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LETTERS TO THE EDITOR

Spontaneous intradural spinal haematoma associated with a cerebral subarachnoid haemorrhage

Hematoma espinal intradural espontáneo asociado a hemorragia subaracnoidea cerebral: descripción de un caso☆

Dear Editor:

Spinal haematoma is an uncommon entity. Depending on its location, it can be classified as epidural (the most common), intradural, subarachnoid, or intramedullary.[1,2] Intradural locations account for 4%of all spinal bleeding.[3] On occasion, the simultaneous spontaneous association of spinal and intracranial bleeding has been reported in the same patient, with a total of 11 cases reported to date (Pubmed search up to 2010).[3-13]

We present a female patient in whom a large spinal intradural haematoma and a diffuse cerebral subarachnoid haemorrhage appeared simultaneously without any apparent traumatic factors. We reviewed the risk factors that foster spontaneousspinal bleedingand propose apathophysiological hypothesis that could account for its intracranial extension.

Our patient is a 74-year old female with a history of cardiac valve disease with biological prostheses in the mitral and aortic positions, high blood pressure that is well-controlled with enalapril and propanolol and paroxysmal atrial fibrillation being treated with acenocoumarol.

The patient came to the Emergency Department at our centre due to the acute appearance of neck pain and weakness in the lower limbs without any prior trauma. At the time of admission, the patient was fever-free and presented normal blood pressure; she was conscious and oriented, although her thought processes were slightly slowed. The neurological examination revealed signs of meningeal irritation and complete paralysis of both legs with hypotonicity and abolished patellar and Achilles' reflexes, as well as bilateral extensor plantar skin reflex. Painful tactile anaesthesia at the low dorsal level.

Figure 1 The magnetic resonance sequence of the dorsal spine with extensive intradural intramedullary bleeding.

Fewer than 12 hours after symptom onset, a nuclear magnetic resonance (NMR) of the spine was performed and revealed extensive intradural bleeding, between the C2 and D10 spaces, displacing the spine toward the front and surrounding 75%of its circumference (fig. 1). Upon discovery of blood in the occipital horns of the lateral ventricles through the upper slices of the study, a cranial computerized tomography (CT) was performed and revealed a predominantly posterior, bilateral, subarachnoid

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Figure 2 Cranial CT with bilateral predominantly posterior ASH.

haemorrhage, with bleeding in the lateral ventricles with blood-fluid levels (fig. 2). In the analytic study no alterations are apparent except for an INR of 4.45 at the time of admission. After reversing the anticoagulation with vitamin K and fresh frozen plasma the risk/benefit ratio of a possible surgical intervention was evaluated, opting for conservative treatment with steroids.

In the week following admission, no improvement was seen in the patient's neurological condition; she expired as the result of an antibiotic-resistant respiratory tract infection.

Spinal haematomas have been reported in association with trauma, anticoagulation, vascular malformations, spinal tap, or different types of tumours.[1] With respect to anticoagulation, most authors suggest that, on its own, it would not suffice to cause spinal haemorrhage, and a *locus minoris resistentiae* at which bleeding begins, or other factors such as old age, atherosclerosis, or high blood pressure would be needed.[1] We believe that, in addition to an overdose of acenocoumarol, the main risk factor (INR: 4.45) in our opinion, our patient was also elderly and hypertensive.

The simultaneous appearance of spinal haematomas and intracranial haemorrhages has only rarely been reported.[3-13] Clinically, in addition to the symptoms of spinal involvement, this association can give rise to other symptoms such as meningeal irritation, headache, vomiting, papillary oedema, decreased level of consciousness or seizures, on occasion without associated medullary compression syndrome.[1]

With respect to the pathophysiology of spinal haematomas and focusing on intradural locations as in the case we report here, the initial cause is probably rupture of vessels in the subarachnoid space, spilling the blood into the cerebrospinal fluid initially, moving into the intradural space.[14] In our patient, part of this blood may have migrated cranially, which would have been favoured by the large amount of bleeding and the fact that the patient was lying down during the initial hours of symptoms. On the other hand, the overdose of acenocoumarol may have favoured the appearance of a simultaneous intracranial haemorrhage.

In conclusion, spinal haematomas may become complicated with haematomas that spread intracranially, mainly large haematomas or related with anticoagulant treatment. We must pay attention to this possibility that might worsen both the vital and functional prognosis of these patients.

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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.

☆ This paper was presented in poster format at the 26th Meeting of the Valencian Society of Neurology (El Albir, 2009).