
Case Report

Mitochondrial Neurogastrointestinal Encephalomyopathy

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Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive disorder in which a nuclear mutation of the thymidine phosphorylase gene leads to mitochondrial genomic dysfunction. Herein, we report a 29-year-old Iranian man with abdominal pain, diarrhea, hearing loss, ophthalmoplegia, sensorimotor axonal neuropathy, and elevated muscle enzymes. Magnetic resonance imaging showed leukoencephalopathic changes. Metabolite analysis revealed a very high thymidine concentration in the patient's urine consistent with the diagnosis of mitochondrial neurogastrointestinal encephalomyopathy.

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Introduction

Mitochondrial neurogastrointestinal encephalo-myopathy (MNGIE) is a rare autosomal recessive disorder in which a nuclear mutation of the thymidine phosphorylase gene leads to mitochondrial genomic dysfunction. Such patients suffer from gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoparesis, myopathy, and polyneuropathy. Magnetic resonance imaging (MRI) shows leukoencephalopathy.^{1,2}

Herein we describe the clinical, biochemical, and neuroradiological features of a case of MNGIE from south of Iran.

Case Report

A 29-year-old Iranian man was referred with abdominal pain, diarrhea, distal muscle weakness, and ophthalmoplegia. At the age of 26, he insidiously developed anorexia, nausea and vomit-

ing, colicky abdominal pain, severe weight loss, bloating, and intermittent constipation and diarrhea. His sister had exactly the same gastrointestinal and neurological manifestations accompanied by primary ovarian failure. The patient had also two brothers who had been passed away because of cardiomyopathy and liver failure, respectively. His parents were relative but healthy.

Co-enzyme Q10 and plenty of vitamins had been prescribed as empirical therapy but the patient's condition had not been improved. Hyperalimentation therapy was started for him but his weight gain and functional improvement was not significant. After 3 years, he became wheelchair bound but his mentality did not change significantly.

His height was 155 cm and he weighed about 32 kg. Abdominal examination revealed increased bowel sounds. He had problem in concentration, recall, and visuospatial orientation.

Neurological examination revealed ptosis and external ophthalmoplegia with difficulty in pursuit movements, absent gag reflex, mild nasal speech, distal muscle weakness, absent tendon reflexes, and glove and stocking sensory loss.

Routine blood tests were normal except for low blood urea nitrogen, mild anemia and thrombocytosis, increased levels of lactate dehydrogenase, and creatine kinase.

Small bowel radiography revealed significant

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dilatation of stomach, duodenum, and ileum with delayed contrast movement. Omental and peritoneal biopsies showed severe congestion with leukocyte margination in small vessels. Ileum wall had congestion, edema, and lymphangiectasia with acute and chronic inflammation. Jejunal wall showed mild chronic inflammation with edematous villi. Evaluation of mesenteric lymph node biopsy showed reactive follicular hyperplasia. In liver wedge biopsy severe diffuse fatty change was detected. The above-mentioned histologic changes were all seemed to be secondary to obstruction.

Brain MRI revealed confluent lesions, which were hypointense in T1 weighted image and hyperintense in T2 weighted image in favor of diffuse leukodystrophic changes in the periventricular white matter and centrum semiovale (Figure 1). Nerve conduction studies and electromyography revealed diffuse sensorimotor axonal neuropathy. Bilateral

sensorineural hearing impairment was evident in pure tone audiometry.

Concentrations of pyrimidines and purines in urine were determined by reversed-phase high performance liquid chromatography (HPLC), which was used by modification of the method described by Simmonds and colleagues.³ The metabolite analysis revealed a very high thymidine concentration and high thymidine/creatinine ratio in the patient's urine. However no thymidine was detected in the urine samples of the parents, and the patient's brother (Table 1). We also found very high thymidine concentration in the patient's plasma, but not in the plasma of any his relatives. Findings were consistent with the diagnosis of MNGIE.

