

Mitochondrial Neurogastrointestinal Encephalomyopathy Imitating Crohn's Disease: A Rare Cause of Malnutrition

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ABSTRACT

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease caused by a mutation in the TYMP gene encoding thymidine phosphorylase. MNGIE causes gastrointestinal and neurological symptoms in homozygous individuals and is often misdiagnosed as anorexia nervosa, inflammatory bowel disease, or celiac disease. We present the case of a 26-year-old female with MNGIE, who was initially diagnosed with anorexia nervosa and Crohn's disease. The diagnosis of MNGIE was established by biochemical confirmation of elevated serum and urine thymidine and deoxyuridine levels after multiple examinations and several years of disease progression and ineffective treatment. Subsequent molecular genetic testing demonstrated a homozygous TYMP gene mutation. MNGIE should be considered in patients with unexplained malnutrition, intestinal dysmotility, and atypical neurological symptoms.

Key words: Genetic disease - MNGIE – thymidine phosphorylase – malnutrition – neuropathy – Crohn's disease – anorexia nervosa.

Abbreviations: BMI: Body mass index; CD: Crohn's disease; CT: Computed tomography; GI: Gastrointestinal; MNGIE: Mitochondrial neurogastrointestinal encephalomyopathy; MRI: Magnetic resonance imaging; PEG: Percutaneous endoscopic gastrostomy; TP: Thymidine phosphorylase.

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INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease caused by a mutation in the TYMP gene encoding thymidine phosphorylase. Although the prevalence of MNGIE has not been determined, approximately 200 cases have been described worldwide [1]. Clinical manifestations, including gastrointestinal (GI) and neurological symptoms, first appear in the second decade of life [2] and may lead to a misdiagnosis of anorexia nervosa, inflammatory bowel disease, celiac disease, or Charcot-Marie-Tooth disease. A definitive diagnosis requires detection of biallelic pathogenic TYMP

gene variants with reduced levels of thymidine phosphorylase enzyme activity in peripheral leukocytes and elevated plasma and urine thymidine and deoxyuridine concentrations [3].

CASE REPORT

A 26-year-old female presented with an 8-year history of intermittent diarrhea, abdominal cramping, early satiety, and weight loss for which she had received neither specific diagnosis nor treatment. The patient was 170 cm tall, weighed 40 kg, and her body mass index (BMI) was only 14 kg/m². Anemia, lymphocytopenia, hypoalbuminemia, and coagulopathy confirmed a malabsorption syndrome. Gastrointestinal infections and parasites were excluded. An abdominal ultrasound revealed small intestinal malabsorption syndrome, abdominal lymphadenopathy, and hepatopathy. Endosonography of the pancreas and fecal elastase level were normal. An enteroscopic examination detected jejunal and ileal diverticulosis. Celiac disease, lactase deficiency, and Whipple's disease were histologically excluded. A colonoscopy revealed terminal ileum inflammation consistent with Crohn's disease (CD). Amyloidosis was excluded by rectal biopsy. We ruled out immunodeficiency diseases including human immunodeficiency virus. The patient underwent

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capsule endoscopy, which was complicated by a small bowel obstruction (Fig. 1) necessitating acute surgical intervention. Intraoperative findings included a pathologically convoluted and structurally altered ileum and the impacted endoscopy capsule. A surgical biopsy showed only reactive inflammatory changes. Subsequently, magnetic resonance (MR) enterography revealed jejunal spasticity, terminal ileum stenosis with prestenotic dilation, lymphadenopathy, an elongated stomach, and hepatomegaly (Figs. 2, 3). Based on the above findings, we diagnosed the patient with CD and prescribed corticosteroid therapy. However, the patient refused this treatment, failed to return for her regular appointments, and was lost to follow-up until she returned to our outpatient clinic three years later. During the interval, she had been diagnosed with anorexia nervosa at an outside gastroenterology clinic. Although she had undergone percutaneous endoscopic gastrostomy (PEG) tube placement for delivery of enteral nutrition, the patient was severely malnourished (weight, 34.2 kg; BMI, 11 kg/m²). Her condition gradually worsened over the next year, and we performed a second complete workup.



Fig. 1. Abdominal x-ray showing an impacted endoscopy capsule in the patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).



Fig. 2. CT enterography showing gastrectasia in our patient.



Fig. 3. Abdominal CT reveals hepatomegaly in the patient.

Gastroscopy and colonoscopy showed normal macroscopic findings, but histological examination of random colonic biopsies revealed eosinophilic infiltration. MR enterography confirmed an elongated stomach. A colon transit study recorded a very low bowel motility rate. A high positive level of fecal calprotectin (about 1800 IU) was repeatedly recorded. Immunological and endocrine laboratory test results were within normal limits. We continued enteral nutrition via the PEG tube.

