

Migraine, White Matter Lesions and Subarachnoid Hemorrhage: Analysis of a Large Pedigree

Migren, Ak Madde Lezyonları ve Subaraknoid Kanama: Geniş Bir Aile Ağacının Analizi

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ABSTRACT

Patients with migraine are at increased risk for white matter hyperintensities detected on magnetic resonance imaging (MRI). A 46-year-old woman had a history of migraine with and without aura for 20 years. Bilateral prominent hyperintense lesions were seen in centrum semiovale, posterior corona radiata, frontal white matter and periventricular regions on her T2- and FLAIR-weighted cranial MRIs. Thirteen members of her family, including her son, had a history of migraine and similar brain MRI lesions. Furthermore, three family members had a history of subarachnoid hemorrhage (SAH) and one member had intracranial aneurysm. Our current knowledge on associations, investigation plan and treatment of patients with migraine with white matter lesions of unknown significance is limited. Herein, for the first time, we report the association of this condition with familial SAH in a large pedigree. (*Archives of Neuropsychiatry* 2010; 47: 162-5)

Key words: Migraine, white matter lesions, subarachnoid hemorrhage, familial intracranial aneurysm, CADASIL

ÖZET

Migrenli hastalarda manyetik rezonans görüntüleme (MRG) ak madde hiperintensitelerin saptanma ihtimali artmıştır. Kırk altı yaşındaki kadın hastanın 20 yıldır auralı ve aurasız migreni vardı. T2 ve FLAIR ağırlıklı MRG kesitlerinde belirgin iki yanlı sentrum semiovale, posterior korona radiata, frontal ak madde ve periventricüler bölgelerde hiperintens lezyonlar görüldü. On üç aile bireyinde migren öyküsü vardı ve benzer MRG lezyonları migrenli oğlunda da görüldü. İlginç olarak üç aile bireyinde subaraknoid kanama (SAK) ve bir aile bireyinde intrakraniyal anevrizma öyküsü mevcuttu. Önemi bilinmeyen ak madde lezyonları olan migrenli hastaların ilişkili olduğu durumlar, inceleme planı ve tedavileri konusundaki bugünkü bilgilerimiz sınırlıdır. Bu durumun ailesel SAK ile birlikteliği ilk kez bu çalışmada geniş bir ailede bildirilmiştir. (*Nöropsikiyatri Arşivi* 2010; 47: 162-5)

Anahtar kelimeler: Migren, ak madde lezyonları, subaraknoid kanama, ailesel intrakraniyal anevrizma, CADASIL

Introduction

Patients with migraine are at increased risk for white matter lesions (WMLs) detected on magnetic resonance imaging (MRI) and these lesions are common, especially in females having migraine with aura (MA) (1). Many studies have reported that brain MRI of migraine patients demonstrated focal cerebral areas appearing as ischaemia-like lesions and prevalence of this finding varies, ranging from 6% to 46% (2-6). The origin and nature of WMLs in migraine patients remain still unclear (1). It is controversial, whether these subclinical brain

lesions relate to a higher risk of cerebrovascular disease. There is evidence for an association between migraine and ischemic stroke, but not for migraine and subarachnoid hemorrhage (SAH) (7).

In this study, we reported an index female patient who has MA with WMLs on MRI and her family members suffering from migraine and SAH (Figure 1).

Report of the Index Patient and Her Family

A 46-year-old woman suffered from headache with paresthesia of the perioral region and hands. She had a history of MA with visual and paresthetic aura lasting 5-7 minutes and

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migraine without aura (according to the International Classification of Headache Disorders published in 2004) for 20 years (8). Her visual auras were shaped as black spots in front of one eye, stereotypic for every migraine attack and preceding headache. Paresthetic auras were rare, bilateral, not stereotypical and also preceding headache.

Her past medical history was uneventful, except for having depression. She had been using amitriptyline and paroxetine for the last three years. Her neurological examination was normal. She had no additional vascular risk factors, such as hypertension, diabetes mellitus and hyperlipidemia, other than smoking (20 pack-years).

Three years ago, she had been admitted to another hospital due to headache and T2- and FLAIR-weighted cranial MRI had showed bilateral hyperintense lesions in centrum semiovale, posterior corona radiata, frontal white matter and periventricular regions (Figure 2a). She had been investigated in order to exclude multiple sclerosis (MS) and related diseases. Markers

of vasculitis (anticardiolipin antibodies, rheumatoid factor, ANA, anti-dsDNA) and procoagulant factors (protein C, protein S, antithrombin III) were all found negative. Homocysteine levels were normal. Wright agglutination test (diagnostic test for Brucellosis), TPHA and VDRL tests were negative; the levels of vitamin B12, thyroid hormones and thyroid autoantibodies were within the normal range. Echocardiography, carotid duplex ultrasonography and vertebral artery investigations were also found normal. She was admitted to our department and the cranial MRI investigation was repeated. No new WMLs were observed (Figure 2b). Intracranial MR angiography, performed to reveal the possible presence of aneurysm or atherosclerosis, gave normal results. Pattern VEP and SEP examinations were within normal limits. Cerebrospinal fluid examination for the presence of oligoclonal bands was also normal.