Discussion

MNGIE is a rare mitochondrial disorder, which occurs secondary to mitochondrial genomic dysfunction. The pattern of inheritance is autosomal recessive and is caused by nuclear mutation of thymidine phosphorylase gene.^{1,2,4}

Progressive external ophthalmoplegia, severe gastrointestinal dysmotility, cachexia, and peripheral neuropathy are among the clinical manifestations of this disease. Diffuse leukoencephalopathy can usually be found on brain MRI. The average age at the onset of the disease is the late teen ages, and death ensues usually by 40 years.²

The gene specifying thymidine phosphorylase, which is located on chromosome 22q13.32-qter,^{5,6} when mutated can lead to MNGIE. To date all affected individuals have had homozygous or compound heterozygous mutations. While in normal individuals homeostasis of plasma thymidine level is maintained by phosphorylytic catabolism of thymidine to thymine; however in patients who are suffering from MNGIE, there is a dramatic rise in plasma thymidine levels (up to 50-fold) secondary to thymidine phosphorylase enzyme activity.⁶

Definite diagnosis is made by measurement of leukocyte thymidine phosphorylase, which is absent or severely diminished in patients but decreased to 40 – 85% in carriers.²

Mitochondrial DNA is hypothesized to be susceptible to increased thymidine, because mitochondrial deoxythymidine pyrophosphate pools are dependent on the thymidine salvage pathway,⁶ producing depletion and deletions in

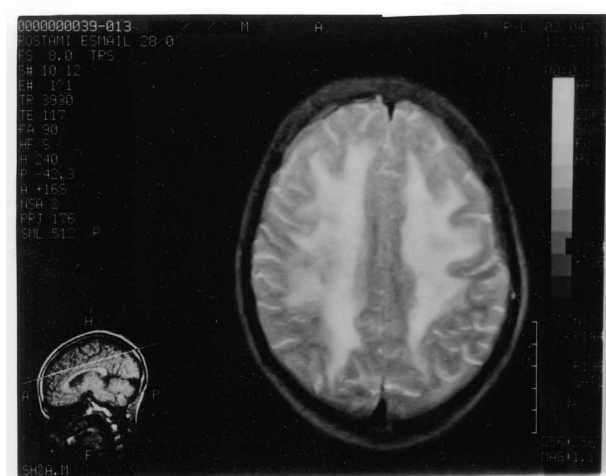
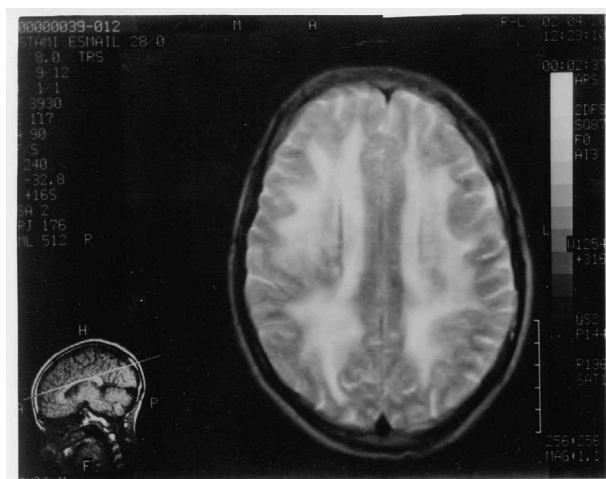


Figure 1. T2-weighted MRI (0.5 T; TR, 3620 ms; TE, 120 ms) shows diffuse leukodystrophic changes in the periventricular white matter and centrum semiovale

Table 1. Urine biochemical analysis of the patient and his first degree relatives

	Creatinine mmol/l(g/L)	Thymidine μmol/L	Thymidine mmol/mol Creat.	Thymidine μmol/mg Creat.	Uric acid mmol/mol Creat.	Xanthine mmol/mol Creat.
Patient	3.94 (0.45)	509	129	1.13	299	ND
Mother	12.07 (1.37)	ND	ND	ND	360	6
Father	13.13 (1.49)	ND	ND	ND	104	ND
Brother	8.22 (0.93)	ND	ND	ND	113	ND

ND= not detected, Creat.=creatinine

mitochondrial DNA over time.

At present no definite treatment is available for MNGIE however it is proposed that allogeneic stem cell transplantation may correct the biochemical derangements in such patients.⁷ There is also a recent report of clinical benefit of peritoneal dialysis for gastrointestinal symptoms in a patient with MNGIE.⁸

Although our case is not the first published report from Iran,⁹ some characteristics such as family history of ovarian failure make it noteworthy to report. The patient had a sister with exactly the same clinical manifestations accompanied by primary ovarian failure who died some years earlier. It is highly possible that his sister was also suffered from MNGIE.

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