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CASE REPORT

CCM1/KRIT1 mutation in monozygotic twins of a polyzygotic triplet birth: genetic, clinical and radiological characteristics

Karl Hartmann[1,2] · Klaus-Peter Stein[2] · Belal Neyazi[2] · Ute Felbor[3] · Sven Hethey[4] · I. Erol Sandalcioglu[2]

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Abstract

Cerebral cavernous malformations are focal vascular lesions of the brain, occurring sporadically or as an autosomal dominant familial form. The genetic background influences not only the clinical course but also patients' consultation and the indication to treat. We here present the rare case of monozygotic male twins of a polyzygotic triplet birth, carrying a *CCM1* mutation, inherited from the mother. Both twins showed an identical site and size of a large frontobasal lesion. The genetic segregation and the clinical course in affected family members are presented and discussed.

Keywords *CCM1/KRIT1* mutation · Monozygotic twins · Polyzygotic triplet birth

Background

Cerebral cavernous malformations (CCMs) are cerebral vascular lesions with a prevalence of approximately 1:200 [1]. Collections of enlarged vascular caverns filled with blood in all stages of thrombosis histologically characterize these lesions [2]. Symptoms largely vary from epilepsy, intracerebral haemorrhage, chronic headache and focal neurological deficits [3, 4].

In approximately 6–7% of all cases, a familial form of CCM has been assumed. Based on large genetic databases, the prevalence of symptomatic hereditary CCM has been estimated to be 1:5400–1:6200 stating that familial CCM is a rare disease [1]. These patients often harbour multiple lesions and an increasing number of lesions with age [1]. Germline mutations in three *CCM* genes (*CCM1/KRIT1*, *CCM2/MGC4607*, *CCM3/PDCD10*) have been identified so far [5–9]. The predominantly affected gene *CCM1* encodes for the protein *krev interaction trapped1* (*KRIT1*), which influences vessel wall morphogenesis and the integrity of endothelial junctions [10, 11].

Considering its heterogeneous phenotype, a genetic two-hit mechanism for familiar CCM has been suggested postulating a secondary somatic mutation following the inherited germline mutation [12, 13]. Numerous publications focus on clinical and genetic features within CCM-affected families, but only one case of monozygotic twins inheriting a *CCM1/KRIT1* mutation is reported so far [14–17].

We here present another rare case of monozygotic male twins of a polyzygotic triplet birth, carrying a heterozygous two base pair deletion within the *CCM1* gene, c.1362_1363delTC;p.(Gln455Argfs*24). Its genetic segregation, clinical and radiological peculiarities are demonstrated and discussed.

Case history

At the age of 9, the male index patient A presented a *status epilepticus*. Anticonvulsive medication with oxcarbazepine was initiated and the patient was scheduled for further radiological evaluation. Cranial MRI revealed multiple disseminated small CCMs and a large Zabramski type II lesion of the left frontal lobe [18]. Surgical removal was carried out, leading to a complete relief of seizures. Constant

✉ Karl Hartmann
karl.hartmann@krh.eu

[1] Department of Neurosurgery, KRH Hospital Nordstadt, Haltenhoffstrasse 41, 30167 Hannover, Germany

[2] Department of Neurosurgery, Otto-von-Guericke-Universität Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany

[3] Department of Human Genetics, University Medicine Greifswald, and Interfaculty Institute of Genetics and Functional Genomics, University of Greifswald, Fleischmannstrasse 43, 17475 Greifswald, Germany

[4] Department of Neuropediatrics, Kinderkrankenhaus auf der Bult, Janusz-Korczak-Allee 12, 30173 Hannover, Germany

MRI controls demonstrate a stable course of the remaining CCMs.

Influenced by the medical history of the family, the monozygotic brother B underwent cranial MRI screening. Likewise, multiple disseminated CCMs and a large type II lesion of nearly identical location and size were depicted (Fig. 1). Clinically, he only presented diffuse neuropsychological alterations. Together with the parents' declared intention to treat and after discussion in our neuropaediatric board, indication for surgical removal was stated. Surgical removal of the large left frontal lesion was carried out and further follow-up was uneventful.

