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Case Report

Atypical clinical and neuroradiological presentation in a patient with mitochondrial neurogastrointestinal encephalomyopathy with anterior leukoencephalopathy

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Abstract. The clinical presentation of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is somewhat varied. Here we report a 14 year old patient who had been followed for iron and zinc deficiency anemia since 1 year old and who did not respond to several regimes of iron and zinc therapy. He was diagnosed with MNGIE when he had developed opthalmoplegia at 14 years of age. In contrast with a diffuse leukoencephalymyopathy generally seen in MNGIE patients, cranial MRI showed that the leukoencephalopathy was localized mainly to the frontal lobes of the patient at his first admission.

Key words: MNGIE, anemia, leukoencephalopathy

1. Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease caused by mutations in the gene encoding thymidine phosphorylase (ECGF1) (1). In patients with MNGIE, severe reduction of thymidine phosphorylase (TP) activity results in systemic accumulation of its substrates, thymidine (dThd) and deoxyuridine (dUrd).

The disease is characterized by progressive external ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, leukoencephalopathy, and mitochondrial dysfunction with alterations in mitochondrial DNA (mtDNA) (2-4).

MNGIE syndrome is a rare disorder in childhood; however, marked delay in diagnosis is common. Here we report a patient who had been followed for iron and zinc deficiency anemia and who did not respond to several regimes of iron and zinc therapy. He had been investigated for many years and was diagnosed with MNGIE when he developed ofthalmoplegia at 14 years of age. Another interesting point about this patient is that brain magnetic resonance imaging (MRI) showed leucoencephalopathy only at the frontal lobes at his first admission and that the leucoencephalopathy became more prevalent later on.

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2. Case report

A 14 year old boy was admitted to our clinic with opthalmoplegia which occurred 1 year before admission. We have learned that he had been followed up for recurrent abdominal pain and vomiting attacks in the Pediatric Gastroenterology Department for 6 years without any clear etiology. Also he had been followed up in the Pediatric Hematology Department since 1 year old for iron and zinc deficiency which was refractory to therapy. Although he had taken several regimens of iron and zinc therapy he still has low amounts of iron and zinc. The etiology of the iron and zinc deficiency anemia was investigated; the dietary habbits were not considered to be the reason because he had enough food that was rich in iron

and zinc. Fecal occult blood test and parasitologic stool analysis were negative. At the age of 8, he had recurrent abdominal pain and vomiting approximately twice a month, The abdominal ultrasonagraphy was normal, upper gastrointestinal endoscopy showed only mild antral gastritis and esophagitis. Although he was given omeprazole therapy for two months there was no difference of his abdominal symptoms. As he was unresponsive to the specific treatment with iron and zinc, he was investigated for Cheliac disease (CD). Measurement of antigliadin IgA and IgG and antiendomysial IgA were negative. The biopsy of small intestine was normal and *Helicobacter pylori* was not detected. At the age of 13 he developed opthalmoplegia, especially upward gaze palsy. He was admitted to our clinic at 14 years of age. He was cachectic, he had total ophtalmoplegia and pes cavus deformity with absent deep tendon reflexes and mild muscle atrophy especially in lower extremities. He was born to consanguineous parents (cousins). He has a healthy 18 years old brother. His mother had been followed for toxic hepatitis due to the use of analgesic medication and his father had chronic active hepatitis due to a hepatitis B infection.

Serum lactate and pyruvate levels were within normal limits. Electrophysiologic studies revealed axonal and demyelinating sensorimotor neuropathy. Brainstem auditory evoked response study was normal. The T2-weighted brain MRI showed leukoencephalopathy especially in frontal regions (Figure 1).

