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Case Report

Caucasian Familial Moyamoya Syndrome With Rare Multisystemic Malformations

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ABSTRACT

Moyamoya disease is an idiopathic progressive steno-occlusive disorder of the intracranial arteries located at the base of the brain. It is associated with the development of compensatory extensive network of fine collaterals. Moyamoya disease is considered syndromic when certain genetic or acquired disorders such as polycystic kidney disease, neurofibromatosis, or meningitis are also present. Although the genetic contribution in moyamoya is indisputable, its cause and pathogenesis remain under discussion. Herein, we report a rare occurrence of moyamoya syndrome in two European Caucasian siblings in association with unusual multisystemic malformations (polycystic kidney disease in one, and intestinal duplication cyst in the other). The karyotype was normal. No mutation in the RFN213 gene was found, and none of the HLA types linked to moyamoya disease or described in similar familial cases were identified. By describing these multisystemic associations, polycystic kidney disease for the second time, and intestinal malformation for the first time in the literature, our report expands the phenotypic variability of moyamoya syndrome. The coexistence of disparate malformations among close relatives suggests an underlying common genetic background predisposing to structural or physiological abnormalities in different tissues and organs.

Introduction

Moyamoya disease is an idiopathic progressive steno-occlusive disorder of the intracranial arteries located at the base of the brain. It is associated with the development of a compensatory extensive network of fine collateral vessels, the “moyamoya” vessels [1]. The list of genetic or acquired conditions associated with moyamoya is in continuous expansion. It includes disorders such as Down syndrome, polycystic kidney disease, neurofibromatosis, fibromuscular dysplasia, and meningitis among others. When these conditions are present, moyamoya is then named *moyamoya syndrome* or “quasi-moyamoya” [1-3]. Most affected patients present with ischemic symptoms. However, in a variable proportion of cases, more often in adults, cerebral hemorrhage can occur [1-4]. Headache, epilepsy, dyskinesia, and cognitive disturbances are other manifestations of moyamoya [1-3]. The familial incidence of affected first-degree relatives is approximately 10% to 12% in Japan and 2% to 6% in the United States [4]. Very few cases of familial moyamoya disease have been reported in Europe. We herein report a rare case of moyamoya syndrome in two European Caucasian siblings coexisting with polycystic kidney disease and intestinal duplication cyst.

Case Report

Two previously healthy European Caucasian sisters, without family history of consanguinity, cerebrovascular disease, malformations, or

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genetic disorders were diagnosed at our institution as having moyamoya syndrome. There was no history of neonatal events, meningitis, or cranial radiation.

The younger sister was the first to be diagnosed. She was admitted at the age of 11 years after acute onset of involuntary movements in the right limbs. Six months before admission she started having frequent falls and difficulty in executing fine motor activities with the right hand. The neurologic examination showed continuous choreoathetosis in the right hemibody. The remaining general and neurologic examination results were normal. The brain computed tomography (CT) result was normal. Magnetic resonance (MR) angiography and digital subtraction angiography disclosed the presence of asymmetric moyamoya with marked occlusion of the left anterior and middle cerebral arteries and a cloudlike flow in the territory of the middle cerebral artery (Fig 1). Renal ultrasonography showed the presence of bilateral multiple renal cysts (Fig 2). The patient underwent successful encepha-duro-arterio-synangiosis with symptomatic remission. The postoperative course was uneventful. She remains symptom free with normal cognitive and academic performance after 8 years.

The older sister was diagnosed 4 years later, at age 27, after the incidental finding of a chronic parieto-occipital ischemic lesion on a brain CT scan, obtained because of worsening of chronic tension headache after a minor head trauma. The general and neurologic examination results were normal. MR angiography and digital subtraction angiography disclosed the typical bilateral findings of moyamoya with extensive cortical brain collateralization (Fig 1). The abdominal CT scan showed an intestinal duplication cyst (Fig 2). The patient was referred for neurosurgical evaluation on two occasions and was not considered a candidate for revascularization because of the presence of spontaneous collateralization and atresic superficial temporal artery limiting direct bypass. She is under treatment with aspirin and remains without neurologic deterioration.

Both siblings were extensively tested to exclude other causes of secondary moyamoya including hematologic profile, coagulation screening, thrombophilias, and autoimmune serologic markers. The HLA findings are described in Table 1. The karyotype was normal, and no mutation in the RFN213 gene was found.

