Meningeal siderosis in a patient carrying the p.Arg92Gln variant *TNFRSF1A* gene☆

Siderosis meníngea en un paciente portador de la variante p.Arg92Gln del gen *TNFRSF1A*

Dear Editor:

Meningeal siderosis is a rare disease caused by haemosiderin deposition secondary to recurrent bleeding in the subpial space. This deposition causes progressive onset of glial proliferation, fibrosis, and finally neuronal damage on the surface of the brain. Tumour necrosis factor receptor—associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disease characterised by prolonged episodes of fever, migratory myalgia and exanthema, aseptic serositis, and increased levels of acute-phase reactants.

We present the case of a 46-year-old man with moderate intellectual disability (65%) of unknown origin. His father had presented secondary amyloidosis, and was a heterozygous carrier of the *TNFRSF1A* variant p.Arg92Gln. The patient had personal history of seizures since the age of 15 years, currently requiring no treatment, and bilateral presbycusis (64% in the right ear and 37% in the left). He consulted due to progressive instability of 2 years' progression, premature ageing, severe abasia without slowness or difficulties turning, disorientation in time and space, and frequent mood swings. He presented positive Romberg sign, with no dysarthria, swallowing alterations, diplopia, nystagmus, signs of long-tract involvement, or limb dysmetria. All blood and biochemistry analyses, including a total protein test and plasma acute-phase reactant levels, yielded normal or negative results. Analysis of the *TTR* gene detected no pathogenic variants.

Abdominal ultrasound and colonoscopy findings were normal, and gastroscopy identified hiatus hernia. Duodenal and rectal biopsies did not detect amyloid deposits. Brain MRI revealed cerebellar atrophy, particularly affecting the vermis, and diffuse deposition of haemosiderin in the posterior fossa (Fig. 1A) and, to a lesser extent, in the cerebral sulci (Fig. 1B), with marked magnetic susceptibility in gradient-echo sequences. Electromyography findings were normal.

Due to the patient's family history, we conducted a genetic analysis with a panel of genes involved in autoinflammatory diseases, including the *MEFV*, *TNFRSF1A*, *MVK*, *NLRP3*, *NOD2*, *PSTPIP1*, and *CECR1* genes. The library was generated by amplification of all exons and adjacent intronic regions. Sequencing was performed with the NextSeq platform (Illumina), and analysis parameters included minimum coverage of 50×. Sanger sequencing was used to confirm all variants classified as pathogenic, probably pathogenic, or of uncertain significance. The study revealed simple heterozygosis for the p.Arg92Gln variant (Fig. 2).

Meningeal siderosis is a rare disease. Before the development of MRI, its diagnosis was incidental, detected either in surgical procedures or in post mortem examinations. Today, MRI findings are pathognomonic, enabling diagnosis of the condition even at early stages. The most characteristic findings are linear hypointensities along the surfaces of the vermian and cerebellar leptomeninges on T2-weighted sequences, with less extensive involvement of the cerebral leptomeninges.

While the cause is not identified in 50% of patients,[1] in other cases the disease is attributed to brain haemorrhage associated with tumours, amyloid angiopathy,[2,3] and vascular malformations.[4,5] Our patient did not present any of these aetiologies, including leptomeningeal amyloidosis, a rare form of presentation of familial TTR amyloidosis.[6] We detected a variant of the *TNFRSF1A* gene. Mutations in this gene cause TRAPS, an autosomal dominant autoinflammatory disease characterised by prolonged episodes of fever, migratory myalgia and exanthema, aseptic serositis, and increased levels of acute-phase reactants.[7] Occasionally, the disease is complicated by AA amyloidosis in adult patients.[8]

The interest of this case lies in the copresence of meningeal siderosis and *TNFRSF1A* variant p.Arg92Gln. Firstly, the patient did not present recurrent febrile episodes, nor was there evidence of AA amyloid deposition. TRAPS usually presents in childhood, although it may appear in adulthood in some carriers of the p.Arg92Gln variant.[9] Finally, patients with this variant constitute a clinically heterogeneous group, ranging from asymptomatic/presymptomatic individuals to patients who require biological anti-inflammatory treatments.

