Mutation of the *Notch 3* Gene in a Thai Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy Family

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Abstract

The authors report the first Thai family with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in which the family members had a classical history of progressive vascular dementia. The proband was a 31-year old Thai male who presented with an acute stroke in the subcortical region. His past history revealed mental disturbance, including poor judgement and regressive behavior as well as mood changes for 1 year. He did not have a history of migraine or any other vascular risk factors except for a strong family history of ischemic stroke and progressive dementia. Magnetic resonance imaging demonstrated multiple small infarctions in the subcortical white matter of the bilateral frontal, parietal and occipital lobes with another small lesion in the pons. Genetic study demonstrated a *Notch 3* mutation consisting of the substitution of a nucleotide at position 406 in exon 3 leading to the replacement of an Arginine by Cysteine at position 110 in the 2nd EGF motif, which is compatable with CADASIL.

Key word : CADASIL, Ischemic Stroke, Dementia, Genetics

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During the past decade, families with a hereditary form of vascular dementia have been reported. The disease is presently known as "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" (CADASIL)[1]. Affected patients typically present with multiple recurrent subcortical ischemic events, resulting in a stepwise mental decline and dementia. Patients sometimes experience migraine and depression. Genetic studies have demonstrated mutations of the *Notch 3* gene on chromosome 19[2]. Despite numerous case reports from Europe, North America and Japan, there has been no report from other parts of Asia, especially South East Asia[3-7]. The authors report a Thai family with a history of multiple infarction and dementia in which one of the family members was documented to have a mutation of the *Notch 3* gene on chromosome 19 compatible with CADASIL.

CASE REPORT

The proband was a 31-year old Thai male who presented with a sudden onset of right sided weakness without aphasia. He had no history of vascular risk factors such as hypertension, diabetes, dyslipidemia or cigarette smoking. There was no history of migraine. His past history revealed some psychiatric problems. At the age of 23, he had had an episode of depression following the ending of his relationship with his girlfriend. The depression lasted for one year and resolved without any therapeutic intervention. He then regained his normal level of functioning. One year before his neurological presentation, he was reported by relatives to have had elevated mood, hyperactivity, a reversed sleep-wake cycle, increased appetite, regressive and childish behavior, hypersexuality, and poor self-care. Impaired judgement was also exhibited by an inability to evaluate the adverse consequence of money lending and the use of verbal obscenities. Physical examination showed a mild right sided weakness (grade 4/5) without sensory impairment. There was also a mild right facial weakness. Speech was fluent and comprehension was good. Generalized hyperreflexia was noted. Mental status examination demonstrated that he had a euphoric and inappropriate affect with normal flow of speech. He appeared to be childish, but without any delusion or hallucinations. Regarding his cognitive function, he was fully conscious but mildly distractible. His recent and remote memory, as well as the executive function seemed to be normal, except for poor judgement.

Magnetic resonance imaging (MRI) of the brain demonstrated multiple hyposignal intensity lesions (equal to that of cerebrospinal fluid (CSF)) on T1-weighted (T1W) images in both basal ganglia, periventricular white matter and the left side of the midbrain (Fig. 1). These lesions were of hypersignal intensity on T2-weighted (T2W) images. Diffuse subcortical white matter lesions in the frontal, parietal and occipital lobes were also noted bilaterally. MRA of the brain and neck vessels showed no evidence of focal stenosis of the large or medium size arteries.

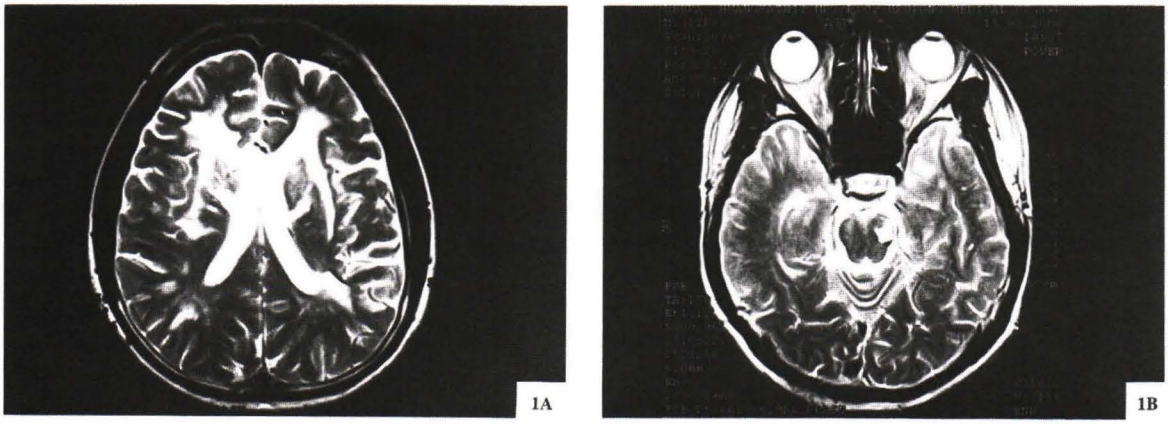

Fig. 1. MRI of the brain (axial T2 weighted image) of CADASIL patient demonstrating hypersignal intensity lesions in the periventricular white matter and left side of midbrain.

The proband is the second child among other four sisters who do not have any symptoms of stroke, dementia or migraine. His 62-year-old mother, however, has been suffering from multiple strokes since her early forties and is presently being cared for in a long-term nursing facility because of her severe dementia. Her MRI also demonstrated multiple subcortical infarctions in the deep white matter. Besides mild hypertension, which developed later in the course of dementia, she did not have any other vascular risk factors. She is the third child among five siblings amongst whom two other affected family members were identified. Her older sister has had multiple strokes since the age of 43 and now has a severe dementing illness. The older brother died of stroke and dementia at the age of 65. MRI of the older sister was available and demonstrated multiple infarctions in the deep subcortical white matter.

