Chronic Intestinal Pseudo-obstruction and Neurological Manifestations in Early Adulthood: Considering MNGIE Syndrome in Differential Diagnosis

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Abstract

The mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) is a rare and life-threatening, autosomal recessive, multisystem disorder, caused by the mutations in the thymidine phosphorylase gene. Herein, we report a case of a 21 year-old male with a long history of intestinal pseudo-obstruction who was diagnosed with MNGIE syndrome after an extensive examination. In this case, our objective was to bring the gastroenterologist's attention to this difficult to diagnose syndrome in the coexistence of intestinal pseudo-obstruction and neurologic manifestations. The patient was a member of a consanguineous family of six children, in whom two sisters had died due to this disorder and one sister was affected and is still alive. The patient presented with cachexia, abdominal pain, diarrhea and muscle weakness, and was previously considered to have gluten sensitive enteropathy and treated with dietary solutions.

Key words

Intestinal pseudo-obstruction – neurologic symptoms – MNGIE Syndrome

Introduction

Among the important consequences of MNGIE syndrome, multiple deletions and/or depletion of mitochondrial DNA (mtDNA) is observed [1]. Clinical appearance of MNGIE can be heterogeneous, but it usually is initiated by the symptoms of gastrointestinal dysmotility, such as diarrhea, vomiting and intestinal pseudo-obstruction. Other clinical hallmarks are: ophthalmoparesis, pitosis, cachexia, sensorimotor peripheral neuropathy, proximal muscle weakness and leukoencephalopathy. The onset of the symptoms is usually before the age of 20. Life expectancy is limited and death usually occurs during the third or fourth decades generally due to cachexia and intestinal complications [2].

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Case report

A 21 year-old male was admitted to our hospital with chronic weight loss, cachexia, abdominal pain and diarrhea attacks for the last three years and walking impairment since a few months. No specific disease had been evidenced in spite of previous hospitalizations several times at various institutions. He had been finally advised a therapeutic trial of gluten free regimen because of equivocal findings associated with celiac disease but his symptoms were not resolved. He was a member of a consanguineous family of six children. Two sisters suffered from similar symptoms and had died and one sister is affected but still alive.

The patient was cachectic (weight: 31 kilogram, height; 155 cm, and body mass index: 12.9 kg/m^2) and physical examination revealed external ophthalmoplegia, proptosis and ataxia. He had generalized muscle weakness and sensory neuropathy in the extremities with absent tendon reflexes. Upper gastrointestinal endoscopy revealed no specific findings and the pathological examination of duodenal biopsy specimen was not compatible with gluten sensitive enteropathy (GSE). Also specific antibodies for GSE were negative in the patient's serum. Direct radiography revealed air-fluid levels in the small intestinal segments (Fig. 1) and showed diffuse thickening of the small intestinal wall following diluted barium ingestion. The mucosal folds could not be observed clearly, but the passage appeared to be normal on imaging (Fig. 2) Endoscopic examination of the large bowel was normal.

Considering the neurologic symptoms, an electromyography was performed and revealed bilateral sensorimotor neuropathy especially in the lower extremities. T2-weighted brain magnetic resonance imaging (MRI) showed an increased signal, affecting the subcortical and periventricular white matter of both hemispheres (Fig. 3).

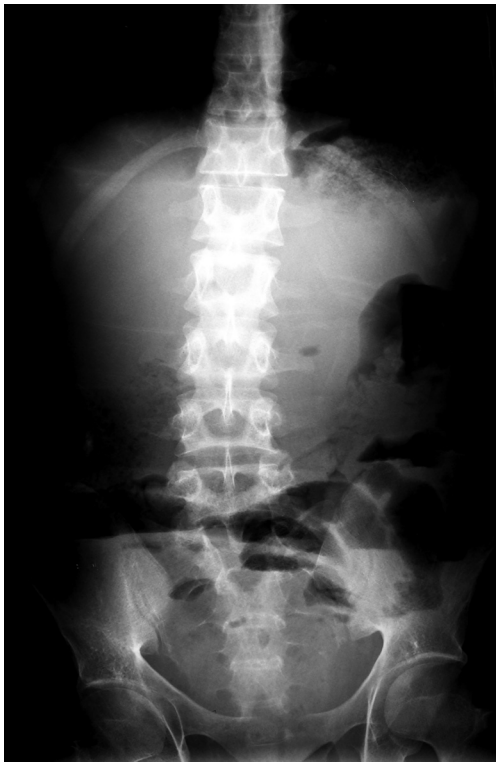

Fig 1. Abdominal radiography revealed air-fluid levels in the small intestinal segments.