A few months later, the patient was hospitalized with an ileus. Laboratory tests at that time revealed microcytic anemia, coagulopathy, hepatopathy, and severe malnutrition. An ultrasound examination showed intestinal malabsorption. Abdominal computed tomography (CT), CT enterography, and x-ray enteroclysis showed hepatomegaly and a convoluted ileal loop (Fig. 4). These findings and the elevated fecal calprotectin were considered consistent with active CD. Total parenteral nutrition, complete bowel rest, and intravenous corticosteroid therapy were initiated. We ordered a neurological evaluation due to the onset of peripheral neuropathy with atypical sensation in the feet (Fig. 5) and blepharoptosis. Electromyography detected a small fiber neuropathy highly suspicious for Charcot-Marie-Tooth disease (later ruled out by genetic testing). MR imaging (MRI) of the brain revealed extensive symmetric changes within the white matter bilaterally and discrete areas of restricted diffusion in the splenium of the corpus callosum (Fig. 6). Corticosteroid treatment was ineffective. The patient experienced nausea and vomiting due to intestinal stagnation. At that point, we performed a laparotomy and found abdominal ascites (approximately 1000 mL), hepatic cirrhosis, and a convoluted ileal segment (length, 120 cm) with stenosis and no apparent peristalsis. We performed a strictureplasty and terminal ileum resection (length, 30 cm) with an ileal-ascending colon anastomosis and protective ileostomy. The intraoperative liver biopsy showed micronodular hepatic cirrhosis. However, postoperatively, the patient still had problems due to GI dysmotility, and her nutritional status continued to decline. Finally, we implanted a Broviac catheter for long-term parenteral nutrition.

We expected a rare disease because the patient had prolonged and progressive atypical GI and neurological



Fig. 4. X-ray enteroclysis: gastrectasia and a convoluted ileal loop.



Fig. 5. Pes cavus in the 26-year-old patient with MNGIE.

symptoms of unknown etiology. Our suspicion on the diagnosis of MNGIE was confirmed. We assessed serum and urine levels of purines and pyrimidines. The results confirmed a thymidine phosphorylase deficiency. The patient's serum deoxyuridine and thymidine concentrations were elevated to 7.2 $\mu\text{mol/L}$ (reference range up to 0.05 $\mu\text{mol/L}$) and 3.6 $\mu\text{mol/L}$ (reference range up to 0.05 $\mu\text{mol/L}$), respectively, and thymine was not detected. Urine levels of deoxyuridine (36.9

mmol/mol creatinine), thymidine (18.4 mmol/mol creatinine), thymine (7.02 mmol/mol creatinine), and uracil (23.0 mmol/mol creatinine) were elevated. Molecular genetic analysis of the TYMP gene (nine exons and the adjacent introns) revealed a homozygous mutation, c.647C>T (Ala216Val), in exon 6. Genetic testing of the patient's parents identified a heterozygous pathogenic TYMP gene mutation (c.647C>T) in both, establishing them as healthy carriers of MNGIE. We ordered a re-examination of the small intestinal biopsy sample obtained during the patient's first presentation. The histologic findings were chronic enteritis with ulceration and focal diverticulitis, compatible with the diagnosis of MNGIE (Fig. 7 a, b). A radiologist confirmed that the changes noted in the patient's brain MRI were typical of MNGIE.

At the time of this report, the patient is receiving symptomatic care including parenteral nutrition through a Broviac catheter with enteral dietary supplements. The protective ileostomy is still maintained, due to depressed rectal sphincter tone. Presently, she does not require liver transplantation as her liver function is stable. She leads a relatively normal life that includes travelling and is followed by our outpatient nutrition services department. Prospectively, there is hope for gene therapy for our patient, a technique under research and still unavailable.

DISCUSSION

Mitochondrial neurogastrointestinal encephalomyopathy is a rare autosomal recessive disease caused by a mutation in the TYMP gene (previously known as ECGF1) located on chromosome 22q13.32-qter [4] that encodes thymidine phosphorylase. Thymidine phosphorylase is an enzyme that normally catalyzes the degradation of thymidine to thymine [5]. Consequently, MNGIE results in increased cellular thymidine concentration and high serum thymidine levels [3]. The disease is associated with errors and multiple deletions of mitochondrial DNA in the skeletal muscle resulting from miscommunication between nuclear and mitochondrial genomes [6]. Homozygous individuals suffer from multiple symptoms including GI dysmotility with pseudo-obstruction manifested as cachexia, abdominal pain, diarrhea, vomiting, borborygmi, and early satiety. Patients are typically unable to gain weight or increase their body fat percentage in late

