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Mitochondrial neurogastrointestinal encephalomyopathy: Case report

Mitokondriyal nörogastrointestinal ensefalomiyopati: Olgu sunumu

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Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive multisystem disorder caused by thymidine phosphorylase deficiency. The disease is characterized clinically by ptosis, progressive external ophthalmoparesis, severe gastrointestinal dysmotility, peripheral neuropathy, leukoencephalopathy, and mitochondrial abnormalities. Herein, we describe a patient with mitochondrial neurogastrointestinal encephalomyopathy who presented intestinal pseudoobstruction.

Key words: Mitochondrial neurogastrointestinal encephalomyopathy, intestinal pseudoobstruction, deafness, diabetes mellitus, hypothyroidism

Mitokondriyal nörogastrointestinal ensefalomiyopati, timidin fosforilaz eksikliğine bağlı, otozomal resesif, multisistemik bir hastalıktır. Hastalığın kliniği pitozis, progresif eksternal oftalmoparezi, ciddi gastrointestinal motilite bozukluğu, periferik nöropati, lökoensefalopati ve mitokondriyal anormalliklerle karakterizedir. Burada intestinal psödoobstrüksiyon ile prezante olan mitokondriyal nörogastrointestinal ensefalomiyopati olgusunu sunduk.

Anahtar kelimeler: Mitokondriyal nörogastrointestinal ensefalomiyopati, intestinal psödoobstrüksiyon, sağırlık, diabetes mellitus, hipotiroidizm

INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive multisystem disorder characterized by external ophthalmoplegia and/or ptosis, progressive gastrointestinal dysmotility and abdominal pain, postprandial emesis, cachexia, demyelinating peripheral neuropathy, symmetrical and distal weakness more prominently affecting the lower extremities, and leukoencephalopathy. The disease is caused by mutations in the gene encoding thymidine phosphorylase (endothelial cell growth factor 1) (ECGF1) (1). MNGIE is a rare disorder that presents in childhood and its prevalence is unknown; however, marked delay in diagnosis is common. Fewer than 80 individuals with features consistent with MNGIE disease have been reported since it was first described.

CASE REPORT

We describe a 22-year-old female having chronic intestinal pseudoobstruction. The patient presented to our clinic with nausea, vomiting and abdominal pain. She had a history of chronic diarrhea (no improvement on gluten-free diet), vomiting, bloating, abdominal cramping since the age of 17, and deafness since the age of 19. Five years ago, insulin-dependent diabetes mellitus and hypothyroidism were diagnosed in this patient, and since that time the mentioned symptoms had started and gradually increased. The patient was treated with insulin and L-thyroxin. The family's medical history revealed that the parents of our case were first-degree relatives and that the patient's brother had died from an unknown etiology at the time of a gastric operation at 14 years of age. Clinically, she was cachectic (weight, 32 kg; height, 160 cm). She had abdominal distention, hyperactive bowel sounds, generalized muscle weakness and atrophy, mild bilateral ophthalmoplegia and ptosis, absent tendon reflexes in the lower extremities, and gait ataxia. Cognitive functions were preserved. Other system examinations were interpre-

