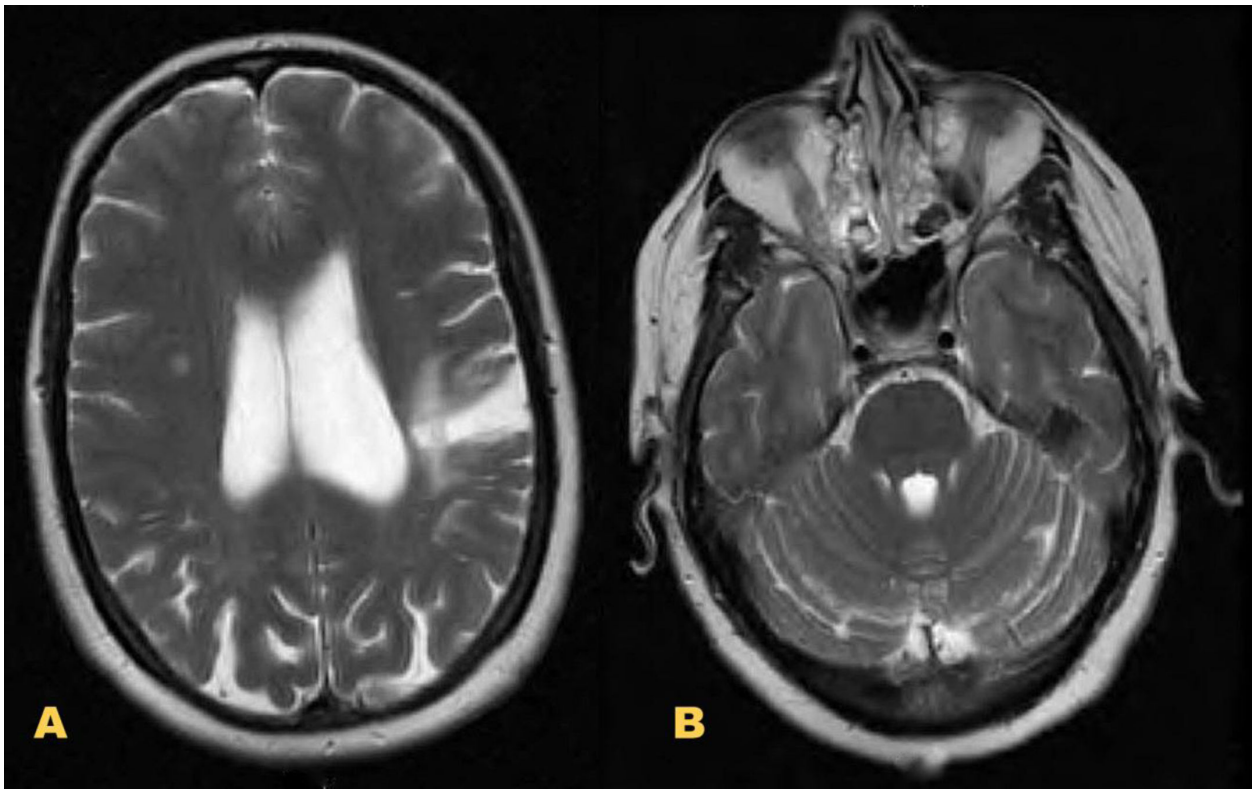

Figure 3. (A) Same T2 weighted images nine months prior showing left parietal and right subcortical hyperintensities. (B) No changes were identified in pontine region.

tebral arteries with tortuosity of the basilar artery. The posterior cerebral arteries were not adequately visualized. A cerebral angiogram demonstrated hypoplastic intracranial vertebral and basilar arteries with minimal filling of right posterior cerebral artery from basilar artery (see Figure 4). An analysis of the protein sequence of NOTCH3 gene did not demonstrate any alterations characteristics of CADASIL disease. A deoxyribonucleic acid variant with transversion of alanine with tyrosine and change of histidine with leucine at nucleotide position 3782 and codon position 1215 was detected. A skin biopsy did not identify any granular deposits in the basal lamina of small arterioles.

