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DOI: 10.1159/000368215**Cerebral Cavernous Malformations and Unilateral Moyamoya in a Patient with a New Mutation in the *KRIT-1/CCM1* Gene**Marta Melis^a, Milena Cau^b, Simona Corraïne^c, Simona Secci^d,
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Radiology, and ^dRadiology Unit, Azienda Ospedaliera G. Brotzu,
Cagliari, Sardinia, Italy**Introduction**

Cerebral cavernous malformations (CCMs) are vascular anomalies with dilated, thin-walled capillaries. The disease can occur in sporadic or autosomal dominant-inherited forms (familial forms), with incomplete penetrance and multiple lesions [1].

Moyamoya disease (MMD) is a dynamic cerebrovascular disease [2] where the outgrowth of small collateral vessels produces the radiological image of a hazy ‘puff of smoke’, giving its name to the disease. According to the diagnostic criteria, MMD is characterized by stenosis or occlusion of the terminal portion of the Internal Carotid Artery (ICA) and/or the proximal portions of the anterior or the middle cerebral arteries (ACAs, MCAs), with irregular vascular networks near the stenosis. The disease is defined ‘probable’ or ‘unilateral’ MMD when findings are unilateral and ‘definite’ MMD, when findings are bilateral [3]. Unilateral MMD occurs in almost 10–15% of all MMD: in children it usually extends bilaterally within 1–2 years, otherwise the disease tends to remain unilateral in adults [4]. We report here a case of cerebral cavernous angiomas associated with unilateral MMD in a patient with a first-ever described mutation in the *KRIT1/CCM1* gene.

Case Report

A 41-year-old Sardinian woman was admitted to our unit with left arm paraesthesia. The brain MRI showed an acute blood collection in the right pons and multiple cavernous malformations (fig. 1a). After 2 months, the patient underwent surgical removal of the right pons malformation with histological confirmation of CCM diagnosis. Afterwards, MRI-angiography showed stenosis of the right ICA and right MCA with collateral vessels at the level of perforant arteries (fig. 1b). Digital subtraction angiography confirmed these findings, suggesting the diagnosis of unilateral MMD.

Direct DNA sequencing analysis of the *KRIT1/CCM1* gene was performed with an automated sequencer (model ABI3130XL Life

Fig. 1. **a** GE MRI showing multiple CCM in the right pons, in the right frontal sub-cortex, in the inferior frontal gyrus and in the right semioval center. **b** MRI-angiography and digital subtraction angiography showing narrowing of distal right ICA and occlusion of the proximal part of MCA right segment for a 10 mm tract and collateral branches, probably perforant hypertrophic branches, from carotid apix. **c** GE MRI of one brother of the patient, showing two CCM, the widest in the left parieto-occipital lobe of 18 mm. R = Right side; L = left side.

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Fig. 2. Patient family-tree. All family members were tested, except for a sister who lives abroad. Genetic screening showed the R140X mutation in all family members tested except for the mother. Brain MRI and brain MRI A evaluation were performed in all family members with the R140X mutation except for one brother who refused any radiological evaluation. Radiological evaluation showed multiple CCMs in one brother and in one sister. MRI = Magnetic resonance imaging; MRI A = magnetic resonance imaging angiography; neg = negative.

Technologies) using a specific subset of 19 primer pairs. This led to the identification of the new p.R140X (c.418C>T) mutation.

No neurological diseases occurred in the family, but genetic screening showed the mutation in all family members tested, except for the mother, and brain MRI evaluation led to the finding of multiple CCMs in one brother and in one sister (fig. 1c, 2). Both clinical and neuroradiological evaluations after two years follow up were stable.

Discussion

Three chromosomal loci have been identified: 7q21.2 (CCM1), 7p15-p13 (CCM2), and 3q25.2-q27 (CCM3) [1] and almost 100 mutations have been so far identified in *KRIT1*/CCM1 gene. These mutations are highly stereotyped as premature stop codons. Surprisingly, our patient did not show the Sardinian C329X typical mutation [5], though we identified a first-ever described mutation: p.R140X (c.418C>T).

To our knowledge the contemporary presence of CCMs and MMD was described only in three full-text papers [6–8]. However, our case is the first reported case of *KRIT1* gene mutation in a patient with CCM and MMD. The detection of a congenital malformation supports the hypothesis of a common defect in the cerebral vascular development. This is also suggested by the neuroradiological features of congenital hypoplasia found in our patient: right maxillary sinus and right carotid bone canal hypoplasia.

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However, from just this single case, we cannot establish whether the contemporary presence of a familiar form of CCM and MMD is the consequence of the p.R140X mutation identified. Meanwhile, we cannot exclude that the same p.R140X mutation could have been found in the cases already described, since none of the authors reported a genetic analysis or described familiarity for CCM [6–8]. Therefore, further specific studies are needed.

In our case, the study of the CCM gene led to the identification of CCMs in one brother and one sister of the patient, who were totally asymptomatic. In conclusion, our case shows that the detailed analysis and genotyping of subjects affected by CCM is a worthy effort to identify new mutations in CCM genes and new useful information for the diagnosis, prognosis, and for the correct follow-up of our patients.

Disclosure

The authors report no conflicts of interest.

Authors Contributions

Dr Marta Melis: study concept, acquisition of data, manuscript preparation; Dr Maurizio Melis: study concept and design, acquisition of data, critical revision of the manuscript; Dr. Simona Secci: MRI analysis and interpretation; Dr. Simona Corraire: digital subtraction angiography and interpretation; Milena Cau and Maria Addis: genetic analysis, molecular and genetic counseling, revising the manuscript including the genetic writing for content.