Genetic testing of the proband performed in the laboratory of Dr. Elisabeth Tournier-Lasserve (Laboratoire Histologie Embryologie Cytogenetique, Hopital Lariboisiere, Paris) demonstrated a *Notch 3* mutation consisting of the substitution of a nucleotide at position 406 in exon 3 (codon CGT was transformed to TGT) leading to the replacement of an Arginine by Cysteine at position 110 in the 2nd EGF (Epidermal growth factor-like) motif. According to the laboratory, this type of mutation is only observed in CADASIL patients and has otherwise never been observed in a panel of 200 control chromosomes.

DISCUSSSION

CADASIL is a hereditary, non-atherosclerotic angiopathy affecting mainly the small penetrating arteries in the subcortical region of the brain. The disease is characterized clinically by recurrent small subcortical infarcts leading to subcortical frontal dementia[1,2]. Other common clinical symptoms are migraine with aura and mood disorders[3].

According to a large series, four characteristic clinical features of CADASIL have been described. The most frequent (80%) manifestations are recurrent ischemic episodes ranging from transient ischemic attack to a complete stroke. These ischemic attacks occur at the mean age of 41[4]. The ischemic symptoms and signs are mostly of the subcoritcal type and may correspond to classical lacunar syndromes. Recurrent infarcts usually occur, resulting in a stepwise or progressive development of subcortical dementia which is generally observed 10-15 years after the initial ischemic episode. Dementia is usually of the subcortical type and is characterized by poor attention, memory impairment, pseudobulbar palsy and urinary incontinence[5]. Another symptom which is of a highly variable frequency among families is the presence of migraine with aura. The first attack of migraine generally occurs at a younger age. The fourth group of symptoms is mood disturbances, which sometimes proceed the onset of ischemic episodes. Depressive illness is a common manifestation[6].

The present patients exhibited a number of features including multiple subcortical stroke and mental problems that are typical of those that have already been described in CADASIL[3]. However, none of these patients had experienced migrainous headache.

MRI of the presented cases demonstrated multiple subcortical white matter infarctions located mainly in the periventricular region. Lesions in the basal ganglia and brainstem were also seen. According to a large MRI study, the periventricular area is the most commonly affected site, whereas basal ganglia and pontine lesions have been described in 29 and 23 per cent of cases, respectively[7].

Regarding genetic study, CADASIL was originally mapped to chromosome 19 in two families [2]. Subsequent linkage analysis showed the genetic homogeneity of this condition. Mutation of *Notch 3* gene has been shown to be responsible for the disease [4,6]. According to the literature, more than 40 mutations have been identified[8]. However, the pathophysiology of the disease and linkage between the abnormal protein and CADASIL phenotype still has to be further investigated. CADASIL has been described in many Europeans such as Italian, Dutch, British and German families as well as in North American families[3,5,9-11]. Among Asian populations, CADASIL has only been reported in the Japanese [4,12]. A study from Japan demonstrated that *Notch 3* mutation was responsible for CADASIL in four out of 11 families[6]. The authors here present a family with CADASIL in Thailand which, to our knowledge, is the first report from South East Asia. The patient had *Notch 3* missense mutation similar to that previously reported in Caucasian and Japanese patients. Therefore, the *Notch 3* gene is responsible for CADASIL across different ethnic groups.

SUMMARY

The authors describe the first family with CADASIL in Thailand. Besides the lack of migraine history, the presented patients had a phenotypic expres-

sion in common with previously reported cases(11). The MRI studies were also typical of CADASIL. Genetic study demonstrated a mutation of *Notch 3* in chromosome 19. The authors thus conclude that *Notch 3* gene is responsible for CADASIL among patients of different ethnics.

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การเปลี่ยนแปลงของยีนนอทช์ 3 ในผู้ป่วยโรคคาดาซิล รายแรกของประเทศไทย

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รายงานครอบครัวผู้ป่วยโรคคาดาซิลซึ่งมีอาการสมองเสื่อมและหลอดเลือดสมองอุดตัน ผู้ป่วยรายแรกเป็นชายอายุ 31 ปี มาด้วยอาการแขนขาอ่อนแรงครึ่งซีกทันทีทันใด เข้าได้กับสภาวะสมองขาดเลือดจากหลอดเลือดอุดตัน โดยที่ไม่มีประวัติโรคปวดศีรษะไมเกรนหรือปัจจัยเสี่ยงอื่น ๆ ของการเกิดโรคหลอดเลือดสมอง แต่ผู้ป่วยรายนี้มีประวัติบุคคลในครอบครัวหลายคนเป็นโรคหลอดเลือดสมองตีบและมีอาการสมองเสื่อม การตรวจทางภาพสะท้อนในสนามแม่เหล็กพบมีลักษณะสมองขาดเลือดหลายตำแหน่งที่บริเวณส่วนลึกของสมองใหญ่และก้านสมอง การตรวจทางพันธุกรรมพบว่ามีการเปลี่ยนแปลงที่บริเวณนอทช์ที่ 3 โดยมีการแทนที่ที่ตำแหน่ง 406 การเปลี่ยนแปลงนี้เข้าได้กับผู้ป่วยโรคคาดาซิลซึ่งเคยมีรายงานจากต่างประเทศในชาวผิวขาวและญี่ปุ่น

คำสำคัญ : คาดาซิล, โรคหลอดเลือดสมอง, สมองเสื่อม, พันธุกรรม

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