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ted as normal. Laboratory investigations showed leukocytosis (13,000/mm^3) and venous lactate concentration of 3.8 mmol/L (normal: 0.2-2) with a pyruvate of 0.2 mg/dl (normal 0.3 to 0.9). Other laboratory tests were normal. Esophagogastroduodenoscopy revealed dilated stomach and excess residue without organic obstruction. Radiological studies of the upper digestive tract showed gastroptosis, air-fluid levels in the small intestine, and almost abolished peristalsis below the duodenum, indicating the presence of intestinal pseudoobstruction (Figures 1, 2). Her electrocardiography and echocardiography were normal (ejection fraction: 57%). T2-weighted cerebral magnetic resonance imaging (MRI) showed diffuse white-matter hyperintensity (Figure 3). Magnetic resonance spectroscopy (MRS) showed lactate peak within the white matter. Audiometric studies confirmed sensorineural deafness with profound defects for high frequencies. Electromyography showed a mixed picture of widespread demyelinating sensorimotor polyneuropathy and signs of myopathy. Cerebrospinal fluid white blood cell count and glucose were normal but protein was 140 mg/dl (normal: 20-45 mg/dl). We had planned muscle biopsy but the patient refused. Small bowel mucosal biopsy was evaluated as nonspecific chronic inflammation. We considered this patient as MNGIE on the basis of these findings: cachexia, bilateral ophthalmoplegia and ptosis, chronic intestinal pseudoobstruction, generalized muscle weakness and atrophy, lactic acidemia, sensorineural deafness, leukoencephalopathy, and demyelinating sensorimotor polyneuropathy. As a result, we started antibiotic treatment for bacterial overgrowth, metoclopramide, insulin, L-thyroxin, and parenteral nutrition. As the symptoms of the patient decreased, she was discharged for follow-up in the clinic.

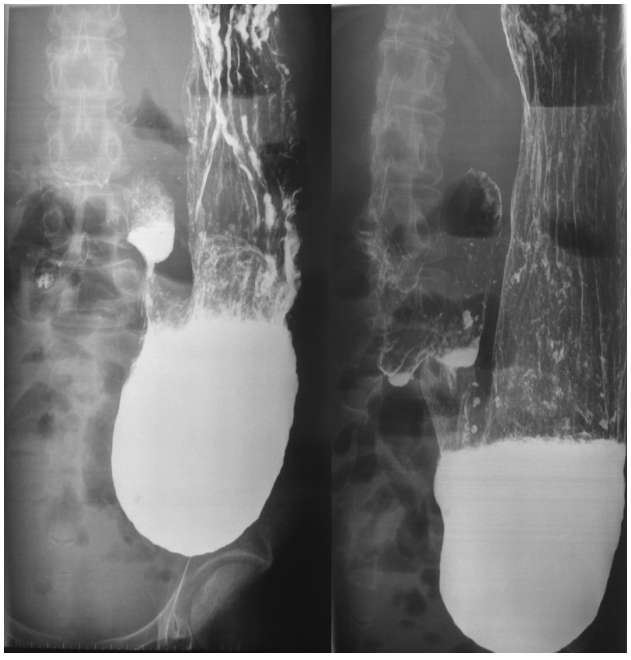

Figure 1, 2. Barium radiography shows ptotic and dilated stomach down to the pelvis and air-fluid levels in the small intestine.

DISCUSSION

Mitochondrial neurogastrointestinal encephalomyopathy is a rare autosomal recessive multisystem disorder. At present, 87 sporadic or familial cases have been reported and 52 different mutations identified (2). Clinically, MNGIE presents between the 1st and the 5th decades, but generally, age of onset is in the second decade (3). Peripheral neuropathy (100%), ophthalmoparesis (85%), ptosis (65%), hearing loss (61%), thin body habitus (100%), limb weakness - muscle wasting (95%), areflexia (40%), and lactic acidemia (64%) are other characteristic clinical features (4). All symptoms described by Hirano et al. (4) were present in our case. In addition, a brother of our patient had died during a stomach operation, which encouraged us to evaluate and consider that the brother had the same disease.