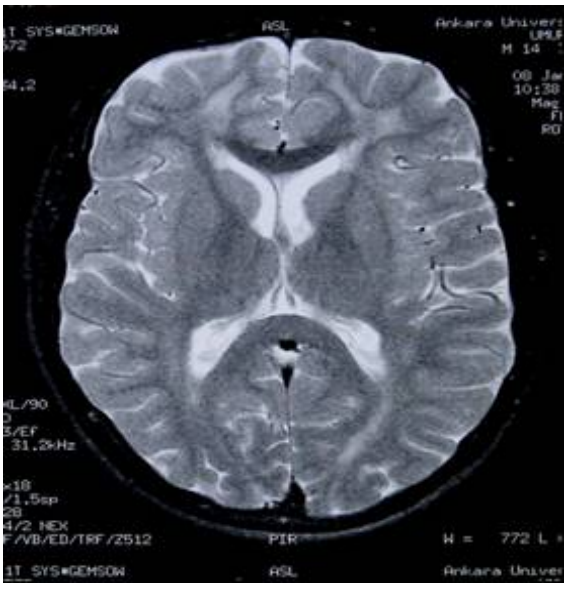

Fig. 1. T2-weighted brain MRI showing leukoencephalopathy especially in frontal regions.

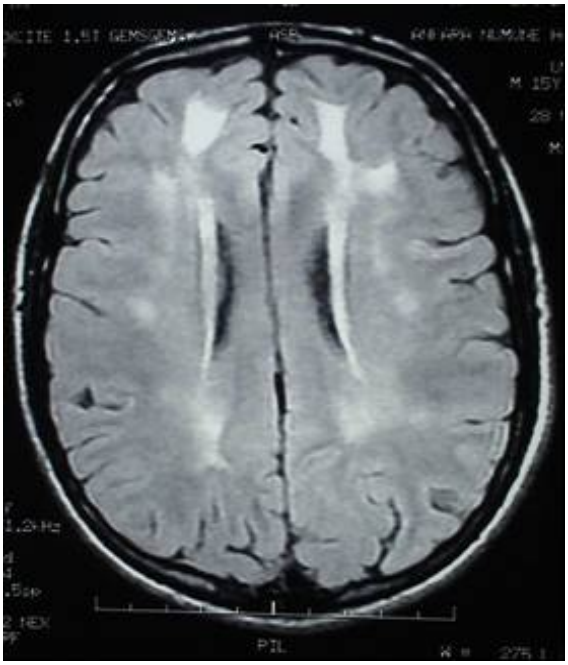

Fig. 2. T1- weighed brain MRI (one year after the first brain MRI) showing that leucoencephalopathy had spread to other periventricular areas other than frontal regions.

One year later the leucoencephalopathy had spread to other periventricular areas (Figure 2). Magnetic resonance spectroscopy (MRS) did not show any lactate-peak and NAA/cholin, cholin/creatinin ratios were within normal limits (Figure 3). TP activities, thymidine levels and molecular genetic studies were assessed according to established methods (5).

Thymidine phosphorylase: 26 nmol/h/mg-protein, (n:634±212). Plasma thymidine: 6.8 micromol/L ($n<0.05$). Plasma deoxyuridine: 8 micromol/L ($n<0.05$).

He has a homozygote for mutation G to A at nucleotide 839 of the ECGF1 cDNA sequence, resulting in a leucine to proline substitution at amino acid 371 of protein. This mutation occurs frequently in the Turkish MNGIE patients.

4. Discussion

The clinical presentation of MNGIE is somewhat varied. Between 45 and 67% of patients have a gastrointestinal complaint as their presenting symptom. These complaints typically include nausea, vomiting, abdominal pain, and/or diarrhea. Neurologic (including hearing loss, weakness, and peripheral neuropathy) or ocular symptoms are the initial manifestation in 42 to 49%. Thin body habitus is a universal finding with the average adult weight for men and women being 37.8 to 40.3 kg and 35.5 to37.5 kg, respectively.

