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Ethylmalonic encephalopathy: phenotype-genotype description and review of its management☆

Encefalopatía etilmalónica: descripción fenotipo-genotipo y revisión de su manejo

Dear Editor:

Ethylmalonic encephalopathy (EE) is an extremely rare disease caused by a recessive defect of the *ETHE1* gene; it presents in infancy and follows a progressive course characterised by psychomotor retardation, hypotonia, and generalised microvascular damage. Delayed growth with diarrhoea and dysphagia is a common symptom. Neurological impairment is accelerated in the context of intercurrent infectious diseases, and patients typically do not live beyond the first decade of life.[1,2]

Diagnosis is based on clinical and laboratory findings. Patients with EE frequently present elevated levels of lactic acid, C4- and C5-acylcarnitine, and thiosulphate in the blood, and ethylmalonic acid in the urine. Diagnosis is usually confirmed in genetic studies.[3,4] Treatment is currently symptomatic.[5]

We present the clinical, biochemical, radiological, and genetic data of a new patient with EE who was diagnosed during an infectious decompensation, and review the available evidence on this rare entity and its management.

The patient was a boy of 1.3 years of age with no relevant family or perinatal history who presented developmental delay, mild language regression with the loss of the 3 words he had learnt, hypotonia, and failure to thrive since the age of 10 months. He also presented capillary fragility, manifesting as petechiae on the limbs.

He was admitted to hospital due to acute decompensation in the context of fever and diarrhoea, with metabolic acidosis (pH, 7.21; pCO_2, 14 mm Hg; HCO_3, 8.8 mmol/L), hyperlactacidaemia (3.8 mmol/L), hyperglycaemia (glucose, 264 mg/dL), and ketonaemia (3.8 mmol/L); the patient was transferred to the intensive care unit for stabilisation. Examination at the paediatric ward revealed body weight of 7.4 kg (< p1; −3.2 SD), length of 72 cm (< p1; −3.24 SD), head circumference of 45.5 cm (p12; −1.18 SD), and a phenotype with dolichocephaly, prominent forehead, retrognathia, low-set ears, and a small mouth with thin lips. He presented petechiae, mainly on the forearms and popliteal and antecubital fossae. Interaction was good, with scarce language (2 or 3 doubtfully referential disyllables), good visual tracking, bilateral grasping, and marked global hypotonia; the patient was able to sit with support but could not stand nor walk. He was unable to push up to hands and knees from a prone position, and presented generalised hyperreflexia, sustained clonus, and bilateral Babinski sign.

Brain MRI (Fig. 1) revealed signal alterations in the putamen and the head of the caudate nucleus bilaterally.

The metabolic study of amino acids, blood acylcarnitines, and urine organic acids at 24 hours revealed elevated excretion of ethylmalonic acid. A targeted genetic panel revealed a homozygous pathogenic mutation of the *ETHE1* gene (*c.488 G > A* [*p.Arg163Gln*]); both parents were asymptomatic carriers of the mutation.

Treatment was started with biotin, coenzyme Q10, vitamin E, riboflavin, thiamine, and L-carnitine due to suspicion of mitochondrial disease; metronidazole and N-acetylcysteine were subsequently added. Two months after admission, we observed considerable improvements in nutrition and in psychomotor development. We continued treatment with a low-protein diet, coenzyme Q10, riboflavin, L-carnitine, metronidazole, and N-acetylcysteine, which stabilised the patient, although failure to thrive and developmental delay (predominantly in motor areas) persisted. At the age of 2.5 years, he was able to walk with the assistance of one hand, uttered words but not sentences, and showed good interaction with his surroundings.

The genetic basis of EE was first described in 2004[1]. The *ETHE1* gene, located on chromosome 19, encodes a metallo-β-lactamase involved in the mitochondrial pathway, which is needed for the catabolism of hydrogen sulphide (H_2S). This defect causes accumulation of H_2S and its derivatives (thiosulphate) in various fluids and tissues, and induces direct damage to cell membranes and inhibits cytochrome c oxidase and short-chain acyl-CoA dehydrogenase. It increases levels of lactic acid, ethylmalonic acid, and C4- and C5-acylcarnitine.[1,5,6] Various mutations have been identified, the majority originating in the Mediterranean and the Middle East,[2,6] with variability between families.[4,7,8] The characteristic mucocutaneous manifestations are caused by microvascular toxicity and include recurring petechiae, cutis marmorata, haemorrhagic mucosal suffusion, and/or distal orthostatic acrocyanosis.[1,8] Hydronephrosis, cryptorchidism, and cardiac anomalies have also been described.[7]

The typical brain MRI alterations are irregular contrast-enhancing hyperintense lesions in the basal ganglia,[7,9] as in our patient, resembling those involved in Leigh syndrome. Other abnormalities described in the literature include

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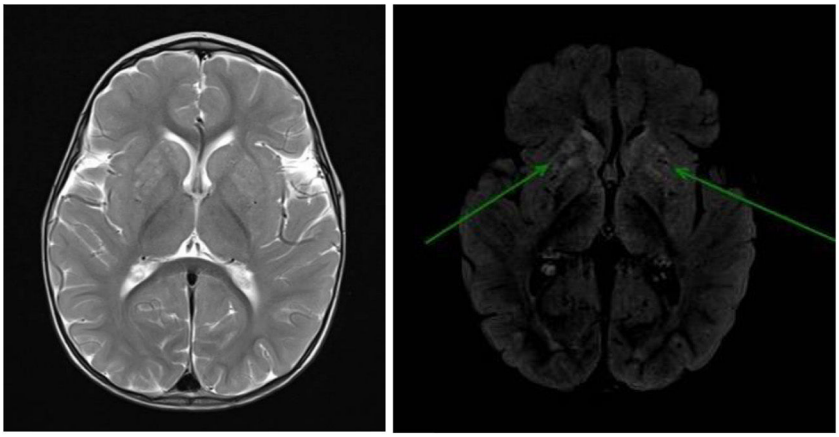

