EJCRIM
European Journal
of Case Reports
in Internal Medicine

GASTROINTESTINAL COMPLICATIONS OF MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS AND STROKE-LIKE EPISODES (MELAS) SYNDROME MANAGED BY PARENTERAL NUTRITION

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Received: 20/12/2023 **Accepted:** 04/01/2024 **Published:** 22/01/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent form is available for review.

How to cite this article: Horná S, Péč MJ, Krivuš J, Michalová R, Sivák Š, Galajda P, Mokáň M. Gastrointestinal complications of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome managed by parenteral nutrition. *EJCRIM* 2024;**11**:doi:10.12890/2024_004268.

ABSTRACT

MELAS – an acronym for mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes – is a multiorgan disease caused by a mutation in mitochondrial DNA (mtDNA). Its clinical manifestations are highly variable; mainly stroke-like episodes, seizures, recurrent headaches, or muscle weakness. However, gastrointestinal complications such as chronic intestinal pseudo-obstruction (IPO), pancreatitis, gastroparesis and hepatopathy are also common.

In this report we describe a young patient with gastrointestinal complication of MELAS which led to superior mesenteric artery syndrome (SMAS). It is rare but not surprising combination and should be considered in cases with significant weight loss and resistance to symptomatic treatment. The optimal energy support is the main pillar of the treatment.

KEYWORDS

MELAS, nutrition, superior mesenteric artery syndrome

LEARNING POINTS

- Gastrointestinal complications of MELAS such as chronic intestinal pseudo-obstruction, pancreatitis and gastroparesis can lead to undernutrition.
- Superior mesenteric artery syndrome is a rare condition but should be considered in cases with significant weight loss and resistance to symptomatic treatment.
- Optimal caloric intake and energy support can improve the condition of patients with MELAS.

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INTRODUCTION

MELAS, first described by this acronym by Pavlakis and Phillips in 1984[1], is a rare mitochondrial disorder inherited from the mother. It typically manifests between ages of 2 and 40; the late onset form of the disease (after 40) usually presents less aggressively[2].

Defects in mitochondrial metabolism cause imbalance between energy generation and its demand. Tissues with the highest metabolic rate such as brain, eyes, inner ear, and skeletal and heart muscle, are the most affected. This leads to multiorgan dysfunction.

Anaerobic glycolytic activities are increased due to impaired function of the mitochondrial respiratory chain and oxidative phosphorylation. As a result, lactic acid is accumulated during acute attacks[3].

At least 30 different mitochondrial mutations associated with MELAS have been described. A3243G (about 80% of patients) and T3271C (7%–15% of patients) mutations in the *MT-TL1* gene encoding the mitochondrial tRNA Leu(UUR) are the most common, but are not specific[4,5].

There is no general agreement regarding treatment of these individuals and the management remains largely symptomatic. This means restoring the nitric oxide production, increasing mitochondrial biogenesis, modulating their autophagy and stabilising mitochondrial membranes[6].

CASE DESCRIPTION

We present a case of 22-year-old male with MELAS syndrome diagnosed in childhood. The main manifestations were stroke-like episodes, but he was also treated for pancreatitis and perimyocarditis in the past. In June 2019, he was admitted to our department for symptomatic hyponatraemia (120 mmol/l) caused by recent change of antiepileptic medication.

In the first year after the hospitalisation, he required repeated medical attention because of gastroparesis-associated vomiting. This was attributed to MELAS syndrome and initially the patient responded well to treatment with parenteral rehydration and prokinetics. After one year, however, the condition became resistant to conservative therapy and patient was unable to tolerate oral intake.

Ultrasound of the abdomen revealed distention of the stomach and duodenum. Diagnostic workup included gastroscopy which revealed a hook-type stomach. During colonoscopy, a polypectomy of a sessile polyp was performed. Histological examination did not confirm a malignant transformation.

