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Reply to: Factors related to immediate response to symptoms in patients with stroke or transient ischaemic attack☆

Respuesta a: Factores relacionados con una respuesta inmediata a los síntomas en pacientes con ictus o accidente isquémico transitorio

Dear Editor:

It was with great interest that we read the article by García Ruiz et al.[1] published in your journal under the title ''Factors related to immediate response to symptoms in patients with stroke or transient ischaemic attack.'' This study demonstrates that when stroke is witnessed by a patient's daughter/son and presents greater severity, the delay in seeking help for stroke symptoms is reduced; emergency departments of hospitals in the Spanish national healthcare system are the main medical contacts in these cases[1]. We observed the same findings in our sample of 425 patients from Northern Spain,[2] and similar factors have been associated with earlier hospital arrival in other countries[3]; therefore, these findings are robust and can be generalised. Another recurrent finding is that the number of patients contacting emergency services to seek help is much higher among patients seeking help in the first 15 minutes than among those seeking help later.[2,3] Unexpectedly, the reason for later hospital arrivals in cases in which emergency services were not contacted is not the transport time, but rather longer delays in seeking help.[2] The reduced delay when stroke is witnessed by a patient's daughter/son may be explained by 2 facts: the witness may better identify the need for help; and witnesses are more easily able to seek assistance than a patient who is alone at stroke onset. However, the fact that greater stroke severity, regardless of the presence of a daughter/son, decreases the delay in seeking help suggests that the perception of the need for help reduces this delay more than stroke-derived motor impairment increases it. As extended families with grandparents, parents, and grandchildren living together continue to be replaced by nuclear families, help-seeking by a witnessing daughter/son will become less frequent. In stroke care protocols, time to hospital arrival is the longest; as has been observed in many countries during the COVID-19 epidemic, it is also the most likely to be affected by external circumstances[4] and shows the most room for improvement. Therefore, we concur with García Ruiz et al.[1] that public awareness campaigns on emergency responses to stroke should stress the importance of immediate action in the event of mild symptoms, and focus on individuals presenting vascular risk factors or living alone.

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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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