Fig. 1 Brain MRI scan: bilateral signal alterations in the putamen and head of the caudate nucleus; hyperintense lesions on T2-weighted (left) and FLAIR sequences (right: arrows). No globus pallidus or internal capsule involvement were observed. No loss of parenchymal volume was observed at the supra- or infratentorial levels.

hyperintensities in the brainstem, cortical atrophy, diffuse leukoencephalopathy, and congenital malformations such as tethered spinal cord and Chiari malformation.[2]

Gene sequencing is recommended for diagnosis. If pathogenic variants are not identified, or are found in a single allele, then targeted deletion and duplication analysis of the gene should be performed.[3,10]

Treatment should aim to guarantee adequate nutritional support.[2] Treatment with riboflavin, L-carnitine, and coenzyme Q10, as administered in our patient, seems beneficial.[11] Diets with restricted intake of sulphurated amino acids also improve symptoms and biochemical markers.[5] Combined use of metronidazole and N-acetylcysteine has been shown to control accumulation of H_2S by reducing the abundance of the bacteria producing sulphide and neutralising H_2S, respectively.[12,13] These patients occasionally require renal replacement therapy.[14]

Liver transplantation seems to be a therapeutic option,[9] and gene therapy with adeno-associated viral vectors is currently under study.[15]

Finally, it should be noted that the phenotype associated with the *c.488 G > A* (*p.Arg163Gln*) mutation of *ETHE1* behaves as a mitochondrial disease, associated with capillary fragility and failure to thrive, and responds well to mitochondrial stimulation, antioxidants, and gastrointestinal decontamination.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Pericallosal lipoma associated with azygos anterior cerebral artery☆

Lipoma pericalloso asociado a arteria cerebral anterior tipo ácigos

Dear Editor:

Intracranial lipomas (IL) are rare congenital lesions composed of adipose tissue that result from anomalous persistence and altered differentiation of the embryonic meninx primitiva during the development of the subarachnoid cisterns. The most frequent type is interhemispheric IL, which is usually located on the corpus callosum. They are frequently associated with callosal hypogenesis or agenesis.[1] ILs are rarely associated with cortical malformations or vascular anomalies, such as aneurysms or arteriovenous malformations. The azygos anterior cerebral artery (ACA) is a rare anatomical variant, with an incidence below 1%, in which the distal (A2) segments of both ACAs fuse into a single vessel that supplies the medial part of both hemispheres.[2] We present the first case, as far as we are aware, of simultaneous presence of pericallosal lipoma and azygos ACA.

Our patient is a 57-year-old woman with history of emotionally unstable personality disorder and previous consumption of amphetamines and cocaine. She has no family history of neurological disease.

The patient reported episodes of dizziness, progressing for several years. Family members witnessing the episodes reported that she presented pallor and was unresponsive to verbal stimuli; they observed no anomalous movements. Episodes lasted 5 minutes and muscle tone was preserved.

Laboratory analysis and electroencephalography yielded normal results.

A contrast-enhanced computed tomography (CT) scan (Fig. 1) revealed a voluminous hypodense lesion compatible with interhemispheric IL, crossed by a single ACA, with partial peripheral calcifications. Brain MRI and MRI angiography (Fig. 2) showed the same lesion, with a signal similar to that of adipose tissue, closely related to the corpus callosum, with agenesis of the splenium. It was also associated with a vascular anomaly consisting of a prominent single ACA inside the lesion, with distal emergence of pericallosal and marginal callosal branches.

Given the patient's clinical situation and the imaging findings, we adopted a conservative approach with radiological follow-up of the lesion.

ILs account for 0.1%-0.5% of all intracranial lesions. Their origin is most likely to be altered differentiation of meningeal tissue. They are made up of normal adipose tissue, and therefore are considered a congenital anomaly rather than a true neoplasm.[1]

Most ILs are located proximal to the midline, and 45% are interhemispheric lipomas. The remaining cases involve the quadrigeminal cistern (25%), the interpeduncular cistern (14%), the cerebellopontine angle (9%), and the Sylvian fissure (5%).[3]

More than half of ILs are associated with brain malformations, especially midline anomalies. The most frequent is callosal agenesis or dysgenesis. Absence of the septum pellucidum, spina bifida, encephalocele and myelomeningocele, and other cortical malformations have also been reported. Vascular anomalies such as aneurysms, arteriovenous malformations, or anomalous venous drainage may be present. Because growth of the IL and arterial development both occur during the first weeks of gestation, it has been suggested that they may be associated.[4]

Azygos ACA is a vessel resulting from the fusion of both pericallosal arteries. Anatomical series report its presence in fewer than 5% of patients. It occurs as a transient stage during embryonic development and is present in some mammals. It is frequently associated with other malformations of the CNS, such as porencephalic cysts, callosal agenesis, hydranencephaly, and arteriovenous malformations. The approximate incidence of aneurysms in these cases ranges from 13% to 71%.[2]

LIs are frequently asymptomatic and are usually incidental findings in imaging studies. However, headache, seizures, psychomotor developmental delays, and cranial nerve involvement have also been reported.[5]

Diagnosis is established by CT and MRI, which reveal a well-delimited, extra-axial, lobulated lesion, displaying the characteristics of adipose tissue. In the CT scan,

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