Discussion

We describe a patient with multiple ischemic strokes with residual deficits and cognitive impairment with sequence alteration in NOTCH3 gene that is not reported previously with CADASIL disease. The clinical syndrome appeared like the CADASIL disease but without any familial transmission pattern (sporadic). The NOTCH3 gene is composed of 33 exons encoding 2321 amino acids. CADASIL mutations are characterized by the gain or loss of a cysteine residue located within the 23 exons (exons 2 through 24) encoding for the 34 epidermal-growth-factor-like repeat domains of the NOTCH3 receptor [4–6]. None of the patient's family members expressed clinical symptoms suggestive of the disease including the offsprings.

Apparently sporadic CADASIL based on MRI criteria should be submitted to screening of entire NOTCH3 gene as new mutations involving cysteine residue have been reported [7]. NOTCH3 gene mutations not involving cysteine residues have already been identified in a few cases. These patients have atypical MRI findings such as a less frequent involvement of the anterior temporal lobes, and onset of disease was later with a slower and a milder clinical course than CADASIL patients [5, 8–10]. Bersano *et al.* [11] described the case of a 49-year-old woman with migraine, sudden falls without loss of consciousness, psychiatric disorders and widespread white matter lesions on MRI carrying a novel cysteine-sparing mutation in exon 29 of the NOTCH3 gene. Wollenweber *et al*. [12] described cysteine-sparing CADASIL mutations, such as D80G might cause a CADASIL with phenotype largely indistinguishable from cysteine

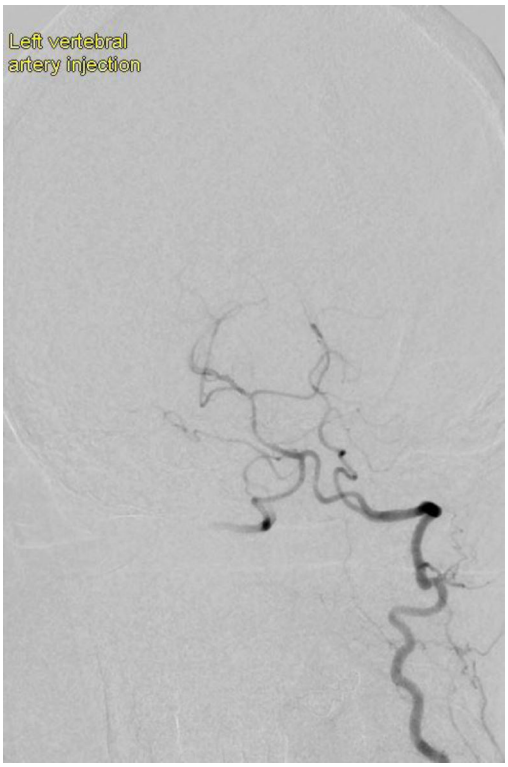

Figure 4. Cerebral angiogram shows hypoplastic intracranial vertebral and basilar arteries with miniaml filling of right posteroir cerebral artery from basilar artery

mutations. Fouillade *et al*. [13] reported a patient with small vessel disease carrying a cysteine-sparing mutation. This mutation increased NOTCH3 signaling and the skin biopsy did not show eosinophilic granular material deposits [13]. Concurrently, Scheid *et al*. [14] reported a cysteine-sparing mutation in notch 3 gene within two German families that presented a CADASIL-like phenotype but there was noeosinophilic granular material deposit on skin biopsy, suggestive of potential existence of more benign CADASIL variants [14]. The stroke severity in CADASIL patients may be altered further by environmental and genetic factors accounting the mild phenotype and the low familial penetrance in some patients [15,16].

Conclusion

A new sporadic variant of the CADASIL disease associated with cysteine sparing mutation in the NOTCH3 gene is reported. The report highlights the role of genetic testing even in patients without any family history of the disease.

Acknowledgements

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