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Case report

Familial moyamoya disease in a Greek family

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Abstract

Moyamoya disease (M-M) is characterized by progressive obstruction of the supraclinoid portion of internal carotid arteries and the proximal middle, anterior and posterior cerebral arteries, associated with the formation of a characteristic net of collateral vessels in the basal ganglia region. Clinical manifestations in childhood include transient ischaemic attacks, seizures and multiple infarcts. Approximately 7% of M-M cases are familial. We report two affected Greek siblings with typical clinical and neuroradiological findings of M-M. Linkage analysis of the whole family was consistent with linkage to the region 3p24-26, as previously reported in other familial Japanese M-M cases. © 2002 Elsevier Science B.V. All rights reserved.

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Moyamoya disease (M-M) is characterized by progressive obstruction of the supraclinoid portion of the internal carotid arteries and the proximal middle, anterior and posterior cerebral arteries, associated with the formation of a characteristic net of collateral vessels in the basal ganglia region. Clinical manifestations in childhood include transient ischaemic attacks, seizures and multiple infarcts [1]. It is well known that approximately 7% of M-M cases are familial [2] and M-M in the Japanese population, where the condition is more common [1,2], is possibly linked to chromosome 3p24-26 [3], but also to chromosomes 6 and 17q25 [4,5]. However, there is growing evidence that cases of familial M-M do exist outside Japan and Asia [6]. We would like to add our own experience in this field by reporting clinical and molecular data of a Greek family with two affected male siblings.

The first patient was a 9.5-year-old male, who was followed-up neurodevelopmentally because of mild motor retardation (he walked at 20 months of age and since then has demonstrated mild clumsiness, however without true pyramidal, extrapyramidal or cerebellar tract signs). He had normal findings on cranial magnetic resonance imaging (MRI) at the age of 3.5 years. At the age of 7 years, he suffered two generalized tonic-clonic seizures. In spite of anticonvulsant medication, he continued to have focal motor seizures and then developed recurrent transient ischaemic attacks with migraine-like headaches and episodes of weakness of the left face and arm, which always subsided after a period of 5-6 h. Serial MRI of the brain demonstrated cortical infarcts in the frontal region bilaterally, as well as small areas with low signal intensity in the basal ganglia and thalami (M-M vessels) on T2-weighted imaging (Fig. 1). His brother, a 4.5-year-old male, presented with focal status epilepticus, which responded to intravenous phenytoin. Computer tomography and MRI were consistent with multiple infarcts, predominantly in the frontal regions bilaterally.

Digital subtraction angiography was performed in both patients and revealed obstruction of the supraclinoid part of the internal carotid artery bilaterally and of the proximal portions of the middle, anterior and posterior cerebral arteries, as well as formation of M-M vessels (Fig. 2). Extensive investigation in order to exclude cardiac causes

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Fig. 1. MRI of the first patient demonstrating increased signal intensity compatible with cortical infarcts in the frontal region bilaterally, as well as small areas with low signal intensity in the basal ganglia and thalami (M-M vessels or the 'salt and pepper' phenomenon) on T2-weighted imaging.

(transesophageal echocardiography), biochemical abnormalities (cholesterol, triglycerides and lipoproteins), infectious causes (serum titres for varicella-zoster, mycoplasma pneumoniae, borrelia, chlamydia and helicobacter), haematological abnormalities (including antithrombin III, proteins C and S, activated protein C resistance, heparin cofactor II, plasminogen, factors VII and VII, folic acid, B6 and B12, MTHFR, prothrombin 20210 and factor V Leiden mutation, lupus anticoagulant and anticardiolipin antibodies) and metabolic disorders (including plasma lactate and ammonia, blood gases, plasma homocysteine, serum and urin–aminoacids, urinary organic acids, sulphite test, very long chain fatty acids and lysosomal enzymes) did not reveal any underlying diagnosis.

Encephaloduro-arteriosynangiosis (EDAS) was performed bilaterally in both brothers (at the age of 9 and 5 years, respectively) and antiepileptic medication with phenytoin was initiated. Two years after EDAS both patients are neurologically normal (no evidence of pyramidal, extrapyramidal or cerebellar tract involvement, normal ocular motility, normal linguistic abilities and an IQ within the normal range), demonstrating only mild behavioural problems together with a slightly aggressive behaviour. Regarding antiepileptic medication, both patients are currently off therapy and the second patient is free of seizures since the acute episode. A third asymptomatic brother (no neurodevelopmental deficits) has a normal MRI and a normal magnetic resonance angiography (MRA) at the age of 6 years. Both parents also demonstrate normal MRI findings and are neurologically normal with an IQ in the normal range.

Linkage analysis of the whole family was performed in order to see if M-M in this family could be linked to the region 3p24-26 (Table 1), as in the cases of familial M-M



Fig. 2. Digital subtraction angiography of the second patient demonstrating obstruction of the supraclinoid part of the internal carotid artery (left) and of the proximal portions of the middle, anterior and posterior cerebral arteries, as well as formation of M-M vessels (M-M phenomenon or 'puff of smoke').

Table 1
Linkage analysis of the family with M-M disease ^a

	Allele type			
	D3A	D3SB	D3SC	
Father	1, 2	1, 8	1, 3	
Mother	2, 2	2, 8	5,7	
Patient 1	1, 2	1, 2	3, 7	
Patient 2	1, 2	2, 8	1, 7	
Healthy brother	1, 2	2, 8	1, 7	

^a The nearest loci responsible for the M-M disease gene at 3p are indicated as D3A, D3SB, D3SC and each pair of numbers, for example 1, 2, represents the allele type. Two brothers (patient 2 and healthy brother) inherited the same haplotype from their father (1 for locus D3A, 8 for locus D3SB, and 1 for locus D3SC) and the third (patient 1) appears to have had a recombination event between D3A and D3SB, resulting in a 1-1-3 haplotype, and thus sharing only the paternal D3A allele with his siblings. This analysis is consistent with autosomal recessive inheritance with reduced penetrance only at the D3A locus.

reported by Ikeda [3] in Japan. Although the family is too small to generate a significant LOD score, the genetic analysis was consistent with autosomal recessive inheritance at the D3A locus with reduced penetrance (since the healthy sibling is haploidentical and unaffected). To the best of our knowledge this is the first familial M-M case in Greece and one of the few reported in patients outside Japan. Detailed molecular genetic testing is worth-while in these patients in order to establish possible candidate loci. Prevention or treatment of M-M based on genetic testing might be possible in the future.

References

- [1] Suzuki J, editor. Moyamoya disease Berlin: Springer-Verlag, 1983.
- [2] Matsushima Y, Aoyagi M, Niimi Y, Masaoka H, Ohno K. Symptoms and their pattern of progression in childhood moyamoya disease. Brain Dev 1990;12:784–789.
- [3] Ikeda H, Sasaki T, Yoshimoto T, Fukui M, Arinami T. Mapping of a familial moyamoya disease gene to chromosome 3p24.2-p26. Am J Hum Genet 1999;64:533–537.
- [4] Inoue TK, Ikezaki K, Sasazuki T, Matsushima T, Fukui M. Linkage analysis of moyamoya disease on chromosome 6. J Child Neurol 2000;15:179–182.
- [5] Yammmauchi T, Tada M, Houkin K, Tanaka T, Nakamura Y, Kuroda S, et al. Linkage of familial moyamoya disease (spontaneous occlusion of the circle of Willis) to chromosome 17q25. Stroke 2000;31:930–935.
- [6] Shetty-Alva N, Alva S. Familial moyamoya disease in Caucasians. Pediatr Neurol 2000;23:445–447.