Discussion

The diagnosis of moyamoya is based on the demonstration of typical angiographic features. Cerebral angiography is the preferred method of diagnosis [1], but high-resolution MR angiography can suffice [2,3]. Both patients fulfilled the criteria for moyamoya attested by the presence of bilateral steno-occlusive changes in the terminal portion of the internal carotid artery, in the proximal portions of the anterior and middle cerebral arteries, and by the presence of abnormal vascular networks in the vicinity of the steno-occlusive vessels [1-3]. The disease has had a benign evolution in both patients, after neurosurgical intervention in the younger sister and after conservative treatment in the older. The incidental finding of a silent stroke in the older sister raises the question of screening in close relatives, which is practically nonexistent in Europe but is increasing in Japan [4].

There is no evidence to support screening for moyamoya; however, the dissemination of MR angiography led to early diagnosis and intervention in countries with relative high prevalence [4]. Table 1 resumes the clinical and HLA characterization of the previously reported cases of Caucasian familial moyamoya [5-10]. Screening was only carried out in one of these reported cases [6]. With increasing evidence of the advantages of early neurosurgical intervention in moyamoya, screening of the closest relatives with a noninvasive invasive method such as MR angiography could reduce the risk of permanent disability from stroke in symptom-free patients. Most cases of familial moyamoya in Caucasians are diagnosed in childhood, but the interval is wide (1-52 years), suggesting that any screening strategy

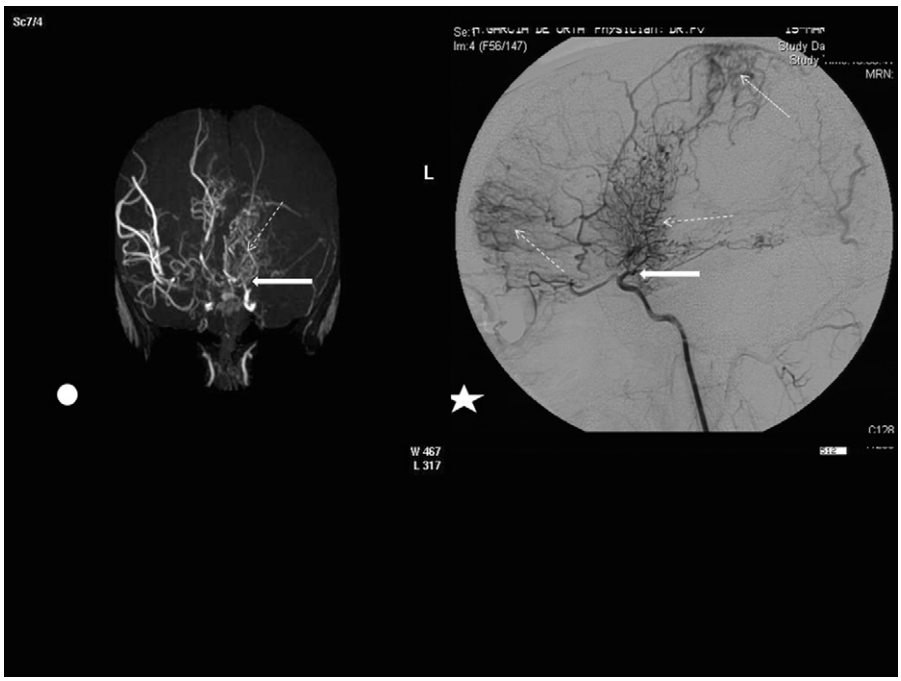

Figure 1. MR angiogram shows bilateral but asymmetric features of moyamoya disease in the younger sibling (circle) and cerebral angiography of the older sibling revealing moyamoya features with extensive collateralization (star). Classic moyamoya "puff of smoke" collateral vessels originating from perforating arteries are evident (dashed arrows), and constriction of the arteries at the base of the brain (arrows) is seen. Abbreviation: MR = Magnetic resonance.