Exons 2, 3, 4, 5, 6 and 11 of NOTCH3 gene were sequenced, but no mutation was revealed. Heterozygous synonymous SNP (rs1043994) in exon 4 and heterozygous synonymous variation

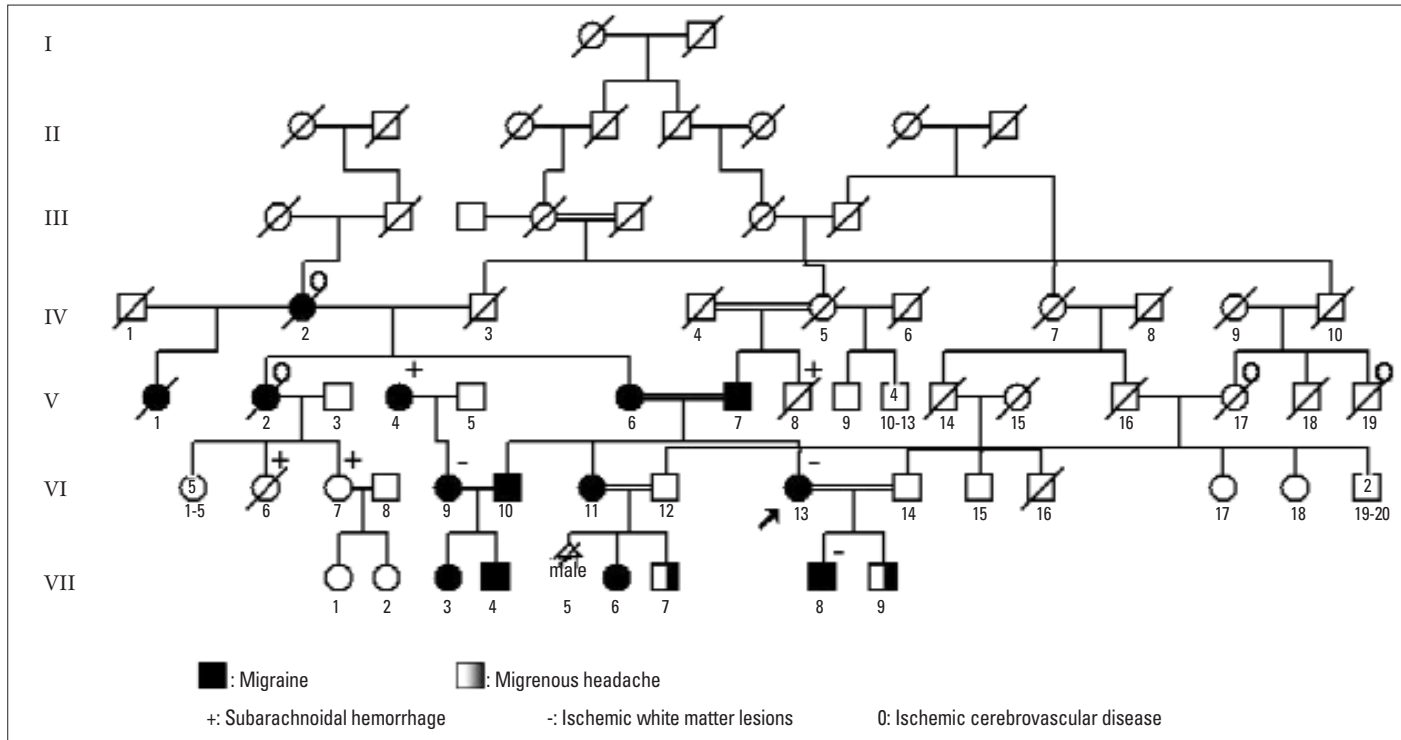


Figure 1. The Pedigree showing the patients with migraine and subarachnoid hemorrhage