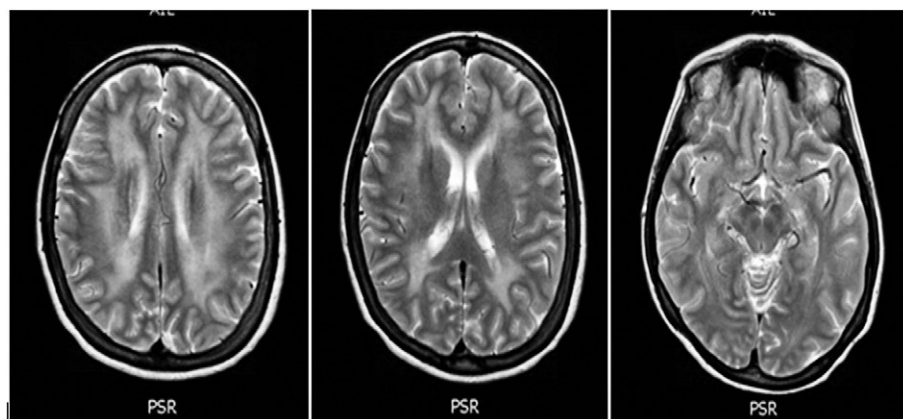


Fig. 6. T2-weighted magnetic resonance imaging of the brain showing diffuse cerebral white matter hyperintensity.

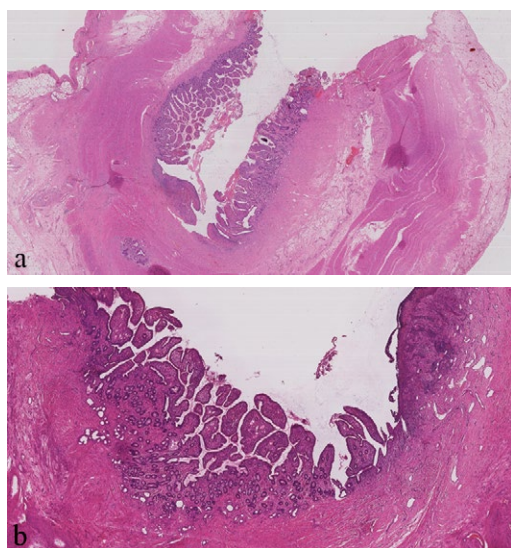


Fig. 7. Histologic evaluation of the small intestinal biopsy: (a) mucosal and submucosal ulcer with granulation tissue at the base of the defect and muscular layer diverticulum; (b) mucosal ulcer with granulation tissue at the base of the defect.

childhood. Diverticulosis, especially atypical small intestinal diverticulosis, can be found in about 67% of patients [3] and may result in intestinal perforation with peritonitis. Radiological studies (x-ray, ultrasound, CT) usually show gastrectasia and intestinal dilation with signs of possible bowel obstruction. Decelerated transit time can be recorded within the GI tract. An endoscopic examination usually determines no macroscopic GI mucosal pathology. Histopathological examination of a biopsy specimen can confirm submucosal ganglion cell eosinophilic cytoplasmic inclusions with abnormal mitochondria, especially in the colorectal mucosa [7]. An upper GI biopsy can verify focal smooth muscle cell atrophy, serosal granulomas, and focal loss and fibrosis of Auerbach's plexus [8]. Typical neurological features are peripheral neuropathy with demyelination of sensory and motor nerves and myopathy causing paresthesia, weakness, and a stocking-glove pattern of sensory loss [4]. A foot deformity (pes cavus) with a high longitudinal arch is frequently found. MNGIE tends to be misinterpreted by neurologists as Charcot-Marie-Tooth disease, but genetic testing rules out this diagnosis. MRI demonstrates diffuse changes within the white matter except for the corpus callosum, confirming brain leukoencephalopathy. Although these changes usually cause no symptoms, the patient may experience blepharoptosis and ophthalmoplegia. Other clinical manifestations can include active hepatic macrovesicular steatosis or cirrhosis with increased liver enzymes. Hepatomegaly is often apparent, and cardiomyopathy occurs in rare cases.

Treatment is primarily symptomatic and supportive; the aim is augment the patient's nutritional intake with enteral or parenteral feeding, and a PEG tube is often needed. Symptomatic treatment of nausea and vomiting is required as these medications control neuropathic symptoms. Management of dysphagia and airway protection are essential measures in severe cases of MNGIE [4]. The clinician should take steps to avoid bacterial overgrowth and infectious complications, and psychological or

psychiatric intervention might also be considered. Currently, there are no proven causal treatments for MNGIE although several novel treatments are under investigation. Allogeneic hematopoietic stem cell transplantation can restore thymidine phosphorylase and improve the clinical condition of patients with MNGIE [9]. However, the relatively high mortality rate associated with this procedure is a prominent drawback. Liver transplantation has also been proposed as a treatment for MNGIE due to the high hepatic thymidine phosphorylase expression that could normalize thymidine levels and decrease serum levels of toxic nucleotides [10]. Other published studies utilized hemodialysis or peritoneal dialysis [11, 12]. Current gene therapy research employs a generated vector containing the coding sequence of the human TYMP gene under the control of a liver-specific thyroxine-binding globulin promoter [13].

CONCLUSION

We presented the case of a patient with MNGIE who exhibited typical features of the disease. MNGIE should be considered in patients with unexplained malnutrition, intestinal dysmotility, and atypical neurological symptoms. The prognosis of patients with MNGIE is poor.

Conflicts of interest: The authors declare that they have nothing to disclose.

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