Gastrointestinal symptoms are common in patients with mitochondrial disease. Gastrointestinal dysmotility is caused by the combined effects of neuromuscular dysfunction and autonomic dysfunction (4). However, the pathophysiology of the gastrointestinal symptoms associated with mitochondrial disease remains uncertain (5). Nausea and vomiting due to intestinal pseudoobstruction are the main gastrointestinal symptoms. In many, nausea and vomiting are presumed secondary to lactic acidosis, which is known to induce gastric stasis (6). This was supported by the increase in the lactic acid level in our case. The major clinical finding in our case was chronic intestinal pseudoobstruction. Chronic intestinal pseudoobstruction is a rare disorder of gastrointestinal motility where coordinated contractions in the intestinal tract become altered and inefficient. In the beginning, we considered autonomic neuropathy as a differential diagnosis as both diabetes mellitus and gastroparesis were present in our case. However, this diagnosis was eliminated as both the symptoms and diabetes mellitus type-I had the same onset (both started at the same ti-

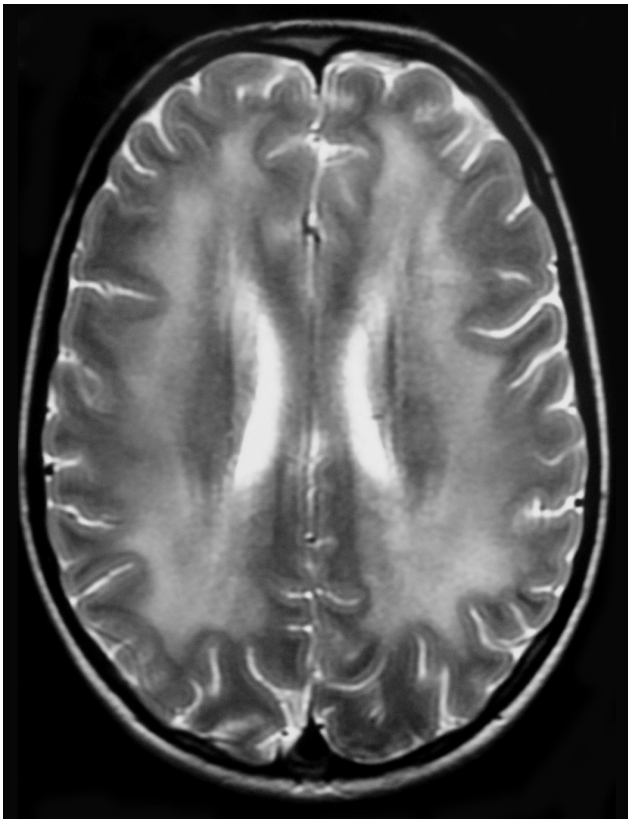

Figure 3. T2-weighted magnetic resonance imaging (MRI) of demyelinization of deep white matter.

me) and also because the other symptoms were incompatible with this diagnosis. Small bowel biopsy was evaluated as nonspecific chronic inflammation, but full-thickness small bowel biopsy was not available; therefore, serosal granulomas in full thickness biopsy of the small intestine and focal loss of Auerbach's plexus with fibrosis could not be shown, as declared in the literature (7).

The main neurological symptoms were peripheral neuropathy and leukoencephalopathy. All individuals with MNGIE disease have peripheral neuropathy. In some, the first symptoms are paresthesias and weakness. The weakness is usually symmetrical and distal (4). The level of arylsulfatase-A was within normal ranges. Cranial nerve involvement in MNGIE usually takes the form of ophthalmoplegia and sensorineural hearing impairment (8). An audiology examination of the patient showed sensorineural hearing impairment.

As the patient had combined diabetes mellitus and hypothyroidism, polyglandular autoimmune syndrome was considered for definitive diagnosis, which was later excluded as other findings of the patient did not correspond with this diagnosis. In MNGIE, endocrinopathies have already been reported as additional features, more frequently in the form of diabetes and hypoparathyroidism, whereas hypothyroidism and hypogonadism are less common (9).

Several drugs have been tried in mitochondrial diseases (like coenzyme Q10, vitamin E, vitamin K3, vitamin C, carnitine), but data on their clinical efficiency in MNGIE are lacking; in addition, hemodialysis to reduce thymidine level does not seem to be effective (10, 11).

In conclusion, we should bear in mind the mitochondrial genetic disturbances in the etiology of chronic intestinal pseudoobstruction, especially when it is associated with neurological symptoms.

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