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Familial multiple cavernomatosis: description of a new mutation ☆

Cavernomatosis múltiple familiar: descripción de una nueva mutación

Dear Editor:

Cavernous angiomas account for as many as 13% of all vascular brain lesions and consist of abnormally large capillary cavities surrounded by a thin layer of endothelial tissue that are unaffected by the cerebral parenchyma.[1-4] With a prevalence rate of 0.1-0.5%, they may be solitary or multiple and sporadic or familial. Familial cases (FMC) represent up to 50%of all cases and generally present with multiple lesions in 84% of the subjects, versus 15-25% of times when they present sporadic lesions.[5,6]

FMC is an autosomal-dominant genetic disorder of variable expression and incomplete clinical and radiological penetrance[7]. Genetic testing is positive in 70% of cases, detecting mutations (inherited or de novo) that lead to loss of function in the protein that is coded in 3 different loci: CCM1/KRIT1 (7q11-q22) in 40%of cases, CCM2/MGC4607 or malcavernin (7p13-15) in 20%, and CCM3/PDCD10 (3q25.2-q27) in 10-20%. More than 90 different mutations have been identified in CCM1, 8 in CCM2, and 7 in CCM3. Genetic screening sensitivity increases in patients with more relatives who are affected (96%) versus sporadic cases with multiple lesions (57%).[7,8]

The two-hit mechanism hypothesis has gained relevance in recent studies into the pathogenesis of this condition: the loss or mutation of both gene alleles would be needed for a person to develop the disease.[9-11]

Clinical manifestations, which begin between 20 and 40 years of age, include epileptic seizures, headache, and neurological impairment due to brain haemorrhage or compression. Most cavernomas are supratentorial, although they can also be found in the brainstem and spinal cord.[12] Magnetic resonance (MR), particularly the gradient echo sequence, is the most sensitive test for detection. The characteristic image is of "popcorn" morphology, with a well-delimited reticulated core, heterogeneous for blood in the various stages and a hypodense, haemosiderin rim.[7]

We report 8 patients (5 males and 3 females), all members of the same family, with multiple cerebral cavernomas on MR scan. Genetic testing was performed and all were positive for a mutation in the CCM1 gene not previously reported in the literature. Four out of 6 siblings are affected, as are 4 of their offspring. The remaining first- and second-degree relatives (fig. 1) were healthy as of the time of this study. Genetic testing was performed in 2 of the asymptomatic cases but was negative for the mutation found in this family; in addition, an MRI of the brain was normal.

The clinical debut comprised seizures in 5 patients (3 males and 2 females), focal neurological impairment in 2 (males) consisting in paraesthesia and lower-limb monoparesis in one case and ataxia with nystagmus and palsy of the left VI cranial nerve in another one, and headache in one case (female). The MR revealed typical multiple cerebral cavernomas in brain hemispheres, brainstem, and, in one case, spinal cavernomas (fig. 2). On serial MR, new lesions were seen, as well as the evolution of the previous lesions. Five patients presented acute bleeding on the MR (3 females and 2 males) in the right pons, 3 exhibited left frontal cavernomas, and one on the root of the cauda equina.

The genomic analysis of the leukocyte DNA performed using the single-strand conformational polymorphism (SSCP)/heteroduplex technique, sequencing of fragments with abnormal mobility, mutational tracing of the exons and neighbouring intronic fragments 1 to 12 of the CCM1 gene, corresponding to exons 8 to 19,[13] revealed a single mutation (c. 1,585. of C) in exon 8 of that gene, namely a cytosine base deletion in position 1,585 (NM_194456.1 was the reference of the coding DNA or cDNA sequence for this nucleotidic numeration according to the Human Gene Mutation Database). This frameshift mutation alters the reading frame leading to a premature STOP codon and, consequently, a truncated protein. This type of mutation represents most of the mutations reported in this gene.

The CCM1 gene, responsible for most cases of FMC in Hispanic families, contains 19 exons that code for the 736-aminoacid Krit1 (Krev Interaction Trapped 1) protein. Almost all the mutations detected in patients with FMC have been reported between exons 8 and 19 of the gene.[8,13]

We present a mutation in the CCM1 gene previously unreported in other families with FMC and apparently related to the disease, thus supporting its aetiopathogenic nature.

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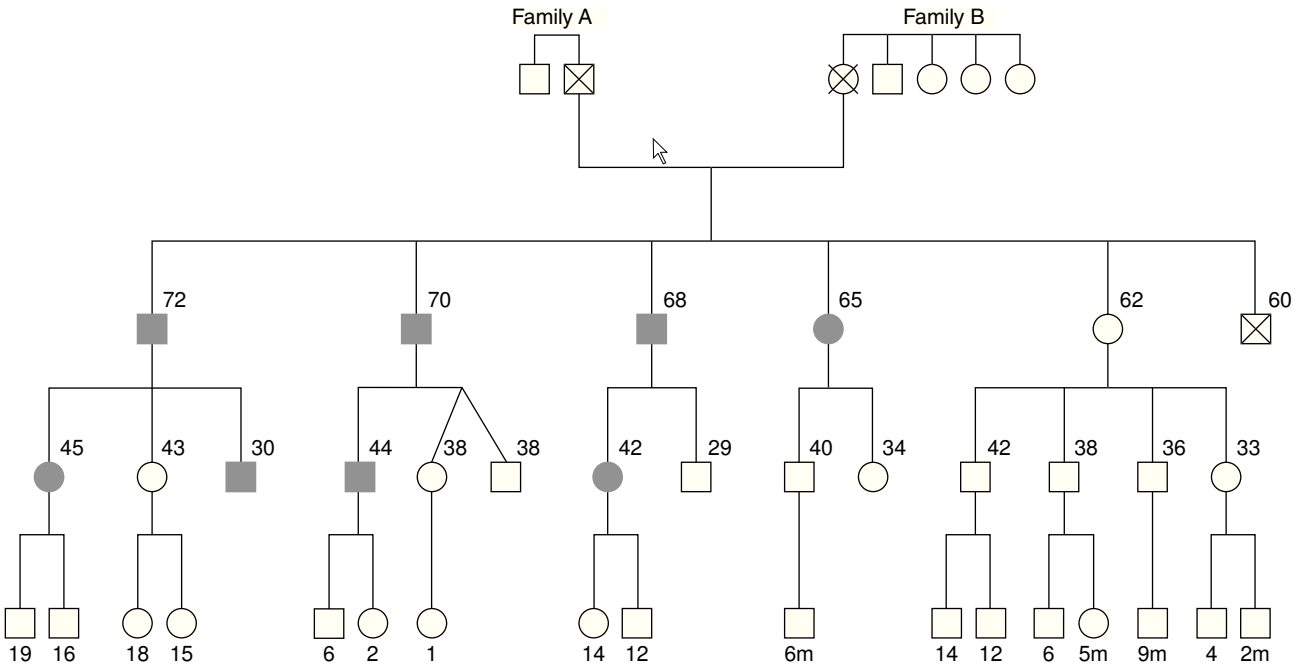

