M. Baraldés-Rovira[a], M. Paul[a], Y. Gallego[a], M.I. Gil[b], C. Vicandi[b], M. Vicente-Pascual[a,c,*]

[a] *Department of Neurology, Hospital Universitari Arnau de Vilanova, Lleida, Spain*
[b] *Institut de diagnòstic per la imatge, Hospital Universitari Arnau de Vilanova, Lleida, Spain*
[c] *Department of Neurology, Hospital de Sant Pau i Santa Tecla, Xarxa Sanitària i Social de Santa Tecla, Tarragona, Spain*

* Corresponding author.
E-mail address: mvpascual.1@gmail.com
(M. Vicente-Pascual).

https://doi.org/10.1016/j.nrl.2021.11.002

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 criteria[3] 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 cytobiochemical 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,

☆ Please cite this article as: Ezcurra Díaz G, Nuñez Marin F, Blanco Guillermo I, Ramo-Tello C. Confusión diagnóstica de lesiones desmielinizantes y diagnóstico incidental de una nueva mutación patogénica del gen *FLNA*. Neurología. 2022;37:818—820.

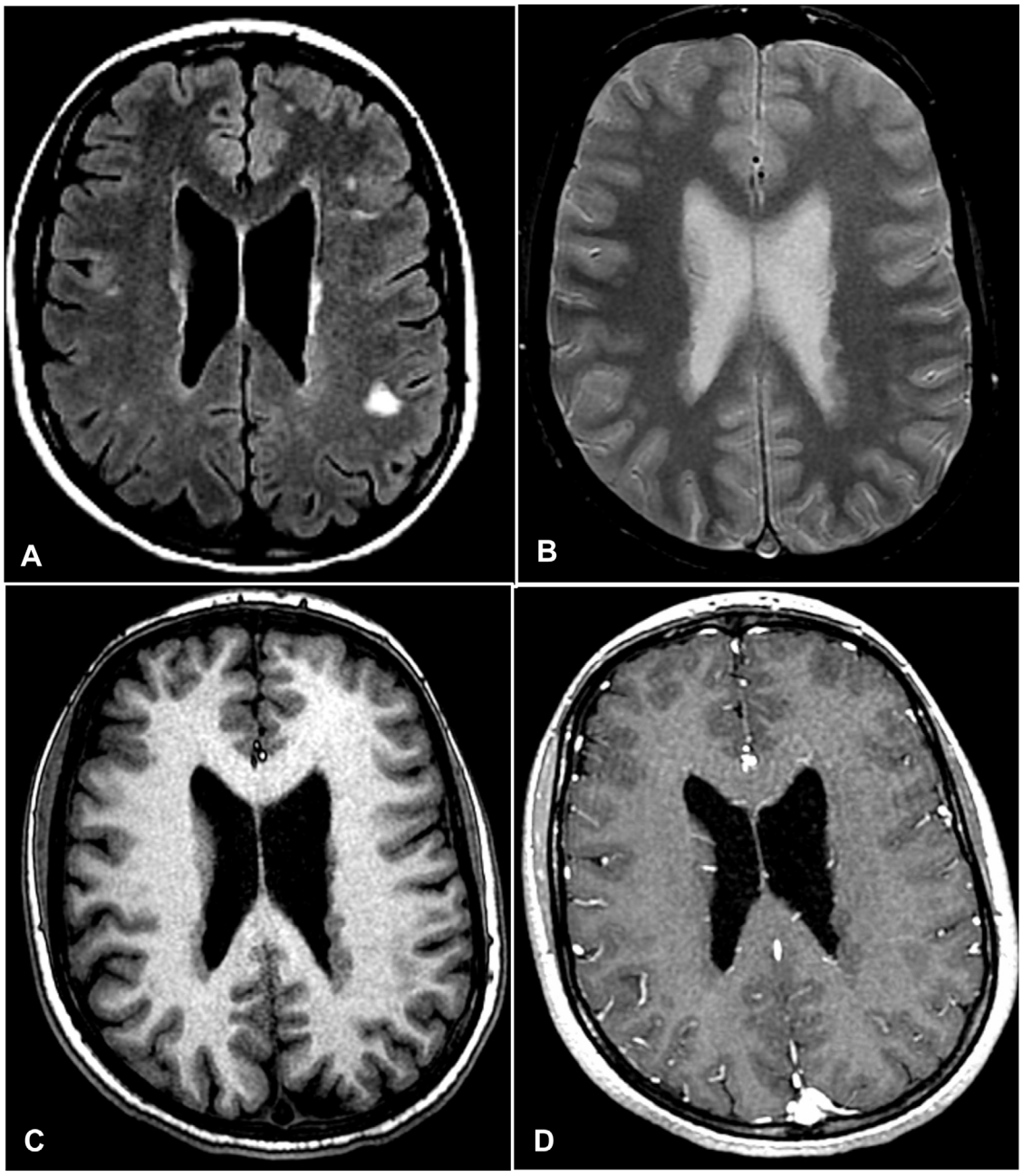

Figure 1 A) FLAIR sequence showing subcortical hyperintensities, some of them isointense with the cerebral cortex; these findings were also observed on the proton density—weighted sequence (B). C) T1-weighted sequence showing periventricular lesions corresponding with isointense nodular images in the 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.

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.

