

Case report

Autosomal dominant leukoencephalopathy with mild clinical symptoms due to cerebrovascular dysfunctions: A new disease entity?

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Abstract

A family with cerebrovascular dysfunctions and extensive white matter lesions was presented. The proband had suffered migraine. His brother showed syncopal episodes and migraine. His mother also suffered severe migraine with aura, and had transient hemiparesis during pregnancy. Their brain MRIs, being quite similar to each other, revealed diffuse bilateral deep white matter lesions, with no changes in serial follow-up. His grandmother showed similar white matter changes on CT, consistent with autosomal dominant inheritance. Lesions were considered to be due to chronic vasogenic edema based upon increased apparent diffusion coefficient (ADC) values on diffusion-weighted imaging, normal spectrum ratio of metabolites on ¹H MR spectroscopy, and decreased regional cerebral blood flows on single-photon emission CT (SPECT). A deficiency of genetically determined factors contributing to the autoregulation of small blood vessels might possibly lead to both clinical symptoms and white matter lesions through the breakdown of the blood–brain barrier and resultant vasogenic edema. Although cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was suspected, neither *NOTCH3* mutation nor granular osmophilic material (GOM) in the arteriole walls were detected. Further accumulation of similar cases is necessary to establish the possibility of a new familial leukoencephalopathy.

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1. Introduction

The advent of magnetic resonance imaging (MRI) made the early detection of white matter lesions (leukoencephalopathies) in living individuals possible. Although increasing numbers of leukoencephalopathies in childhood have been reported, and among them some new disease entities have been recognized, more than 50% of white matter lesions observed by MRI cannot yet be specifically diagnosed despite repeated MRIs and extensive laboratory investigations [1].

Patients with migraine (migraineurs) sometimes display white matter lesions. Familial leukoencephalopathy with migraine is known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). We report here a family with migraine and other symptoms related to cerebrovascular dysfunctions, and also with extensive white matter lesions.

2. Cases

Case 1: A 6-year-old boy was born to a dizygotic twin without complications, and his physical and mental development was normal. He suffered headache and

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cyclic vomiting occasionally, which led him to have a brain MRI. He underwent a range of physical examinations including head circumference and also neurological examinations and the results were normal.

Case 2: A brother of Case 1 was also found to have a white matter lesion by MRI at the age of 13 years, when he received a brain concussion as a result of sports activity. He was developmentally normal, but sometimes had the syncopal episodes upon hot bathing, physical activities or sudden standing-up. He also had difficulty awakening in the morning, and was diagnosed as having orthostatic dysregulation (OD). Dihydroergotamine mesylate was effective in eliminating these symptoms. During senior high school (between ages 15 and 17 years), migraine with aura emerged, while OD symp-

toms subsided. His school results and both physical and mental exams were normal.

Case 3: The mother of Cases 1 and 2, who had worked as a medical professional, was seen at the age of 41 years. When she was first pregnant at the age of 29, she experienced a loss of consciousness for about 1 h followed by right hemiparesis and numbness. Though these symptoms resolved spontaneously, subsequent severe headaches eventually resulted in an artificial abortion in the 5th month of pregnancy. After that, she suffered migraine with aura, and memory lapses for some time. She had five siblings, three of whom also suffered migraine. She had no vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia or smoking.

