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LETTER TO THE EDITOR

Multiple acyl-coenzyme A dehydrogenase deficiency: diagnosis in adulthood, intensive care management and sequelae

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Dear Editor,

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is a rare autosomal recessive disorder that affects fatty acid beta oxidation due to specific electron transfer flavoprotein (ETF) deficiency: subunits α and β, and dehydrogenase (ETFDH).[1] Different phenotypes determined by mutation heterogeneity in ETFα, ETFβ and ETFDH genes impede diagnosis and treatment.[1] A case with a previously unknown mutation is presented. A 46-year-old man was admitted to ICU with GCS score of 10 after two days of light fever and diarrhoea. Since childhood he had suffered from recurrent weakness and spontaneous vomiting after prolonged muscular effort, usually resolved by 24-48 hours' rest and carbohydrates. Coexisting diseases were: early-onset hypertension and echocardiographic signs of hypertensive heart disease, hypertensive retinopathy, chronic gastritis, and nephrolithiasis. Severe metabolic acidosis and increased anion gap without lactacidemia was diagnosed. Brain high-resolution CT, electroencephalogram and cerebrospinal fluid examination were negative. Neurologic impairment worsened, with flaccid paralysis combined with rhabdomyolysis requiring orotracheal intubation and mechanical ventilation (MV). Analgosedation entailed intravenous propofol and remifentanil. Laringoscopy showed vocal cord paralysis in adduction. Laboratory tests revealed cytolytic enzyme release and multiple organ failure needing high-flux continuous veno-venous hemodiafiltration (CVVHDF). Specific enteral and parenteral nutrition for kidney disease was prescribed. Invasive haemodynamic monitoring showed hyperdynamic circulation with central venous oxygen saturation over 99%, suggesting tissue oxygen extraction failure. Severe metabolic acidosis was refractory to CVVHDF. Glycemia was normal on admission but later hypoglycemia was observed. Neurological evaluation suggested a neuromuscular metabolic disease. Brain MRI showed a mild cortical fronto-parietal atrophy and white matter signal changes compatible with MADD.[2] Proton MR spectroscopy (^{1}H MRS) provides non-invasive metabolic information of the brain, even in the absence of morpho-structural lesions on conventional MRI. ^{1}H MRS in the parietal white

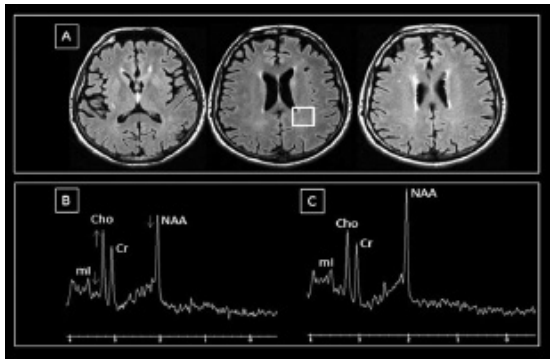

Figure 1.—A) Structural brain MRI performed upon admission. Axial Fluid-Attenuated Inversion Recovery, FLAIR T2 showed areas of increased signal intensity in the periventricular and subcortical white matter. In the middle of the image a volume of interest in the parietal white matter is shown, where ^{1}H MRS was acquired. Single voxel ^{1}H MRS, performed using the PRESS sequence, showed in the patient before therapy (B), a reduction of NAA, N-acetyl-aspartate, (-14% of the normal mean); and mI, myo-inositol, (-24%); and an increase in choline, Cho, (+24%), compared to eight sex- and age-matched healthy volunteers. These metabolic alterations normalized (C) in the scan performed 47 days after the beginning of the riboflavin treatment, whereas structural MRI remained unchanged.

Table I.—*Acylcarnitine profiling cultured fibroblasts.*

Acylcarnitine profiling cultured fibroblasts	nmol/4 days.mg protein	Reference values
C2-carnitine	1.2	2.3-43.3
C4-carnitine	0.2	0.0-2.0
C5-carnitine	8.9	0.0-2.5
C6-carnitine	0.6	0.0-1.4
C8-carnitine	2.0	0.1-2.6
C10-carnitine	3.2	0.2-3.1
C12-carnitine	5.1	0.0-0.8
C14-carnitine	6.6	0.0-0.4
C16-carnitine	11.2	0.0-4.3
OH-C16-carnitine	0.0	0.0-0.1

The risults descrive above show a markedly abnormal acylcarnitine profile dominated by elevated C16-, C14-, C12-, C10- and C5 acylcarnitines. These results point to MADD.

matter demonstrated reduced content of the neuronal and mitochondrial marker N-acetyl-aspartate and the glial marker myo-inositol, whereas choline, a membrane/myelin integrity marker, was increased (Figure 1). This metabolic pattern is not pathognomonic of MADD, but is detectable in multiple sclerosis and other de- or dysmyelination processes.[3] Interestingly, in the lateral ventricules, a pathological accumulation of lactate was found, although very mild, indicating an oxidative metabolism dysfunction (data not shown).[4] Muscle biopsy was performed to study fatty acids beta-oxidation[5] and it revealed MADD (Table I). Molecular fibroblast analysis showed two heterozygous mutations in the ETFα gene: c.354C>A (p.Asn118Lys), unknown mutation; c.494T>C (p.Val165Ala), known mutation. Intravenous propofol was suspended and enteral and parenteral lipid intake avoided. Adult nutritional mixture was not available, so non-fat pediatric milk formulation was used, enriched with a multivitamin complex with riboflavin. Gradually partial lipid content was restored in enteral feeding. On day 11 of MV, Percutaneous Tracheostomy was performed with bronchoscopic guidance for airway inhalation risk protection. The next day breathing was spontaneous and CVVHDF was not needed. Ear, nose and throat evaluation revealed right residual deficit of velum palatinum, tongue and vocal cord with a deficient lingual and pharyngeal pump. Percutaneous Endoscopy Gastrostomy was performed. After 38 days he was transferred to a rehabilitation physiotherapy unit and then discharged after 118 days of LOS with surgical indication for posterior cordectomy for decannulation.

Coma and metabolic acidosis without lactacidemia and with increased anion gap and high central venous oxygen saturation might suggest a mitochondrial defect. The rarity and specificity of the disease make the diagnosis complex in adulthood but the onset was in childhood. Muscle biopsy with cultured fibroblasts and the study of the acylcarnitines profiling is fundamental as not influenced by nutrition. Failure to diagnose in the absence of therapeutic measures and pharmacological interference in the process of hospitalization can aggravate the clinical course until the development of permanent neuromotor complications as described by Brain MRI. ^{1}H MRS highlights the normalization of metabolic panel after appropriate therapy. Routine sedation with propofol and nutritional lipid component should be questioned.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization related to the material discussed in the manuscript.

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