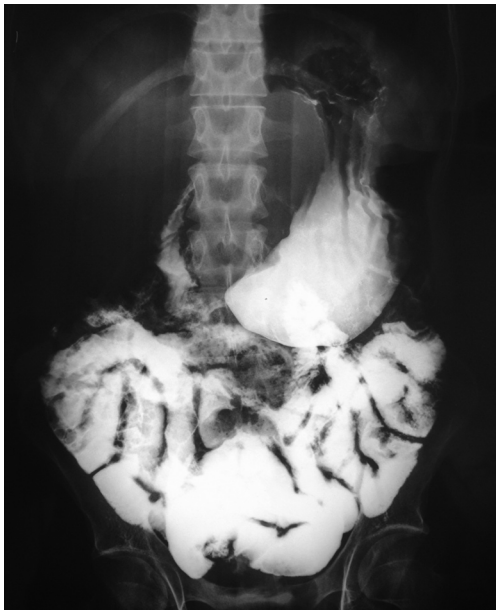

Fig 2. After diluted barium ingestion, radiography showed diffuse thickening of the small intestinal walls. The mucosal folds could not be observed clearly, but the passage appeared to be normal.

Based on the phenotypic manifestations, radiological findings and also the family history, MNGIE disorder was suspected. For the definitive diagnosis we performed genetic testing. Genomic DNA was extracted from peripheral blood using standard procedures. DNA samples were PCR amplified using sequence specific primers for the coding

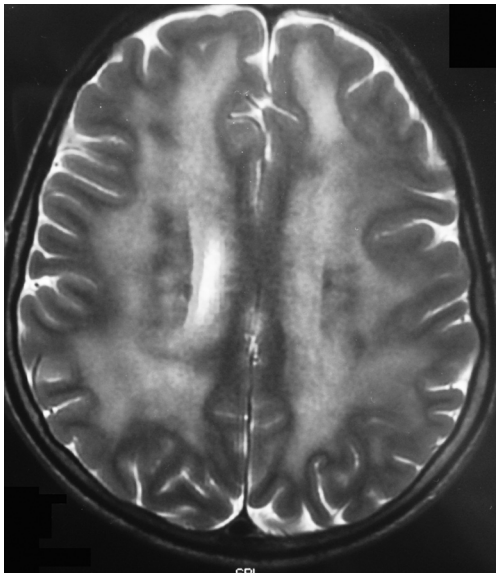

Fig 3. T2-weighted brain magnetic resonance imaging showed increased signal, affecting the subcortical and periventricular white matter of the both hemispheres.

exons of the thymidine phosphorilase gene. Amplified products were cycle-sequenced on ABI prism 3130 DNA sequencing system. Our patient was found to be homozygote for a mutation in chromosome 22q13.32-ter Exon 8 at T5162C and this caused a GCT to GCC codon change. Reflecting itself as L371P at the protein level [3], the patient was diagnosed with MNGIE syndrome.

After a three weeks supportive treatment including antibiotics, intravenous fluids and parenteral nutrition, his symptoms resolved partially and he was discharged to be followed up on an outpatient basis.

Discussion

MNGIE syndrome is a multisystemic disorder with manifestations in mitochondrial DNA, which results in intestinal pseudo-obstruction and neuro-ophthalmologic abnormalities and caused by mutations in the thymidine phosphorylase gene [4, 5]. Clinical presentation can be variable. Approximately 45-67% of patients have had a gastrointestinal complaint as the presenting symptom, including nausea, vomiting, abdominal pain, diarrhea and weight loss. Most of these symptoms suggest a possible malabsorption syndrome. If neurologic symptoms are present, GSE should be involved in the differential diagnosis because GSE long has been associated with neurologic and psychiatric disorders including cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, and depression [6].

Although clinical manifestations are relatively constant in MNGIE syndrome, age of onset and disease progression are quite variable. These symptoms determine physicians to misdiagnose the condition as a malabsorption syndrome such as GSE, as happened in our patient. Although he had a strong family history, he could not be diagnosed previously because the other members of the family, affected by MNGIE, could

not be examined in a tertiary hospital since they were natives of a small village. The L371P mutation has been previously documented in Turkish and Italian patients and this case further suggests a plausible Mediterranean origin for this variation.

The diagnosis of MNGIE was based upon the criteria described by Hirano et al [8]: 1) ptosis and/or ophthalmoparesis; 2) gastrointestinal dysmotility; 3) peripheral neuropathy; 4) ragged-red fibers or succinate dehydrogenase activity in muscle biopsy [1]. Also the diagnosis can be supported by brain MRI demonstrating leukodystrophy. Direct evidence for diagnosis is obtained with genetic studies revealing mtDNA defects in peripheral blood or muscle biopsy specimens.With his gastrointestinal and neurologic symptoms, abnormal MRI and electromyography findings, our patient met almost all these criteria and diagnosis was confirmed with genetic testing.

The poor quality of life and early death in patients with MNGIE call for a treatment, but so far, therapy has largely been supportive, including total parenteral nutrition, pain relief, and treatment of infections. Abdominal pain was treated with some success in a patient by celiac plexus neurolysis [7]. Hemodialysis is another treatment strategy but re-accumulation of the nucleosides is too rapid. Recently, two other treatment strategies have been suggested: allogenic stem cell transplantation and platelet infusion, showing promising results [8].

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