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CASE REPORT

Therapeutic options in a patient with MELAS and diabetes mellitus: follow-up after 6 months of treatment

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome are a maternally inherited mitochondrial genetic disorder characterized by defective oxidative phosphorylation. The adenine-to-guanine transition at position 3243 in the MT-TL1 gene is the most common mutation of mitochondrial DNA found in patients with MELAS syndrome. As other mitochondrial disorders, MELAS syndrome can develop in the neonatal phase, childhood, or adulthood, and show a broad spectrum of clinical presentations. Neurological and muscular disturbances (i.e., stroke-like episodes, recurrent migrainous headaches, seizures, and muscle weakness with exercise intolerance) are the earliest and most frequent manifestations of the disease. However, mitochondrial diseases, including MELAS syndrome, are multi-organ disorders including cardiomyopathy, nephropathy, hypothyroidism, and diabetes (DM).

On January 2017, a 42-year-old woman, following a determination of fasting plasma glucose for other purposes, received the diagnosis of DM (Hb1Ac 56 mmol/mol) and a prescription of metformin. Her body mass index was 18.2 kg/m^2 and antibodies for glutamic acid decarboxylase and protein tyrosine phosphatase were negative. The patient's renal function was slightly reduced (creatinine 0.99 mg/dl and clearance creatinine 70.8 ml/min). She was also affected by Wolff–Parkinson–White syndrome, bilateral sensorineural severe hearing loss, and migraine. Eight months later the patient was admitted to the hospital for sudden spatio-temporal disorientation and confusion. The neurological examination revealed no further abnormality. T2 and FLAIR-weighted MRI scans showed a high-intensity lesion on the right parieto-temporal region, detectable even on DWI sequence, suggestive of or a ischemic or an inflammatory lesion. To discriminate the nature of the lesion, a lumbar puncture was performed; cerebrospinal fluid showed a normal white cell count and glucose level. Lactate (28 mg; normal range [NR]: 10–25 mg) and total proteins (77 mg/dl; NR: 10–30 mg) were slightly increased.

On the basis of those data, the hypothesis of MELAS syndrome was formulated; thus, an evaluation of the REDOX state and a specific genetic test were carried out. REDOX state titration in two fasting plasma samples drawn 60 min apart demonstrated increased values of lactic acid (4.06 and 3.61 mM; NR: 0.63–3.61 mM) and pyruvic acid (244.93 and 214.79 mM; NR: 45–190 mM). Genetic examination revealed an m.3243 A > G point mutation. According to these results, the Japanese diagnostic criteria for MELAS [1] were fulfilled and the diagnosis was made (Table1).

To evaluate the systemic involvement of the disease, further investigations were performed. Liver function was normal, as was the ultrasound of the abdomen. The patient's renal function persisted slightly reduced (creatinine 0.94 and GRF 69.7 ml/min). She also had positive macroalbuminuria (341.9 mg/g creat, NR < 10 mg/g) and proteinuria 24 h (728 mg/24 h NR 149 mg/24 h). Therefore, therapy with enalapril was started. The thyroid function appeared altered with a typical picture of euthyroid sick syndrome (TSH 0.39 mU/l, NR 0.36–3.74; FT4 14.64 ng/ml, NR 9.8–18.8; FT3 1.91 pmol/l, NR 3.30–6.10). At the next check, the values were back to normal (TSH 1.82 m U/l).

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Table 1 Diagnostic criteria for MELAS

Diagnostic criteria for MELAS
Category A. Clinical findings of stroke-like episodes
Headache with vomiting
Seizure
Hemiplegia
Cortical blindness or hemianopsia
Acute focal lesion observed via brain imaging
Category B. Evidence of mitochondrial dysfunction
High lactate levels in plasma and/or cerebral spinal fluid or deficiency of mitochondrial-related enzyme activities
Mitochondrial abnormalities in muscle biopsy
Definitive gene mutation related to MELAS
Definitive MELAS
Two items of Category A and two items of Category B (four items or more)
Suspicion of MELAS
One item of Category A and two items of Category B (at least three items)

During hospitalization, when the diagnosis was still uncertain, high-dosage glucocorticoids were administered. When the patient was discharged from the hospital, a therapy with coenzyme Q10 300 mg twice a day, riboflavin 100 mg twice a day, and l-arginine 1.66 g twice a day was started.