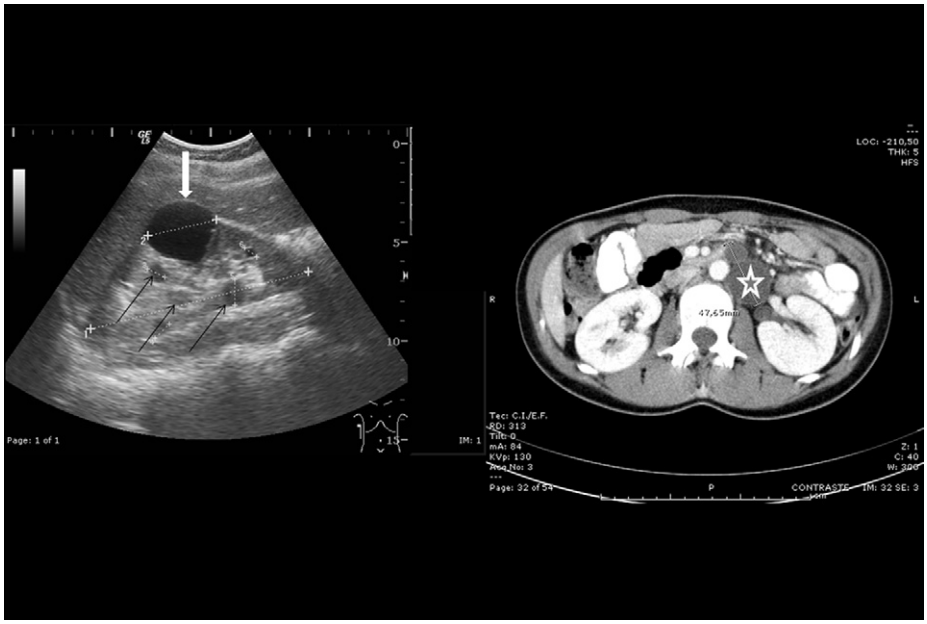

Figure 2. Renal ultrasonoound scan of the younger sibling shows multiple renal cysts (black arrows for the small cysts and white arrow for the biggest cyst), and abdominal CT scan of the older sibling revealing intestinal duplication cyst (star). Abbreviation: CT = Computed tomography.

should probably include not only siblings but also progenitors. The ideal timing for screening is yet to be determined. The youngest diagnosed patient was 2 months old, leading the authors to consider that the disease could have started in uterus [11].

This is the second report of polycystic kidney disease occurring in association with moyamoya [12], and the first to document intestinal malformation in a patient with moyamoya. The co-occurrence of these disparate malformations within a family could be a consequence of an

Table 1. Clinical and HLA characterization of the previously reported cases of Caucasian familial moyamoya

Cases	Age and Sex	Presentation	HLA Typing	Author (Year)
Siblings	11 y/F	Hemidistony	**A***02:01, 03:01; **B***13:02, 44:02; **DRB1***07:01, *13:01;**DQA1***01:03, *02:01; **DQB1***02:03, * 06:03	Current report
	27 y/F	Headache	**A***03:01, 23:01; **B***44:02, 44:03; **DRB1***13:01, *13:01;**DQA1***01:03, *01:03; **DQB1***06:03, * 06:03	
Father-to-child	46 y/M	Ischemic Stroke	**A***02, *24; **B***18, * 58; **DRB1***03; **DQB1***02, *03	Kraemer et al., 2012 [10]
	23 y/M	Ischemic Stroke	**A***02, *24; **B*** *35, *58; **DRB1***03; **DQB1** *11, *03	
	24 y/F	Ischemic Stroke	Unavailable	
Mother-to-child	23 y/F	Ischemic Stroke	Unavailable	Papavasiliou et al., 2007 [9]
	11 months/F	Epilepsy/Ischemic Stroke		
Mother-to-child (Three generations)	52 y/F (Grandmother)	Hemorrhagic stroke	Unavailable	Papavasiliou et al., 2007 [9]
	23 y/F (Mother)	Asymptomatic		
	19 y/F (Aunt)	Ischemic Stroke		
	6 y/F (Sister)	Epilepsy		
	5 y/M	Epilepsy/Ischemic Stroke		
Siblings	7 y/M	Epilepsy/TIA/Headache		Zafeiriou et al., 2003 [8]
	4.5 y/M	Epilepsy		
Siblings	7 y/M	Epilepsy/Ischemic Stroke	Unavailable	Shetty-Alva and Alva 2000[7]
	5 y/M	Epilepsy/TIA		
Siblings (twins)	31 y/F	Ischemic Stroke	**A*** *01; **B*** *35, *57; **DRB1** *11:04, *11:07; **DQB1** *03:01, *03:03	Andreone et al., 1999 [6]
	31 y/F	Asymptomatic		
Father-to-child	1.5 y/M	Epilepsy/Stroke	Unavailable	Setzen et al., 1999 [5]
	28 y/M	TIA		

Abbreviations:
F = Female
M = Male
TIA = Transient ischemic attack
y = Years

underlying common genetic background, predisposing or causing structural or physiological abnormalities. There is little knowledge of how genes contribute to moyamoya syndrome, probably because of its multifactorial nature and also because of the heterogeneity of the associated genetic disorders. Mutations in the RNF213 gene, which are now recognized as a risk factor and that are associated with aggressive moyamoya, were not found [13,14]. This is in agreement with the relatively late and benign disease shown here. None of the HLA types linked to moyamoya or described in other Caucasian familial cases were identified. Furthermore, the HLA alleles found in both siblings are common in our country, Portugal, which precludes conclusions on the basis of the HLA type. Our case reinforces the occurrence of familial moyamoya in Caucasians and describes a unique combination of multisystemic malformations that contribute to expansion of the phenotypic variability of moyamoya syndrome.

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