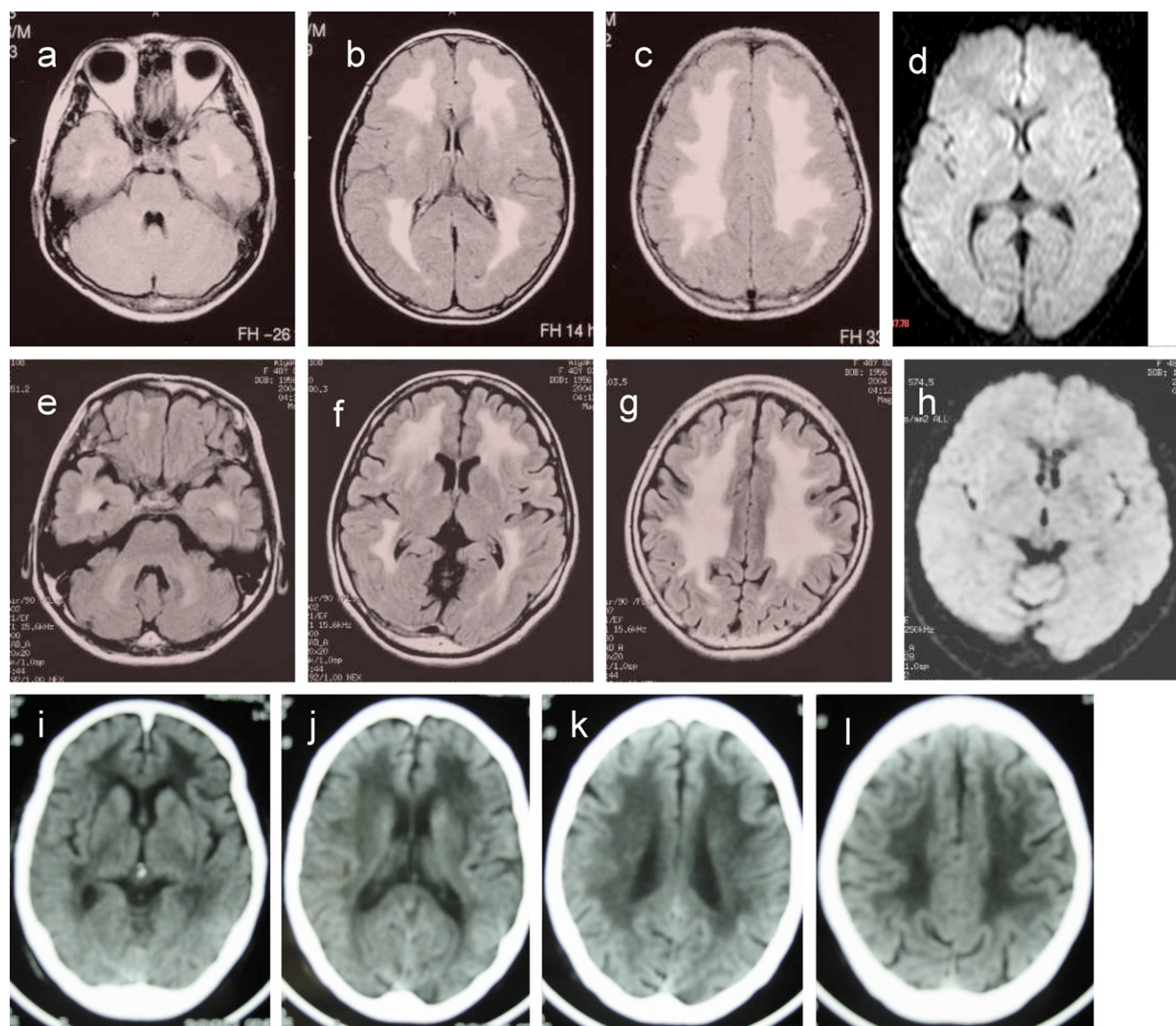


Fig. 1. Brain imagings. (a–d) MRIs of Case 1 at the age of 12 years. (a–c) FLAIR (TR/TE/TI = 6000 ms/120 ms/2000 ms). (d) DWI (TR/TE = 2700 ms/100 ms, $b = 1000$ s/mm²). (e–h) MRIs of Case 3 at the age of 49 years. (e–g) FLAIR (TR/TE/TI = 8000 ms/120 ms/2000 ms). (h) DWI (TR/TE = 8000 ms/75 ms, $b = 1000$ s/mm²). (i–l) CT of Case 4 at the age of 75 years.

Case 4: Case 3's mother, the grandmother of Cases 1 and 2, gradually developed dementia in her 70s, with no paresis or Parkinsonism. She had a blood pressure of around 140/80-90, and showed age-appropriate atherosclerotic change with mild aortic insufficiency. Other vascular risk factors were not seen. No history of migraine was observed. A brain CT, which was taken after the dementia appeared, disclosed diffuse, bilateral low densities of the deep white matter, reminiscent of the MRI lesions of Cases 1, 2 and 3 (Fig. 1). The pedigree tree is shown in Fig. 2.

All of Case 1's laboratory data were normal, including lysosomal enzymes, very long chain fatty acids, adrenal and pituitary hormones, cytomegalovirus antibodies in the cerebrospinal fluid (CSF), lactic and pyruvic acids in the CSF, organic acids and amino acids profiles in the urine, electroencephalogram, evoked potentials (SEP, VEP, P₃₀₀) and nerve conduction velocities. Repeated ophthalmologic examinations including examination of the retinal arteries revealed normal findings. A muscle biopsy, performed to exclude merosine-negative non-Fukuyama congenital muscular dystrophy, revealed normal pathology without ragged red fibers. ^{99m}Tc-ECD SPECT in Case 2 showed no perfusion defects, with decreased regional cerebral blood flows by the Patlak Plot (rCBF mean ± SD: R/L = 31.4 ± 3.0/31.5 ± 3.5 ml/100 g/min). We could not find any mutation in the coding region of *NOTCH3* gene in genomic DNA from the peripheral blood of Case 3. The skin in Case 3 and the muscle in Case 1 did not show any abnormalities including granular osmophilic materials (GOM) in the media of arterioles under the electron microscope.

