SCIENTIFIC LETTER

Stroke in a patient with marked thinness, diabetes mellitus and basal ganglia calcifications

Ictus isquémico en paciente con delgadez marcada, diabetes mellitus y calcificaciones en ganglios de la base

Mitochondrial DNA mutations are uncommon causes of diabetes mellitus in adults and are related to a wide spectrum of diseases. Its association with myopathy, lactic acidosis, and stroke is an even less frequent syndrome. We report the case of a young woman who was diagnosed with mitochondrial disease upon admission for a stroke.

This case is that of a 46-year-old patient urgently admitted to the neurology department for speech difficulties during the previous week. Physical examination revealed marked thinness, myopathic facies with palpebral ptosis more marked in the left eye, mild dysarthria, mixed (predominantly motor) aphasia with difficulty in understanding complex commands and unstable gait, and was otherwise unremarkable. Computed tomography (CT) of the head disclosed coarse calcifications in basal nuclei and an extensive left temporal hypodense lesion related to subacute ischemic stroke in the territory of the left middle cerebral artery.

The personal history of the patient included constitutional thinness, bilateral sensorineural deafness of unknown cause diagnosed at 20 years of age, secondary amenorrhea starting some 15 years earlier, type 2 diabetes mellitus since 2008, and non-specific ST segment changes with negative T in the inferior lateral aspect followed up by cardiology. As regards family history, a brother also had juvenile onset sensorineural deafness and type 2 diabetes mellitus treated with basal insulin. The patient received no specific treatment because she had discontinued the oral antidiabetic drug prescribed by her physician (metformin 850 mg twice daily) due to poor tolerance (gastrointestinal symptoms, malaise, and characteristic body odor).

Laboratory test results included 153 mg/dL of glucose and 499 U/L of lactate dehydrogenase (normal range [u], 135–230 U/L), 5.9% of glycosylated hemoglobin (HbA1c), 8.8 μU/mL of insulin (NR, 2.6–24.9 μU/mL), and 3.3 ng/mL of reactive C-peptide (NR, 0.5–14 ng/mL). The gonadal axis was consistent with hypothalamic-hypogonadism: follicle-stimulating hormone, 8.2 mIU/mL (NR, 3.5–21.5 mIU/mL); luteinizing hormone, 5.5 mIU/mL (NR, 2.4–95.6 mIU/mL); estradiol, 10.37 pg/mL (NR, 12.5–211 pg/mL); and progesterone, 0.6 ng/mL (NR, 0.2–27 ng/mL). Parathormone and 25-hydroxyvitamin D levels were decreased (12.5 pg/mL [NR 15–65 pg/mL] and 7.5 mg/dL [NR, 20–30 mg/dL] respectively), while there were no changes in the serum levels of calcium (9.3 mg/dL, NR 8.9–10.5 mg/dL), phosphorus, and magnesium. The metabolic study showed elevated levels of ammonium (47 μmol/L, NR 11–32 μmol/L) and lactate (2.7 mmol/L, NR 0.4–2 mmol/L) together with slightly increased values (ammonium 35–57–71–58–51 μmol/L and lactate 3.2, 6.4, 6.7, 7.1, and 6.9 mmol/L at baseline and 1, 2, 5, and 10 min) after exercise. An electrophysiological study of muscle was consistent with myopathy.

Based on these results, a diagnosis of mitochondrial cytopathy with mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome (MELAS), mitochondrial myopathy, bilateral sensorineural deafness, calcifications in basal ganglia, non-specific cardiac repolarization changes, diabetes mellitus of mitochondrial origin, thinness in the setting of myopathy of mitochondrial origin, and hypothalamic amenorrhea was suspected. A genetic study of the mitochondrial respiratory chain in DNA from a blood sample was requested, and a positive m.3243G-MTTL1 point mutation was found.

Treatment consisting of a hypercaloric and hyperprotein diet, repaglinide 1 mg before each main meal, anti-aggregation with acetylsalicylic acid 300 mg daily, and gastric protection was prescribed. This regimen achieved almost complete resolution of the stroke sequelae. Moreover, the patient achieved and continues to have a good metabolic control of diabetes.

Mitochondrial diseases are a clinically heterogeneous group of disorders resulting from a dysfunction in the mitochondrial respiratory chain. The most common clinical presentation is the syndrome of maternally inherited diabetes and deafness, caused by a point mutation in the nucleotide pair m.3243A–G of mtDNA, encoding for tRNA of leucine. This is the most common form of point mutation in this gene. Pigmentary retinal dystrophy and neuromuscular disease may also occur. The same mutation may cause a less common disease, mitochondrial encephalopathy with

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lactic acidosis and events similar to stroke, which is the condition suffered by our patient.5,6

Diagnosis is made based on the characteristic clinical picture of a specific mitochondrial disease and is confirmed by a molecular genetic study of DNA extracted from a blood sample.7 The management of mitochondrial diseases largely consists of support measures and includes the early diagnosis and treatment of diabetes mellitus and cardiac arrhythmia, the correction of eye ptosis, and the treatment of cataracts with intraocular lenses. Supplementation with coenzyme Q10 and treatment with l-carnitine may provide some benefit.1 As regards diabetes, although some patients may be treated with secretagogue drugs, insulin therapy is eventually required, and metformin is associated with an increased risk of lactic acidosis, to which patients affected with these diseases are more predisposed than all other patients with diabetes.8,9 In the reported case, metformin was poorly tolerated due to the predisposition of the patient to acidosis.

In conclusion, maternally inherited diabetes and deafness are a rare cause of diabetes whose clinical identification and genetic diagnosis are important for the management of treatable symptoms and associated comorbidities, and also for detecting relatives affected, providing genetic counseling, and allowing for research into diabetes prevention strategies.

References


Antonia García-Martín a,1, Rebeca Reyes-García a, José Miguel García-Castro b, Manuel Muñoz-Torres a

a Servicio de Endocrinología y Nutrición, Hospital Universitario San Cecilio, Granada, Spain
b Servicio de Medicina Interna, Hospital Universitario Virgen de las Nieves, Granada, Spain

1 Corresponding author.
E-mail address: garciamartin.t@hotmail.com (A. García-Martín).

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