Over six months, the patient lost 7 kg of body weight and his body mass index (BMI) dropped from 14.88 kg/m^2 to 12.46 kg/m^2. A nasojejunal tube was inserted to provide enteral nutrition but was dislocated. An abdominal CT scan *(Fig. 1)* showed dilatation of stomach caused by superior mesenteric artery syndrome (SMAS or Wilkie's syndrome). This occurs when the aortomesenteric angle decreases to less than 14°.

The patient refused both surgical treatment and jejunostomy insertion. Considering this, home parenteral nutrition (HPN) was chosen as a treatment with a nasogastric tube for decompression.

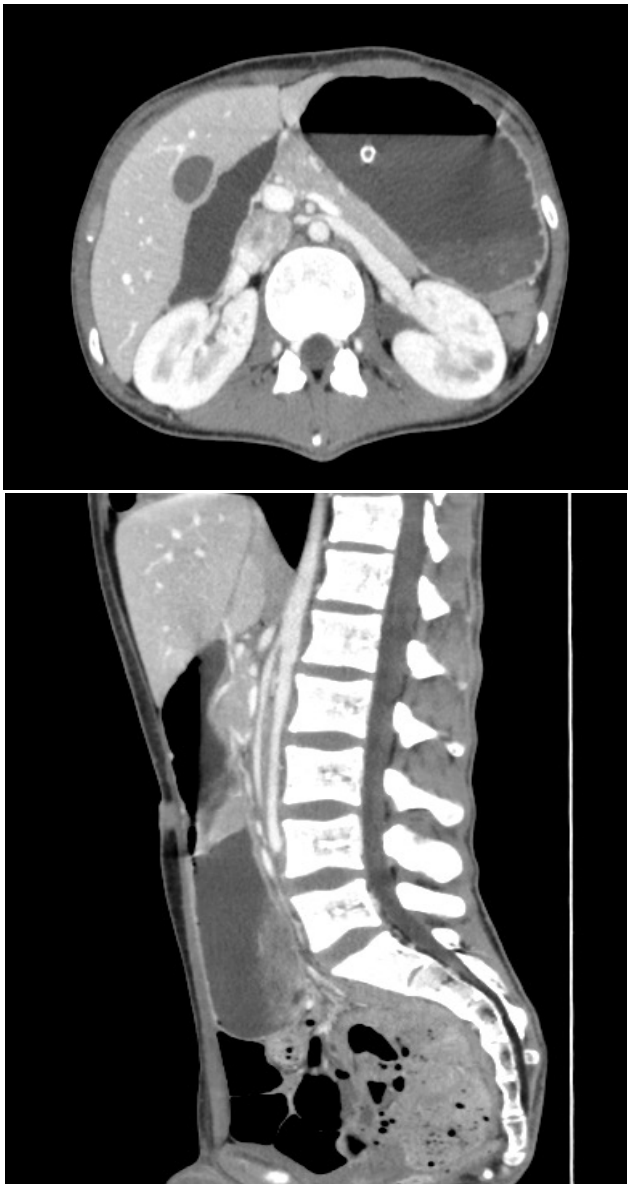

Figure 1. Abdominal CT scan (sagittal and axial plane) – the duodenum is compressed between the aorta and the superior mesenteric artery (aortomesenteric angle less than 14°).

According to his energy requirement and the need for arginine supplementation for MELAS syndrome, a commercially prepared all-in-one bag was chosen, containing 1,600 kcal and 8.37 g of arginine. On this regimen the patient gained 13 kg and his BMI increased to 16.96 kg/m^2 after one year. The nasogastric tube could then be removed.

Tolerance of oral intake also improved, starting with liquids and later solid foods without recurrence of vomiting. Gastrointestinal complications were ameliorated; constipation was managed by lactulose. We have been able to slowly reduce parenteral nutrition and oral supplementation with L-arginine, and L-citrulline was started.

Throughout the duration of HPN (2020–2022), four admissions to department of neurology were necessary for intravenous administration of L-arginine because of the stroke-like episodes *(Fig. 2)*. These were probably evoked by

prolonged and recurrent infections of the respiratory tract. Currently, a supplementary HPN still continues due to the intolerance of enteral nutrition formulas and therefore an inability to achieve an adequate energy intake by a normal oral diet.