Brain MRIs of the family members were investigated. Case 1's twin brother, his father and another elder brother were normal, whilst Cases 1, 2 and 3 displayed abnormalities, which were basically very similar to each

other (Fig. 1). Diffuse, but frontal predominant, bilateral deep white matter lesions, with sparing of the U-fiber, the corpus callosum, the internal capsule and the optic radiation, were the common findings among them. The putamen was involved in Cases 1 and 2, whereas in Case 3 the external capsule and the cerebellar deep white matter around the dentate nuclei were involved. In Case 1, no enhancement was observed as a result of Gadolinium injection. Diffusion-weighted imaging (DWI) of all three cases revealed normal diffusion capabilities with increased apparent diffusion coefficient (ADC) values of the lesions: 1.6 in Case 1 and 1.4 in Case 3 (normal ADC values are 0.67 ± 0.03 , $n = 4$). In ¹H MR spectroscopy of Case 1 (TR/TE = 2000/270 ms), spectrum ratio of *N*-acetyl aspartate (NAA)/creatinine (Cr), choline (Cho)/Cr and NAA/Cho in the region of abnormal signal intensities (the centrum semiovale) was 3.35, 1.40 and 2.39, respectively (normal values are 2.71 ± 0.15 for NAA/Cr, 1.20 ± 0.08 for Cho/Cr and 2.27 ± 0.12 for NAA/Cho, $n = 3$). A lactate peak was not evident. MR angiography in Case 1 disclosed no abnormal vascular architectures.

During an 8 year follow-up of these three cases, no obvious changes were observed in clinical symptoms or in serial MRIs, except for the emergence of migraine in Case 2. Brain imaging of the siblings of Case 3 could not be obtained.

3. Discussion

A family with cerebrovascular symptoms, such as migraine, syncope and transient ischemic attack, and with extensive white matter lesions has been presented. Among this family, two siblings and their mother showed quite similar deep white matter lesions. The maternal grandmother probably had the same lesions. Therefore, the mode of inheritance appears to be autosomal dominant. Though both X-linked or mitochondrial inheritance is possible, no symptomatic differences between sex and no characteristic symptoms commonly seen in mitochondrial diseases make them unlikely.

Childhood white matter lesions with high intensity T₂-weighted spin echo or FLAIR images and low intensity T₁-weighted images are due to highly variable pathologic changes, such as hypomyelination, demyelination, gliosis, vasogenic edema, cytotoxic edema, intramyelinic edema, cystic degeneration, and diffuse infiltration of tumor cells [2]. Recently, DWI has been introduced in routine MRI examination [1]. This is a very sensitive technique to show changes in the mobility and compartmentation of water. Structures with restricted diffusion of water molecules, such as seen in cytotoxic edema, collection of mucinous fluid, tumor with high cellular densities

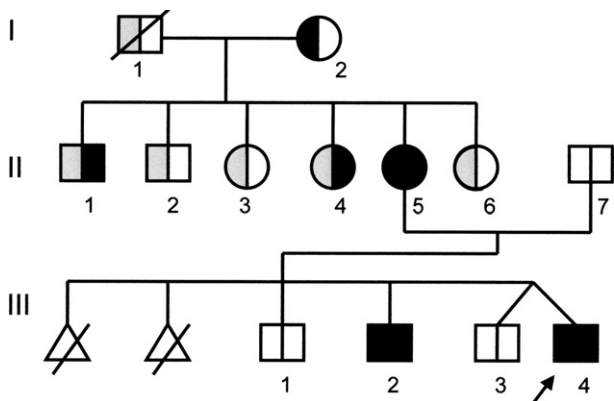


Fig. 2. Pedigree tree. Case 1: III-4, Case 2: III-2, Case 3: II-5, Case 4: I-2. The left and right half of each circle or square indicates white matter lesions and migraine, respectively. In both halves, "presence" is indicated by black, "absence" by white, and "not examined" by grey.

or hemorrhage show decreased ADC values, whereas vasogenic edema or many cases of myelin disorders, in which free water is increased, show increased ADC values [2].