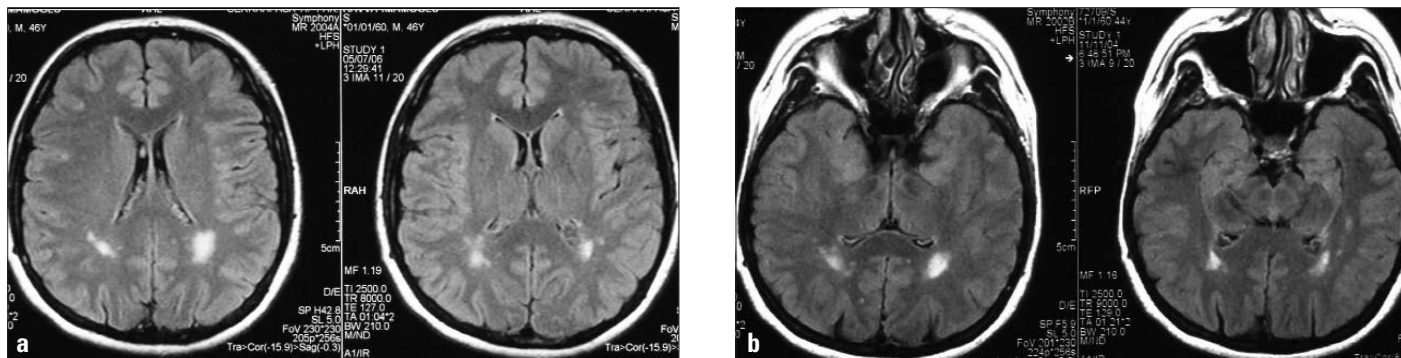


Figure 2a-b. Cranial MRI study of the index case in 2004 (a) and 2006 (b) Axial FLAIR sequences

(c.G1725A; p.T575T) in exon 11, which have not been previously described in SNP database by NCBI (<http://www.nlm.nih.gov>), were shown. Skin biopsy specimens from the patient and her son were analyzed by electron microscopy. The diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was excluded with high certainty, because granular osmiophilic deposits in the capillaries, which are diagnostic for CADASIL, were not observed.

Deterioration in elementary attention and verbal fluency, borderline impairments of visuospatial functions were detected on her neuropsychological evaluation.

Four members of the family had an additional clinical history of SAH as depicted in the pedigree (Figure 1). One of them, a 66-year-old woman (V:4), had migraine without aura for forty-two years and hypertension for twenty years. She had presented with a seizure and left hemiparesis in 2003. An aneurysm in the lateral wall of the right internal cerebral artery (ICA) was detected by cerebral digital subtraction angiography (DSA). She was operated and has left slight hemiparesis. She has not suffered from headaches since the operation. The patient (V:8) had suffered from SAH and died for that reason at forty-two years of age. He did not have any history of headache. The third subject (VI:6) also had died when she was thirty-two years old due to SAH. The fourth subject (VI:7) was examined in the asymptomatic period by cerebral DSA, since her sister (VI:6) had SAH, and an aneurysm at the bifurcation of the right ICA was observed, for which she was operated in 2007 and did not have any related health problems afterwards.

Thirteen members of the pedigree (IV:2, V:1, V:2, V:4, V:6, V:7, VI:9, VI:10, VI:11, VII:3, VII:4, VII:6, VII:8), except for the index patient, had a history of migraine without aura and two members (VII:7, VII:9) had probable migraine. Besides the index patient, nine members of the family (VI:9, VI:10, VI:11, VII:3, VII:4, VII:6, VII:7, VII:8, VII:9) were examined in detail and investigated by MRI and MR-Angiography (MRA). There were three patients (VI:9, VI:13, VII:8) showing nonspecific WMLs (Figures 2a-b, 3 and 4). The eldest son of the index patient (VI:13) has migraine and also ischaemic WMLs (Figure 3); his SEP and VEP investigations were normal. Deterioration in verbal fluency was revealed on his neuropsychological evaluation.

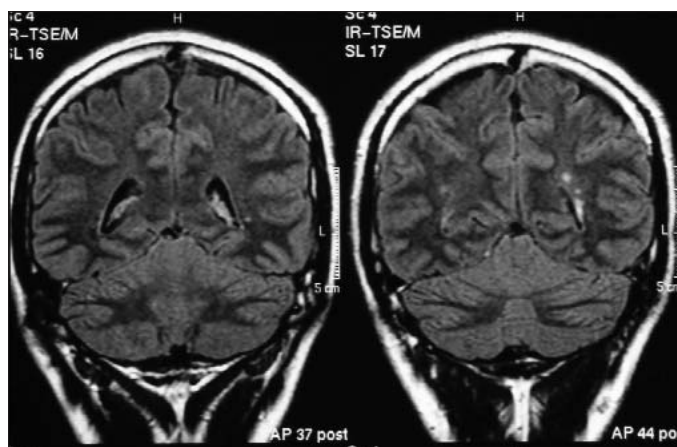


Figure 3. Cranial MRI study of the index case's son. Coronal FLAIR sequences

Discussion

Migraine is a primary neurovascular headache affecting approximately 19,3% of the adult population (9). Cerebral WMLs with unknown significance can be observed on cerebral MRI scans. Some clinical studies and anecdotal case reports suggest that WMLs are more frequently observed in patients with migraine than in the general population. However, their clinical relevance and causes remain to be uncovered. Future studies should also investigate, whether these WMLs are predictors of a subsequent cerebrovascular disease in patients with migraine (1). The presence of white matter foci was significantly higher in the migraineurs with aura (40%) than in those without aura (20%) (1,10). A new meta-analysis reported by Schürks and colleagues showed that MA is associated with a twofold increased risk of ischaemic stroke and their results also suggested a higher risk among women who were aged less than 45, smokers and women who used oral contraceptives (11). Our patient was aged around 45 and a smoker.

