LETTER TO THE EDITOR

Diagnostic confusion of demyelinating lesions and incidental diagnosis of a new pathogenic mutation of the FLNA gene

Confusión diagnóstica de lesiones desmielinizantes y diagnóstico incidental de una nueva mutación patogénica del gen FLNA

Dear Editor:

The increased availability and technical quality of magnetic resonance imaging (MRI) has made it possible to achieve an earlier and more precise diagnosis of demyelinating lesions, such as those seen in multiple sclerosis (MS). However, it has also broadened the range of findings that may lead to a misdiagnosis of MS and, consequently, to unnecessary treatment. A multicentre study conducted in the United States gathered patients misdiagnosed with MS and analysed the possible causes.1 With the exception of neuromyelitis optica spectrum disorders, almost all definitive diagnoses (conversion disorders, migraine, fibromyalgia, etc) lacked a specific biomarker, as is also the case with MS. Up to 24% of patients misdiagnosed with MS were diagnosed by a neurologist specialising in the disease, and up to 70% received disease-modifying treatments (occasionally with significant iatrogenic effects) and the incorrect diagnosis was maintained for years. One of the most significant factors in misdiagnosis was the misinterpretation of MRI findings, which may be explained by several reasons.2 Therefore, the new 2017 McDonald criteria3 highlight the importance of clinical symptoms, describing red flags and situations in which criteria should be applied with caution (patients who are asymptomatic or present atypical symptoms), and recommend expanding the analytical and radiological workup in these cases.4

We report the case of a 19-year-old woman with migraine and no other neurological symptoms, who was referred to our MS unit due to the detection of subcortical and periventricular white matter lesions potentially suggestive of MS in brain MRI studies performed to diagnose her migraines. The patient had history of Caroli disease (congenital ectasia of the intrahepatic bile ducts) and Laubry-Pezzi syndrome (congenital heart malformation characterised by high interventricular communication and secondary aortic valve insufficiency). Results of the neurological examination were strictly normal, with no evidence of previous episodes suggesting MS relapses. CSF analysis revealed normal cytochemical and immunological results. Given the diagnostic uncertainty, the radiological images were reassessed in detail (Fig. 1). The subcortical lesions were non-specific and were considered an incidental finding in a patient with history of migraine.5 The periventricular lesions presented lower signal intensity on T2-weighted sequences (isointense with regard to the cerebral cortex) and presented a nodular morphology, protruding into the lateral ventricles, with no contrast uptake. They were finally classified as periventricular cortical heterotopia. The patient had no relevant family history. In the second examination, we observed joint hypermobility and hypertelorism.

The patient was referred to the clinical genetics department in view of her multiple congenital malformations. A first array comparative genomic hybridisation study was conducted after the patient received proper genetic counselling, showing no noteworthy alterations; a clinical exome sequencing study identified a probably pathogenic novel variant of the FLNA gene in heterozygosis. This gene encodes the filamin A protein (FLNA), which binds to actin and many other ligands with a range of cellular structural functions.6 The variant consisted of a deletion of 4 nucleotides (c.6981_6984del) in exon 42, which presumably leads to a frame shift with the appearance of a premature stop codon (p.T2328Ffs*9). Pathogenic variants of the FLNA gene have been described in association with cardiac valvular dystrophy,7 nodular periventricular heterotopia,8 and otopalatodigital spectrum disorders with characteristics of Ehlers-Danlos syndrome (skin hyperlaxity and joint hypermobility).9,10 As the patient presented these symptoms, this novel variant was classified as probably pathogenic. FLNA presents an X-linked inheritance pattern, and we are awaiting a genetic study of the patient’s mother. The patient received genetic counselling after the test was performed, including preconception counselling.

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Figure 1   A) FLAIR sequence showing subcortical hyperintensities, some of them isointense with the cerebral cortex; these findings were also observed on the proton density–weighted sequence (B). C) T1-weighted sequence showing periventricular lesions corresponding with isointense nodular images in the cerebral cortex, without gadolinium uptake (D). The periventricular findings are highly indicative of periventricular cortical heterotopia, whereas the hyperintense subcortical lesions on FLAIR sequences present non-specific characteristics and are not conclusive for the diagnosis of multiple sclerosis.

In summary, we present a case in which incidental brain MRI findings were initially attributed to an inflammatory demyelinating aetiology but were ultimately diagnosed as periventricular heterotopia. A genetic study of the patient led to the description of a novel pathogenic mutation of the FLNA gene. This is just one example of the great relevance of correct radiological interpretation of white matter lesions, considering the clinical context of each patient.

References

una aproximación diagnóstica. Radiológi,


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