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Global cerebral involvement and L-arginine use in a patient with MELAS syndrome☆

Afectación encefálica global y uso de L-arginina en un paciente con síndrome de MELAS

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome is classified within the group of mitochondrial diseases. The lack of large series of patients with the same molecular defect and clinical manifestations is a fundamental problem, as these may lead to conclusive studies on the effectiveness of the different drugs applied.[1] We present the case of a 30-year-old man with no relevant history who in January 2013 presented an episode compatible with secondarily generalised focal-onset seizures with subsequent status epilepticus, requiring admission to the intensive care unit. A brain MRI scan only revealed focal cortical thickening of the left lingual gyrus, suggesting focal cortical dysplasia as the first diagnostic hypothesis. The patient remained asymptomatic until early September 2014, when he was admitted to our centre due to sudden-onset visual loss affecting the left hemifield. An initial neurological examination only revealed left homonymous hemianopsia and slight dysmetria during the finger-to-nose test with the left arm. The patient presented a surprising, rapid decline during the following days, developing cortical blindness, cortical deafness, and global aphasia. He also presented significant psychomotor agitation and occasional marked agitation with continuous jargon aphasia and unmotivated actions. His only contact with his environment was by touch, and he was able to recognise his wife by touching a ring she was wearing. A laboratory analysis showed high lactate concentrations in the blood (2.7 mmol/L) and the cerebrospinal fluid (3.36 mmol/L), as well as high blood L-carnitine and total carnitine levels; creatine kinase level was normal. No signs of myopathy were observed in the electromyography study, and a hearing test revealed bilateral mild sensorineural hearing loss. A further MRI scan showed significant lesion extension with cortical involvement in the left hemisphere (predominantly occipital, parietal, and temporal), with hyperintensities on T2-weighted and FLAIR sequences. Oedema, mass effect areas, and diffusion restriction were also observed. The patient also presented occipito-parieto-

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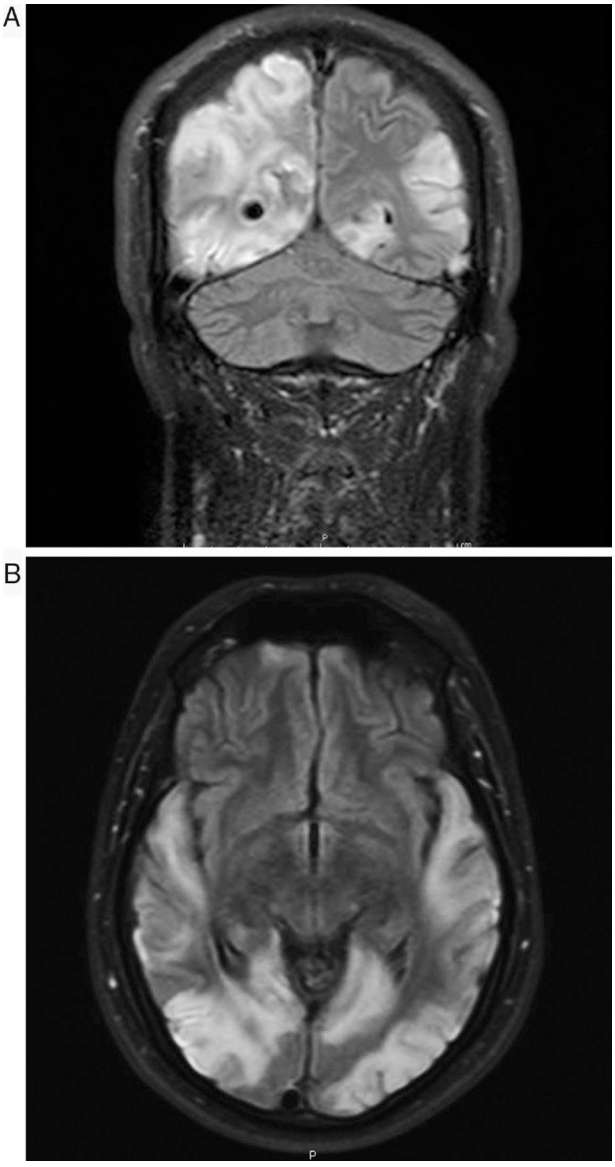

Figure 1 Coronal (A) and axial (B) FLAIR sequences showing hyperintense lesions affecting the bilateral temporo-parieto-occipital cortex, which do not correspond to vascular territories.