Figure 1 Pedigree of the family indicating affected members (in black) and ages.

Genetic testing and radiological monitoring of possible asymptomatic carriers in families with FMC or multiple sporadic cavernomatosis is fundamental for the study of new genetic alterations, clinical monitoring, and early treatment of the lesions if necessary.

Figure 2 Cerebral MR (gradient echo sequence) revealing multiple, typical cavernomas in one of the members of the family affected.

The recent discovery of the common pathways of action of the CCM genes and future prospective studies carried out with genetic studies in large patient series, as well as studies conducted to inactivate said genes specifically in the CNS of mouse embryos, seek to clarify fully the pathogenic mechanisms of these malformations and to discover other possible mutations in these three or in a possible fourth related gene.[14]

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Facial variant of Guillain-Barré Syndrome in a patient, days after being vaccinated for influenza A

Variante facial del síndrome de Guillain-Barré en un paciente, días después de vacunarse de la gripe A

Dear Editor:

Simultaneous bilateral facial paralysis is an uncommon neurological manifestation; a possible case is Guillain-Barré syndrome (GBS).. Although the facial nerve is often involved in this syndrome, it is rare for its only manifestation to be bilateral facial palsy. There are regional variants of GBS, such as Miller-Fisher syndrome, lumbar plexopathy, pharyngeal-cervical-brachial weakness, and facial diplegia.[2]

In 1976, the national influenza immunization programme in the United States was suspended after an increase in the number of cases of GBS was reported. A subsequent epidemiological study revealed a 4.0 and 7.6 relative risk at 6 and 8 weeks post-vaccination, respectively, with a risk of less than one per 100,000 vaccinations.[3] Some later works failed to reveal this increased risk.[4] Insofar as the data on the H1N1 influenza vaccine are concerned, the adverse effects reported in USA as of December 30th, 2009, were as follows: 37 GBS (with 99 million doses distributed, although the number of doses actually administered is not known).[5]

We report a case of a patient who suffered the facial variant of GBS days after having been vaccinated against influenza A.

A sixty-year-old male with a history of high blood pressure, renal colic, acute myocardial infarction in 2005 and placement of a cardiac stent in 2007. He consulted in December for moderate lumbar pain. The pain was increasing in intensity and radiated toward his waist. Five days later, he presented difficulty speaking, eating and moving his lips. These symptoms grew worse over the course of three days. The neurological examination revealed moderate bilateral peripheral facial palsy. Examination showed the remaining cranial nerves to be normal. Muscle balance and sensitivity were normal in the upper and lower limbs; osteotendinous reflexes were abolished. His gait was normal.

The following testing procedures were performed: CT and cranial NMR, chest X-ray, NMR of the lumbar spine and ECG, all of which were normal. The most striking results of the general work-up: GGT 105 U/l; 14,400 leukocytes; with normal VSG and PCR. The serological tests for mycoplasm, HIV, syphilis, Epstein Barr, CMV, *Borrelia* and *Brucella* were negative. A spinal tap was performed in which the cyto-biochemical analysis detected elevated proteins (137 mg/dL), with 4 cells; the bacteriological culture and PCR (herpes simplex, herpes zoster, enterovirus, CMV) and CSF were negative. A neurophysiological study was also performed which revealed very little alteration (responses in the blinking reflex, with stimulation of both supraorbital nerves, low amplitude desynchronization, with normal direct responses in both facial nerves).

When the patient was re-interviewed, he commented that he had been vaccinated for influenza A two weeks prior to the onset of symptoms. After receiving the vaccine, he presented intense, flu-like symptoms for 3 days (his lumbalgia and facial weakness began 14 and 18 days after having been vaccinated, respectively). He began to improve one week after maximum deficit, without treatment. He was asymptomatic one month later and the neurological examination was strictly normal.

Facial diplegia accounts for 0.3-2% of all facial paralyses and is defined as paralysis affecting both sides of the face in a period of time of no more than 4 weeks. The most common aetiologies of this bilateral involvement are: bilateral idiopathic Bell's palsy (23%), GBS (10%), multiple cranial neuropathies, multiple sclerosis, Parkinson's disease, meningeal and brainstem tumours (21%), infections (*Borrelia*, syphilis, HIV, herpes virus, mononucleosis, etc.), congenital causes (Moebius syndrome, myopathies),