DISCUSSION

Gastrointestinal complications are common in MELAS, estimated to affect 64%–77% of patients[6]. The most common symptoms include gastroesophageal reflux, constipation, gastroparesis, vomiting, progressive intestinal pseudo-obstruction (IPO), pancreatitis and hepatopathy.

The underlying pathophysiological mechanisms of gastrointestinal dysmotility in mitochondrial diseases are not completely understood[7]. The aetiology may include loss of interstitial cells of Cajal, marked atrophy of *muscularis propria* and the presence of cytochrome c oxidase (COX) deficiency within the layers of smooth muscle[8,9]. Histological examination of tissue samples from affected individuals shows visceral myopathy. There were different levels of heteroplasmic mtDNA mutation[9,10], extensive microvacuolation and necrosis in the intestinal muscle layers, while the ganglion cells were intact[9,11]. Endothelial dysfunction, which results in a decreased vasodilatory capacity in the small arteries, has also been reported. A centrally mediated mechanism called a neurogastrointestinal crisis has been hypothesised. It could explain concomitant occurrence of stroke – such as episodes and IPO[9].

The study by Belal et al.[12] has revealed glutamate as a promising biomarker of disease severity. Metabolisation through the glutamate pathway was significantly increased in the cells from individuals affected by MELAS, with direct correlation between its concentration and the heteroplasmy level.

The first documented gastrointestinal problem in our patient was an attack of acute pancreatitis; then gastroparesis, constipation and IPO occurred.

There is no known causal treatment for MELAS or its gastrointestinal complications. It is hypothesised that the key therapy is an optimal energy supply[13]. Based on the limited amount of clinical studies, several supplements have been used to try and improve its symptoms. This includes immunonutrition, arginine and/or citrullin, antioxidants, cofactors and mitochondrial substrates (coenzyme Q10, riboflavin, taurine, L-carnitine) as well as symptomatic therapies such as prokinetics, nutritional support and surgery[6,9,14].

Arginine and citrulline are both precursors of nitric oxide (NO), so their reduced availability can contribute to its decreased production. During stroke-like episodes, intravenous administration of arginine hydrochloride is essential. The recommended dose is 500 mg/kg in children or 10 g/m^2 of body surface in adults, followed by a continuous intravenous infusion for 3–5 days. Once an individual with MELAS has the first stroke-like episode, arginine should be administered prophylactically to reduce the risk of its recurrence. In this case, 150–300 mg/kg/day of oral arginine divided into three doses should be administered[6].

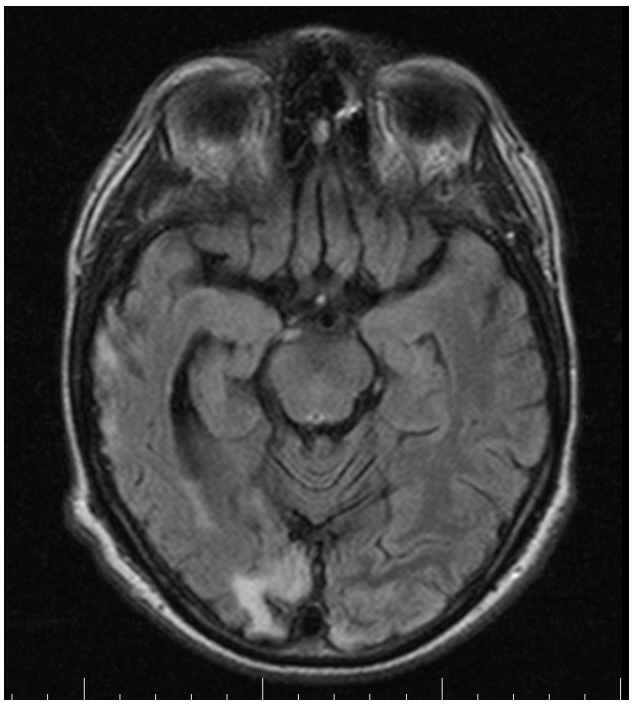

Figure 2. A brain magnetic resonance scan after a stroke-like episode.