temporal involvement with similar characteristics in the right hemisphere, and some areas of cortical laminar necrosis (Fig. 1A and B). Muscle biopsy showed non-specific changes and a lack of morphological changes diagnostic of mitochondrial myopathy (no ragged red fibres and no COX-negative fibres). Results of the genetic study were positive for the A3243G mutation. During hospitalisation, the patient was treated with phenytoin 100 mg (dosed at 100-50-100 mg), levetiracetam 1000 mg/12 h, clonazepam 0.5 mg/12 h, ubiquinol 200 mg/8 h, idebenone 90 mg/8 h, arginine 6 g/8 h, and vitamin complexes (thiamine [B_1] 300 mg [1/2 tablet/12 h], riboflavin [B_2] 50 mg/8 h, vitamin C 2 g/day; vitamin E 200 mg/day on Mondays, Wednesdays, and Fridays). His condition improved to a certain extent. This case presents several interesting features. Firstly, late onset is noteworthy, occurring in approximately 20% of cases. It is also surprising that the patient did not show muscle involvement, which is especially frequent in carriers of the A3243G mutation. Various studies have reported that the A3243G mutation provokes a severe combined defect in the respiratory chain of myoblasts. Muscle biopsies normally reveal fat deposits, and ragged red fibres are also observed frequently. According to some studies, the percentage of patients diagnosed with MELAS syndrome (regardless of the mutation) after a negative biopsy is approximately 10%.[2] The aggressive symptom progression is also of interest, with the patient progressing from hemianopsia to blindness, deafness, and mixed aphasia in only 3 days, which made him practically unable to communicate with his environment. Central deafness has very rarely been reported.[3] Regarding treatment, vitamin complexes (B_1, B_2, C, and E) would act as antioxidants in this case, which appears to correct the oxidative damage; however, there are no conclusive studies on the effectiveness of this treatment.[4] We should also stress the administration of L-arginine, a nitric oxide precursor; several studies report a decrease in its levels both in the acute phase and in the interictal phase, compared to controls. Arginine is considered one of the most promising drugs[5,6] and, although its action mechanisms are not fully understood, it seems to have an impact on vascular regulation, causing vasodilation by increasing nitric oxide concentration. This would increase aerobic capacity and improve muscle metabolism.[6] Arginine can be administered by intravenous infusion in the acute phase and acts rapidly (less than 24 h), improving symptoms. However, symptoms may worsen subsequently if oral supplementation is not continued, with a recommended dose of 0.5 g/kg/day. Our patient is currently receiving oral arginine at 6 g/8 h. The patient was hospitalised for approximately one month and a half, and showed some degree of improvement. At discharge, he was able to follow simple instructions and produce short, coherent sentences. His vision improved slightly, and he is currently able to identify colours, shapes, and movement. Speech impairment with paraphasia persisted and the patient continued receiving speech therapy on an outpatient basis. No motor deficit was observed at any time. He continued treatment with vitamin complexes, oral arginine 6 g/8 h, clonazepam 0.5 mg/8 h, levetiracetam 500 mg/12 h, and lacosamide 100 mg/8 h; phenytoin was suspended. The patient remains stable and has not been readmitted again to date.

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Occipital epilepsia partialis continua induced by non-ketotic hyperglycaemia☆,☆☆

Epilepsia parcial continua con foco occipital inducida por hiperglucemia no cetósica

Dear Editor:

Numerous neurological manifestations of glycaemic alterations have been described, with hypoglycaemia being a well-known cause of epileptic seizures.[1] It is less well known that neurological symptoms may present as the initial manifestation of hyperglycaemia,[2] with epilepsia partialis continua being a characteristic form; these patients usually present focal motor seizures, unlike those with hypoglycaemia.[3] Hyperosmolar non-ketotic hyperglycaemia is the type of hyperglycaemia most frequently associated with these symptoms, and is occasionally the initial manifestation of undiagnosed diabetes mellitus.[4] The specific pathophysiological mechanism underlying this association is not fully understood, and ketosis may protect against seizures in patients with hyperglycaemia.[4] We present the case of a patient with occipital epilepsia partialis continua in the context of non-ketotic hyperglycaemia, resolving with metabolic control. This case underscores the need to consider this entity, which, though rare, has considerable therapeutic and prognostic implications.

The patient was a 61-year-old man with hypertension, dyslipidaemia, and type 2 diabetes mellitus, which had previously been well controlled. He was being treated with telmisartan, simvastatin, fenofibrate, metformin, acetylsalicylic acid, and omeprazole. He had no history of seizures or any other relevant history. He began to present simple visual hallucinations of sparkling lights; onset was sudden and episodes were of variable duration (seconds to hours). Visual hallucinations affected both eyes and the entire visual field, and persisted when the eyes were closed. He reported reversal of vision metamorphopsia when the symptoms initially presented, although this resolved spontaneously. The patient presented no visual field deficits, headache, or any other focal neurological sign. These symptoms had progressed for 20 days before the patient consulted the department; the frequency of the episodes ranged from 5 to 20 per day, with no defined temporal or circadian pattern.

Neurological examination revealed no focal neurological deficits. A complete blood count revealed a glucose level of 382 mg/dL, with 14% glycated haemoglobin. The only other alteration detected was known hypertriglyceridaemia. Results for ketone bodies were negative. The patient displayed EEG asymmetry, with abnormal occipital alpha waves in the right hemisphere (Fig. 1). The brain MRI study revealed T2 hyperintensity and diffusion restriction in the right occipital cortex, with T2 hypointensity in the adjacent subcortical region (Fig. 2). We also performed a head and neck MRI angiography and a transcranial and supra-aortic trunk Doppler ultrasound study, with no relevant findings. Insulin therapy was started and the visual symptoms resolved within hours and have not recurred to date (15 months of follow-up), with the patient presenting optimal glycaemic control. Findings from subsequent EEG and MRI studies were normal (Figs. 1 and 2).

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☆☆ This study was presented as a poster at the 15th Annual Meeting of the Madrid Association of Neurology, held in October 2017.