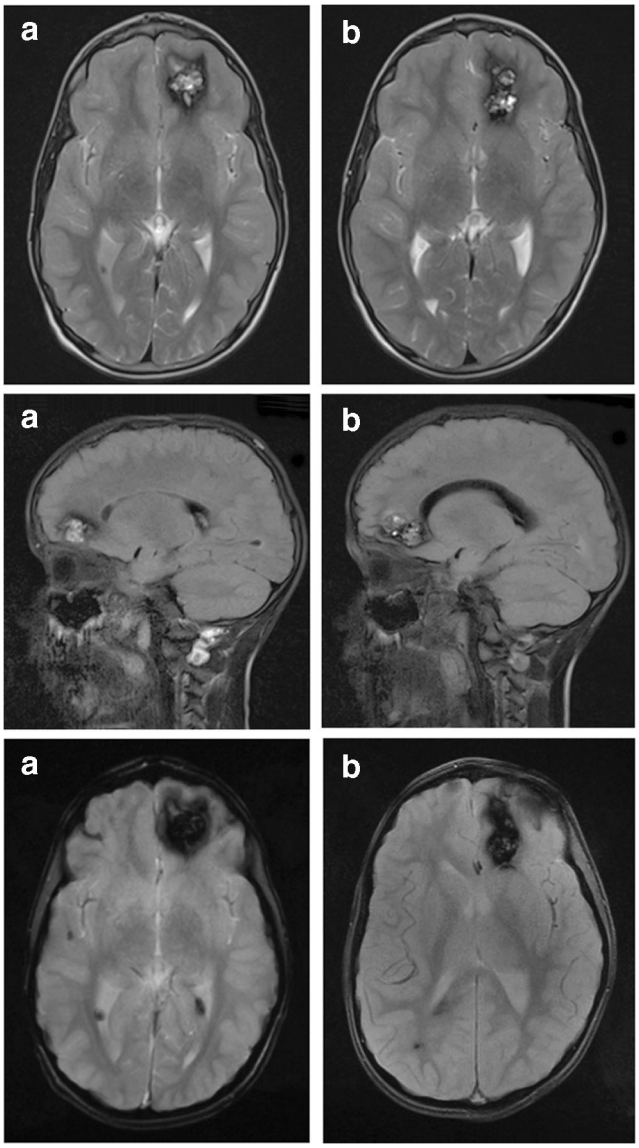

Fig. 1 Axial T2-weighted (above), sagittal FLAIR-weighted (in the middle) and axial T2*-weighted (below) sectional MRI imaging of monozygotic triplet brothers depicting a symptomatic left frontobasal CCM with identical location and similar extension. On the left are MRI scans of the index patient A and on the right his brother B

The two monozygotic brothers notably suffered from a twin-to-twin transfusion syndrome during pregnancy, which was successfully treated by fetoscopic laser occlusion. Neither the third and dizygotic triplet nor the older sister presented neurological symptoms or pathological findings on cranial MRI.

The mother of the two affected triplets experienced focal seizures since the age of 7. First MRI at the age of 17 revealed multiple cranial and spinal CCMs. Among others, characteristic lesions could be found in the left temporal lobe, the tectum mesencephali and the thoracic spinal cord. Despite anticonvulsive medication, seizures were persistent and thoracic myelopathy was progressive. Subsequent surgical removal of the symptomatic left temporal and intramedullary lesions was carried out.

Molecular genetic analysis of the family detected a previously described heterozygous two base pair deletion c.1362_1363delTC;p.(Gln455Argfs*24) within the *CCM1* gene [19]. Segregation of the familial pathogenic variant with clinical symptoms is shown in the pedigree in Fig. 2.

Discussion

To the best of our knowledge, only one report described clinical and radiological characteristics in monozygotic twins harbouring a *CCM1/KRIT1* mutation so far [17]. These twins primarily presented with seizures at the age of 19 years. Cranial MRI revealed different locations of their lesions resulting in divergent disease manifestations.

Our family showed the following characteristics:

1. The mother and the index (A) presented with early onset of seizures before age 10. This is in line with previous findings demonstrating that 25% of *CCM1* mutation carriers become symptomatic before age 15 [20].

2. Both siblings harboured a large lesion of identical location and similar size but only one developed a distinct phenotype. Considering the aetiological two-hit theory in familial CCMs with a stochastic distribution of lesions due to the second somatic mutation, identical locations are highly unlikely.

3. A twin-to-twin transfusion syndrome treated with fetoscopic laser occlusion was present. The fetal periventricular germinal matrix shows a high fragility in general. Alterations of cerebral perfusion, caused by placental anastomoses and a concomitant unequal blood supply are postulated reasons for an increased risk of cerebral periventricular haemorrhages in monochorial twin pregnancies treated with fetoscopic laser occlusion [21]. The fetal periventricular germinal matrix shows in general a high fragility

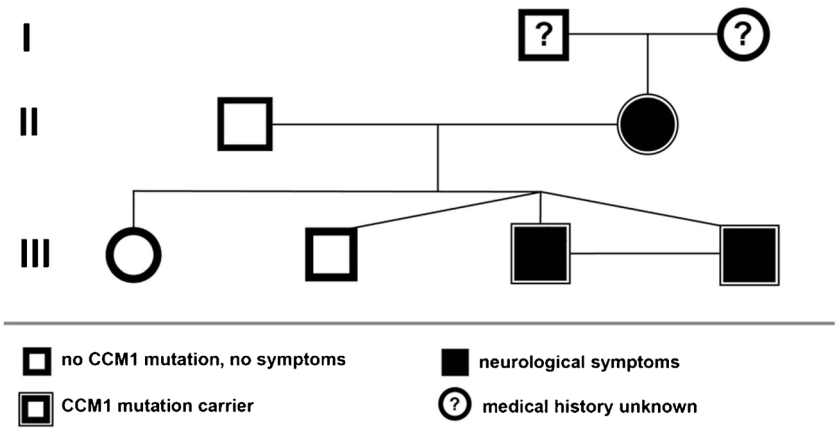

Fig. 2 Family pedigree demonstrating segregation of the familial *CCM1* mutation with the occurrence of cavernous lesions

and states preferential site of birth-associated intraventricular haemorrhages.

This case report raises questions towards possible cofactors of CCM formation. Further studies are necessary to determine individual genetic or haemodynamic aspects that might influence lesion formation in CCM.

Compliance with ethical standards All family members gave written informed consent.

Conflict of interest The authors declare that they have no competing interests

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