Lactic acidaemia resulting from the inability of dysfunctional mitochondria to generate sufficient adenosine triphosphate is also a common finding. In addition, deficiency of NO can result in hypoperfusion due to decreased oxygen delivery to peripheral tissues and a shift to anaerobic glycolysis, further worsening the condition[6].

If metabolic decompensation occurs in these patients, identifying the underlying cause and deciding on the best treatment strategy while maintaining an adequate balance of proteins and nutrients is important. There are no exact data, and the individual state of catabolism should be taken into account[14].

In high-risk patients (starvation lasting longer than 10 days, BMI under 16 kg/m^2) nutritional support should be started slowly to prevent development of refeeding syndrome. Thiamine, a cofactor of glucose metabolism, is in higher demand after refeeding; its supplementation (200–300 mg/day for at least the first 3–5 days) is therefore important[15].

Phosphate is part of adenosine triphosphate and adenosine diphosphate, which are involved in energy processes. Its deficiency can lead to cellular dysfunction, hypocontractility of respiratory muscles and myocardium, but also neurological complications such as paresthesis, convulsions and paralysis[15].

Supplementation of vitamins and antioxidants (ascorbic acid, vitamin E, riboflavin) or more specifically immunonutrition (arginine, leucine, isoleucine, valine, glutamine, omega-3 fatty acids) plays crucial role in the metabolic compensation of patients with MELAS. In case of patients who are critically ill or the absence of oral feeding, this can be achieved by parenteral nutrition. Energy intake generally recommended during the rehabilitation phase is 30 kcal/kg of ideal body

weight, or it can be estimated by various prediction formulas such as the Harris-Benedict equation. When there is a high risk of refeeding syndrome it is advised to start at 10 kcal/kg/day with slow increases when stabilisation is achieved[15].

Superior mesenteric artery syndrome (SMAS) also known as Wilkie's syndrome, is caused by vascular compression of the third part of the duodenum in the angle between the aorta and the superior mesenteric artery. It is a rare but well-recognised clinical entity[16]. The presence of the retroperitoneal fat in this region typically protects the duodenum by maintaining the aortomesenteric angle at 25°–60°. However in the case of Wilkie's syndrome it decreases to only 6°–15°[17]. According to studies, its prevalence in the general population varies between 0.013% and 0.78%[18].

Aside from significant weight loss[19], SMAS can also be caused by incomplete rotation of the duodenum, abnormally high insertion and shortness of the ligament of Treitz, and surgical correction of scoliosis[20]. These conditions result in complete or partial duodenal obstruction[20], and typically present with epigastric pain, nausea, eructations, voluminous vomiting (bilious vomit or partially digested food), postprandial discomfort and sometimes subacute small bowel obstruction[17].

Initial management of this condition is largely symptomatic, which includes decompression by nasogastric tube, parenteral rehydration, and nutrition. Surgical procedures, such as duodenojejunostomy, should be considered if there is no improvement[19]. Delay in diagnosis of SMAS can result in malnutrition, dehydration, vomiting with electrolyte imbalance, gastric pneumatosis[16], hypovolemia, massive gastrointestinal haemorrhage[21] and even death secondary to gastric perforation.

There are only a few case reports of MELAS associated with Wilkie's syndrome[16,22], or recurrent SMAS[23], and in our patient malnutrition caused by MELAS led to SMAS. Symptoms of these two conditions can be similar; this can be one of the reasons why was the diagnosis of SMAS was delayed.

There is a strong predisposition to malnutrition in patients with MELAS which can result in significant weight loss. Association with SMAS is therefore not surprising. Based on current knowledge about pathophysiology of MELAS, optimal caloric intake including supportive treatment by parenteral nutrition improves the condition of these patients.

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