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

1. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, et al. The contemporary spectrum of multiple sclerosis misdiagnosis. Neurology. 2016;87:1393—9, http://dx.doi.org/10.1212/WNL.0000000000003152.

2. Medrano Martorell S, Cuadrado Blázquez M, García Figueredo D, González Ortiz S, Capellades Font J. Imágenes puntiformes hiperintensas en la sustancia blanca: una aproximación diagnóstica. Radiologia. 2012;54:321—35, http://dx.doi.org/10.1016/j.rx.2011.09.015.
3. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162—73, http://dx.doi.org/10.1016/S1474-4422(17)30470-2.
4. Solomon AJ. Diagnosis, differential diagnosis, and misdiagnosis of multiple sclerosis. Continuum (Minneap Minn). 2019;25:611—35, http://dx.doi.org/10.1212/CON.0000000000000728.
5. Honningsvåg LM, Håberg AK, Hagen K, Kvistad KA, Stovner LJ, Linde M. White matter hyperintensities and headache: a population-based imaging study (HUNT MRI). Cephalalgia. 2018;38:1927—39, http://dx.doi.org/10.1177/0333102418764891.
6. Nakamura F, Stossel TP, Hartwig JH. The filamins: organizers of cell structure and function. Cell Adh Migr. 2011;5:160—9, http://dx.doi.org/10.4161/cam.5.2.14401.
7. Kyndt F, Gueffet JP, Probst V, Jaafar P, Legendre A, Le Bouffant F, et al. Mutations in the gene encoding filamin A as a cause for familial cardiac valvular dystrophy. Circulation. 2007;115:40—9, http://dx.doi.org/10.1161/CIRCULATIONAHA.106.622621.
8. Fox JW, Lamperti ED, Ekşioğlu YZ, Hong SE, Feng Y, Graham DA, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human Periventricular heterotopia. Neuron. 1998;21:1315—25, http://dx.doi.org/10.1016/S0896-6273(00)80651-0.
9. Ieda D, Hori I, Nakamura Y, Ohshita H, Negishi Y, Shinohara T, et al. A novel truncating mutation in FLNA causes periventricular nodular heterotopia, Ehlers-Danlos-like collagenopathy and macrothrombocytopenia. Brain Dev. 2018;40:489—92, http://dx.doi.org/10.1016/j.braindev.2018.01.010.
10. Robertson SP, Twigg SRF, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D, et al. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet. 2003;33:487—91, http://dx.doi.org/10.1038/ng1119.

G. Ezcurra Díaz[a,*], F. Nuñez Marin[b], I. Blanco Guillermo[c], C. Ramo-Tello[d]

[a] *Servicio de Neurología, Departamento de Neurociencias, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[b] *IDI (Institut de Diagnòstic per la Imatge), Badalona, Barcelona, Spain*
[c] *Servicio de Genética Clínica, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[d] *Unidad de EM-Neuroinmunología, Departamento de Neurociencias, Hospital Universitario Germans Trias I Pujol, Badalona, Barcelona, Spain*

* Corresponding author.
E-mail address: gaezdi@gmail.com (G. Ezcurra Díaz).

https://doi.org/10.1016/j.nrleng.2021.11.003

'Wine Glass' sign following COVID-19 vaccination in a previously healthy adult

Signo del ''vaso de vino'' tras vacunación del COVID-19 en un adulto previamente sano

Dear Editor,

The 'wine glass' appearance refers to a characteristic sign wherein the coronal T2-weighted imaging (T2-WI) sequences show hyperintensities of the corticospinal tracts bilaterally.[1] This sign has been infrequently observed in motor neuron diseases,[1] and rarely in adult-onset leukodystrophies (especially in Krabbe disease),[2,3] osmotic demyelination syndrome (ODS),[4] celiac disease,[5] Lyme neuroborreliosis,[6] and human T-cell lymphotropic virus type 1 (HTLV-1) infection,[7] among others. The 'wine glass' sign has not been described following receipt of any type of vaccine.

We herein report the first case of 'wine glass' pattern following COVISHIELD vaccination (ChAdOx1 nCoV-19; recombinant, replication-deficient chimpanzee adenovirus vector vaccine).

Case report

A 47-year-old previously healthy man from rural West Bengal (India) was brought to the emergency department with abrupt onset rapidly progressive stiffness of bilateral lower limbs and clumsiness of both upper limbs for the last five days. It was associated with slurring of speech, gait unsteadiness, and behavioral changes in the form of inappropriate laughter, crying spells and inappropriate intermittent anger outbursts. According to his family members, these symptoms started within five days of the second dose of COVID-19 vaccination (COVISHIELD). There was no cognitive impairment, dysphagia, nasal regurgitation, sensory, visual, or sphincter disturbance. He denied trauma or exposure to neurotoxins, radiation, or drug abuse/addiction. His family history was noncontributory. Neurological examination revealed normal mental status with emotional lability and brisk jaw jerk. There was spastic-ataxic dysarthria with a spastic tongue, without atrophy or fasciculations. Motor system examination showed bilateral symmetrical spasticity involving all four limbs. The muscle power was 4/5 in lower limbs and 5/5 in upper limbs. All deep tendon reflexes were exaggerated. Gait was spastic-ataxic and tests for several cerebellar functions were abnormal. There was no sensory or autonomic dysfunction.