A previous study demonstrated the presence of microangiopathic changes in the brain of a patient with TRAPS.[10] Despite this, there is no clear evidence on the causes of the relationship between meningeal siderosis and TRAPS. One potential explanation may be disruption of blood-brain barrier (BBB) permeability. TRAPS is characterised by a marked increase in levels of multiple circulating inflammatory cytokines. Interleukin-1β plays such an important role that treatments to block this cytokine currently constitute the most effective approach to treating the syndrome.[11] In the BBB, increased interleukin-1β levels cause an increase in monocyte chemoattractant protein-1, which may alter the tight junctions of the BBB, increasing its permeability[12] and altering the transport of transferrin across the barrier; this would result in ferritin deposition in the brain tissue.

In conclusion, we present the first reported case of a patient with meningeal siderosis and the *TNFRSF1A* variant p.Arg92Gln. Due to the possible association between the 2 entities, we believe it would be beneficial to include this monogenic autoinflammatory disease in the differential diagnosis of meningeal siderosis.

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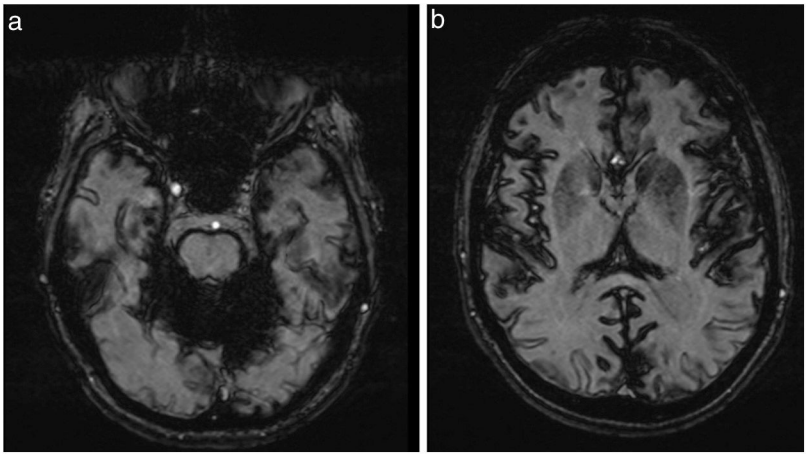

Figure 1 A) Gradient-echo sequences revealed pronounced magnetic susceptibility in the posterior fossa due to diffuse haemosiderin deposition. B) T2-weighted sequences revealed linear hypointensities along the surfaces of the cerebral leptomeninges.

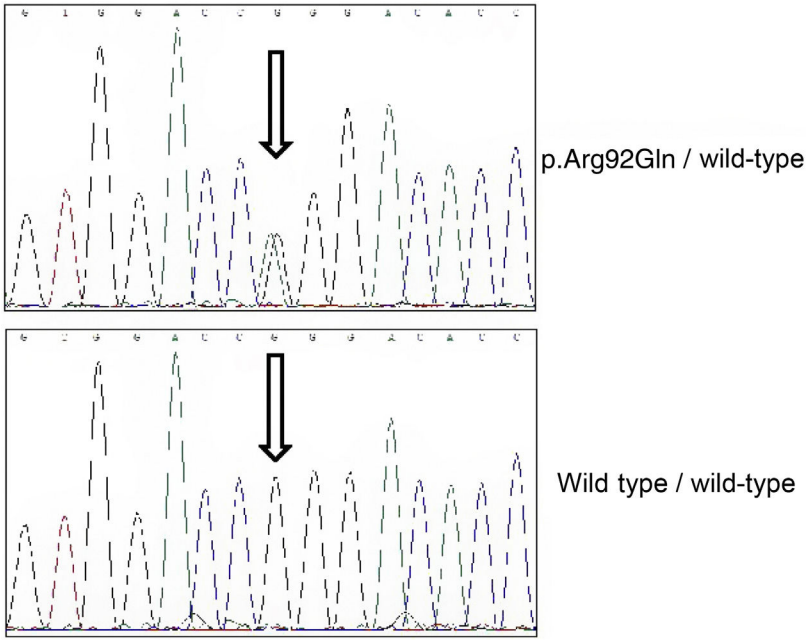

Figure 2 The genetic study of *TNFRSF1A* revealed simple heterozygosis for variant p.Arg92Gln.