Metformin was withdrawn to avoid lactic acidosis and insulin therapy was introduced; considering capillary blood glucose profiles, showing a predominantly post-prandial hyperglycemia, a bolus-only scheme with lispro insulin at meals was chosen. One month after hospital discharge, despite the very low dose of lispro insulin (1–2 U per meal), the patient complained of recurrent mild hypoglycaemia. Her C-peptide was 1.11 nmol/l (NR 0.6–17 nmol/l). Therefore, insulin therapy was stopped and replaced with the dipeptidyl peptidase 4 (DPP4) inhibitor linagliptin, 5 mg/day. This treatment granted an optimal glycemic control: after 3 months Hb1Ac was 35 mmol/mol (5.4%) and C-peptide 1.61 nmol/l. After 6 months, Hb1Ac was 39 mmol/mol (5.7%).

The pathogenesis of DM in mitochondrial diseases remains largely unknown with three proposed mechanisms: impaired insulin secretion, decreased glucose utilization, and increased glucose production. Normally, pancreatic β-cells respond to increased blood glucose levels by increasing insulin secretion. An increased insulin concentration suppresses hepatic glucose production and stimulates glucose utilization by muscle and adipose tissues. In pancreatic β-cells, an ATP-sensitive potassium channel allows insulin release. Therefore, a decreased ATP synthesis as a result of mitochondrial dysfunction can result in an impaired insulin secretion. Impaired glucose utilization by muscle can occur due to insulin resistance. Increased ROS production due to mitochondrial dysfunction can play a role in impaired insulin responsiveness and in the development of insulin resistance. In addition, increased lactate concentration in mitochondrial diseases can result in higher hepatic glucose production, since lactate is a major substrate for gluconeogenesis.

Due to the very low prevalence of the disease, there are no formal studies assessing the safety and efficacy of different treatments for diabetes in MELAS syndrome. Metformin is not recommended, because it increases the risk of lactic acidosis. The insulin-sensitizer thiazolidinediones (TZDs) suppress hepatic gluconeogenesis and enhance glucose utilization in muscular and adipose cells. Furthermore, these drugs have an antiapoptotic action on pancreatic β-cells. However, TZDs also inhibit MPC 1–2 (mitochondrial pyruvate carrier) activity, thus reducing pyruvate uptake by the mitochondria and potentially increasing lactate levels. Although treatment with TZDs is not associated with lactic acidosis [2], some caution should be used in considering these drugs as a potential treatment for diabetes in MELAS syndrome.

Available studies show that among people with MELAS syndrome, only subjects with a relevant impairment of insulin secretion develop diabetes [3]. Therefore, it would seem logical to approach hyperglycemia with drugs which stimulate insulin secretion. Sulphonylurea are a possible option; however, they are capable of inducing hypoglycaemia and they have documented pro-apoptotic effects on β-cells in longer term treatments [4]. Incretin-based drugs are more suitable candidates, based on their profile of actions. In fact, both DPP4 inhibitors and GLP-1 receptor agonists enhance glucose-stimulated insulin secretion, suppress glucagon production reducing gluconeogenesis, and have an antioxidant and anti-inflammatory action. Thus, they potentially counteracting several pathogenic mechanisms of MELAS. In this specific case, considering that the patient was lean, our choice fell on the weight-neutral DPP4 inhibitors rather than on GLP-1 receptor agonists which induce weight loss. In addition DPP4 inhibitors, which increase circulating levels

of endogenous incretins, secreted mainly after meals, are likely to be more effective on post-prandial hyperglycemia. Notably, DPP4 inhibitors have already been suggested as an effective and well-tolerated therapeutic option in other genetic forms of diabetes associated with impaired insulin secretion [5].

Further studies would be needed to define the best therapeutic choice in subjects affected by MELAS and DM, but they may be difficult to perform due to the rarity of the disease. Based on mechanistic considerations, DPP4 inhibitors appear to be a good option as confirmed by this observation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient included in the study.

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