MR spectroscopy has also been shown to be useful in differentiating childhood white matter disorders, especially with myelin disorders [2]. It was reported that many demyelinating disorders showed marked abnormalities. Even in a hypomyelinating disorder, total Cre and myoinositol levels were elevated, though ADC was close to normal. On the contrary, there was no significant NAA depletion, nor was there an abnormal Cho/NAA ratio shown in vasogenic edema [3]. Therefore, normal Cho/NAA in MR spectroscopy, together with increased ADC values, suggests that the white matter lesions in this family are possibly due to chronic vasogenic edema, rather than due to myelin disorders. Decreased rCBF revealed by the SPECT is also compatible with this speculation, as vasogenic edema can induce cerebral hypoperfusion.

It is surprising that their clinical symptoms were so extraordinarily mild considering the extensive white matter changes revealed by the MRIs. Migraine was observed in Cases 1, 2 and 3 with syncopal episodes in Case 2 and the stroke-like episode in Case 3. These symptoms seem to be derived from autoregulatory dysfunctions of the cerebral perfusion. It has been well known that migraineurs sometimes have white matter lesions [4]. Several hemodynamic features of migraine may contribute to the pathogenesis of white matter lesions: repeated and prolonged reduced perfusion pressure, reduced blood flow, and oligemia in large and/or small arteries, combined with activation of the clotting system or vasoconstriction. The damage of brain blood vessels induced by these factors could cause blood–brain barrier dysfunctions and induce plasma leakage through injured endothelium, eventually leading to chronic vasogenic edema [5].

Reversible posterior leukoencephalopathy is another example of the white matter change due to vasogenic edema. Autoregulatory dysfunction of the small vessels and breakdown of the blood–brain barrier, caused by malignant hypertension, or the use of immunosuppressive or cytotoxic drugs, have been suggested for this disorder [6]. The white matter changes seen in merosin-deficient congenital muscular dystrophy, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) are also reported to be due to vasogenic edema [7,8]. Although these diseases can be ruled out in our cases, it seems possible to postulate that some genetically determined dysfunctions, contributing to the autoregulation of small blood vessels, result in chronic vasogenic edema and hypoperfusion, eventually leading to extensive white matter changes.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) exhibits leukoencephalopathy with migraine (30–40%), stroke-like episodes upon onset of mid-adulthood, cognitive or behavioral disturbances, and dementia with relatively early onset. In almost half of affected individuals, migraine, predominantly with aura, is an initial symptom. Some families in which migraine with aura is the most prominent symptom are reported [9]. Imaging abnormalities evolve as the disease progresses, showing the age-dependent pattern. In symptomatic individuals, the lesions are symmetrical and located in the periventricular and deep white matter, often associated with small infarcts in the white matter, basal ganglia and brainstem. Distinctive white matter lesions first appear in the anterior temporal lobes from 20 to 30 years of age. In diffusion study, it was found that the more severe the white matter lesions were, the higher the ADC values became. The pathogenesis of the white matter lesions remains unclear, though chronic hypoperfusion or ischemia has been the most supported hypothesis, and axonal loss replaced by interstitial water may explain the increased ADC values [10].

The MRI findings of our cases are not inconsistent with those seen in the symptomatic CADASIL cases. Clinical symptoms of our cases, including migraine or transient hemiparesis, are also common in CADASIL. These led us to examine *NOTCH3* gene, for mutations of this gene had been reported to be responsible for CADASIL [11]. Also we examined for the existence of a characteristic pathological finding, namely granular osmophilic material (GOM) in the arteriole walls. But, the results were both negative. In addition, extremely early appearance of diffuse white matter lesions (Cases 1 and 2) is unusual in CADASIL, as it was reported that these lesions were consistently visualized from the age of 21 years [12]. Also, the onset of dementia in the 70s for Case 4 is late compared to CADASIL, in which dementia usually emerges before the person's 70s. Taken into consideration all these indicators, the diagnosis of CADASIL is unlikely in this family. Some possibility of an unknown subtype of CADASIL still remains, because *NOTCH3* gene mutations are detected in less than one fourth of Japanese CADASIL families, suggesting the presence of other causative genes [13].

In conclusion, chronic vasogenic edema and hypoperfusion derived from the autoregulatory dysfunctions of small blood vessels were suggested as the underlying pathophysiological features, though extensive laboratory investigations could not reveal a specific diagnosis in this family. Further accumulation of similar cases is required to establish the possibility of a novel familial leukoencephalopathy or, less probably, a subtype of CADASIL.

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