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Hemifacial spasm followed by predominantly unilateral upper limb monochorea unmasking type-2 diabetes mellitus

Espasmo hemifacial, seguido de corea predominantemente braquial unilateral, como forma de presentación de una diabetes mellitus tipo 2

Dear Editor,

The conclave of acute onset movement disorders in diabetes mellitus (DM) is ever-evolving.[1] Even, on many occasions, movement disorder itself has been the presenting manifestation of previously undiagnosed DM, especially reported from developing countries like India, where health-related awareness is considered still inadequate.[1,2] Amid several kinds of movement disorders in DM, hemichorea/hemiballism is a well-recognized entity, unlike others such as hemifacial spasm (HFS) and upper limb monochorea, which have been rarely reported.[2—6] Further, a combination of both HFS and predominantly upper limb monochorea is unheard of in diabetic striatopathy.

Authors hereby report a case of a previously healthy elderly man from rural India presenting with recent onset left-sided HFS. This case was evaluated clinico-radiologically and treated accordingly without any improvement for two weeks, following which he came to our clinic having a predominantly left upper limb monochorea. He was finally diagnosed to be a case of diabetic striatopathy and managed successfully. This single case, again, emphasizes upon the fact that blood glucose status should be checked at point-of-care especially in cases of both common and rare types of recent onset movement disorders.

Case report

A 61-year-old male visited the clinic of the department of General Medicine at Burdwan Medical College & Hospital, Burdwan, West Bengal, India, as he had been experiencing increasing involuntary intermittent twitching of the muscles of the left side of the face, including the left upper eyelid, for last one month. Alongside that, he was having sudden onset involuntary semi-purposeful dancing movements (flowing from distal to proximal limb) predominantly affecting his left upper-limb for the last 36 h.

He had consulted several physicians and one neurologist for the last one month before visiting us. The initial phenomenon was diagnosed as left-sided HFS, but etiologic diagnosis remained elusive. On probing, he complained of malaise, increased thirst, and excessive frequency of urination and generalized weakness for last few days. Past medical, surgical and family history was unremarkable, except both his parents were having type-2 DM. His vital signs were all stable. Neurological examination displayed left-sided HFS along with predominantly left upper limb monochorea and subtle truncal chorea (video, see supplementary data associated with this article). His cognitive functions were intact. The patient's oropharyngeal swab test for SARS-CoV-2, by qualitative real-time reverse-transcriptase—polymerase-chain-reaction assay, was negative. Measured capillary blood glucose level was 640 mg/dL. Complete blood cell count, liver, kidney and thyroid function tests were normal. Arterial blood gas analysis, serum electrolytes, C-reactive protein, urine and plasma ketones, electrocardiography, chest-X-ray, abdominal ultrasound, and blood and urine cultures were negative too. Cerebrospinal fluid (CSF) study excluded infectious etiologies. HbA1c was 8.1%. Type-1 DM was excluded as the tests for anti-GAD 65 antibodies, anti-islet cell antibodies, anti-insulin antibodies, and anti-IA2 (protein tyrosine phosphatase) antibodies were negative. On the other hand, serum fasting C-peptide level was 3.80 ng/ml (normal 0.81—3.85). Computed tomography (CT) scan of the brain and temporal bones with intravenous contrast was normal. Brain magnetic resonance imaging (MRI) revealed right striatal hyperintensity on T1-weighted imaging (Fig. 1). Magnetic resonance angiogram of the brain was otherwise normal. Acute symptomatic hyperglycemia associated with predominantly left upper limb monochorea and left-sided HFS with striatal abnormalities on neuroimaging pointed towards a diagnosis of diabetic striatopathy due to non-ketotic hyperglycemia. Continuous intravenous insulin infusion and rapid rehydration with intravenous fluids and were started.

After two days, blood glucose level stabilized. The abnormal movements reduced in frequency and intensity, but persisted with sustained normalization of blood glucose levels. He was discharged after seven days with a basal-bolus regime of insulin and diabetic medical nutrition therapy. The patient was followed-up at regular intervals with achievement of good glycemic control and no evidence of exacerbation of abnormal movements (though subtle infrequent unilateral HFS and mild choreiform movements in the left upper limb were persisting). On follow-up visit after six months, a new brain MRI was performed showing partial resolution of the striatal lesion.

Discussion

Acute metabolic insults, like hyperglycemic, can result in glutamatergic and dopaminergic excitotoxicity and thereby can cause direct neuronal damage, particularly at striatum, a metabolically vulnerable structure.[7,8] Depletion of gamma-amino-butyric acid (GABA) may result from anerobic cerebral metabolism in uncontrolled hyperglycemia.[7,8] Altered GABA metabolism in striatal neurons, cytotoxicity, hyperviscocity, obliterative angiopathy, and hyperglycemia itself might lead to gemistocyte accumulation