Ischaemic cerebral vascular disease caused by vasculitis, antiphospholipid syndrome, CADASIL, leukoaraisosis, or MS should be kept in mind in the differential diagnosis of cerebral WMLs. MS was excluded in our case by the history and laboratory results showing absence of oligoclonal bands and normal SEP and VEP studies. Furthermore, all markers for vasculitis and procoagulant factors were negative, homocysteine levels were normal, MRA examination were normal. Therefore, cerebral vascular disease was also excluded on clinical and laboratory basis.

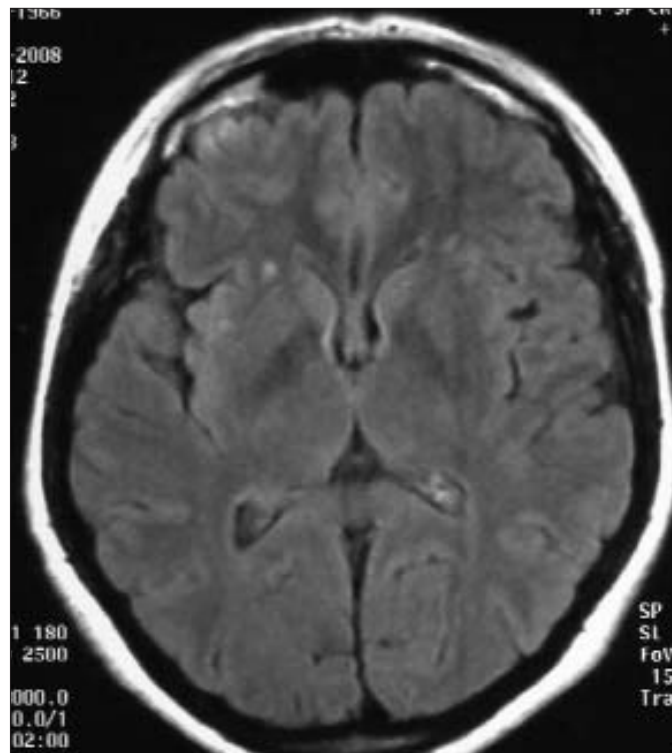


Figure 4. Cranial MRI study of the index case's sister-in-law. Axial FLAIR sequences

Prolonged migraine aura with atypical features associated with WMLs should lead to suspicion of CADASIL, which has a wide clinical spectrum. It is well-known that migraine could be the only clinical manifestation of CADASIL in some cases and phenotype of CADASIL did not clearly associate with genotype. Therefore, all clinical and imaging data should be interpreted with caution and available pathological and genetic investigations should be done in suspected cases (12,13).

Markus et al. have found 15 different point mutations in the NOTCH3 gene in 48 families, 73% of them being at exon 4.8% at exon 3 and 6% in exons 5 and 6 (14). Peters et al. (15) have identified 54 distinct mutations in the NOTCH3 gene in 120 (96%) of 125 patients; 58,3 % of the mutations were located in exon 4 and 85.8% in exons 2 through 6. In our family, mutations in exons 2, 3, 4, 5, 6, and 11, which account for more than 90% of CADASIL causing mutations, were excluded by direct sequencing. The possible diagnosis of CADASIL was further excluded by the negative biopsy results on electron microscopy examination. In this family, excluding the diagnosis of CADASIL leads us to assume that similar pictures can be seen due to different currently unknown mutations.

In our large family with consanguinity, 4 members have had SAH and one has had suspicion of SAH. Carter et al. (7) reported that the frequency of migraine was similar in patients with SAH and in the general population. No evidence was found for an association between recurrent headaches and SAH. An association between WMLs and migraine with familial SAH is being reported for the first time in a large pedigree in this study.

In conclusion, due to the limited current knowledge about the association between migraine patients and WMLs of unknown significance, the work-up and follow-up plans and treatment of the patients remain controversial. Our index patient and two members of the family had bilateral hyperintense lesions associated with migraine with and without aura. An association of the condition with familial SAH is being reported for the first time in this study in a large pedigree. Further epidemiological and genetic studies are needed to clarify the possible association between these entities.

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