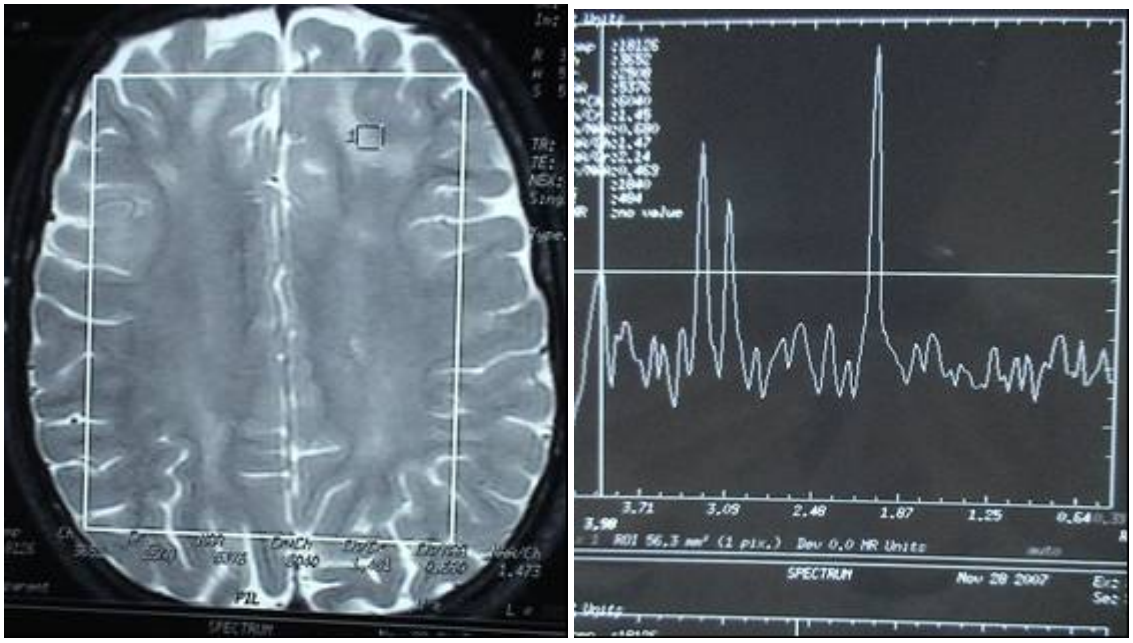

Fig. 3. MRS did not show any lactate-peak and NAA/ cholin, cholin/creatinin ratios were in normal limits.

The etiology of this is thought to be multifactorial including malnutrition from inadequate intake (due to nausea, emesis, and abdominal pain), malabsorption and increased metabolic demand secondary to inefficient production of ATP within the mitochondria. 30 to 67% of patients previously reported have small bowel diverticula, a finding that often heralds systemic pathology (6).

Although our patient had been followed with iron and zinc deficiency anemia since 1 year old and recurrent abdominal pain since 8 years old, he was able to be diagnosed with MNGIE when he had developed opthalmoplegia at 14 years of age. Other reasons for the anemia, like inadequate dietary intake of iron and zinc, parasitic infection of the GIS and occult blood loss from GIS, were excluded. Malabsorption related with CD and *Helicobacter pylori* infection were also excluded.

Gastrointestinal dysmotility is the most prominent and severe clinical feature in MNGIE. This is mainly characterized by dysphagia, borborygmi, gastroparesis, early satiety, abdominal cramps, nausea, vomiting, intestinal pseudo-obstruction, and diarrhea that lead to progressive weight loss and cachexia of the patient. Giordano et al. reported that the GI dysmotility in their patient with MNGIE is mainly caused by myopathy of the small intestine wall. This was limited to the external layer of muscularis propria where marked mitochondrial proliferation and profound mtDNA depletion were found. They also showed that in normal subjects, the small intestine has a constitutive lower amount of mtDNA copy number compared with the other segments of the GI tract. This may significantly predispose MNGIE patients to visceral myopathy and development of small intestine dysmotility (7).

Small intestinal hypomotility is an important cause of small intestinal bacterial overgrowth (8). Intestinal motility represents one of the major control systems of gut microflora, through the sweeping of excessive bacteria from the lumen (9). We think that the etiology of the anemia which is nonresponsive to the therapy is the result of malabsorption due to this bacterial overgrowth.

As seen in our patient the diagnosis of MNGIE is very difficult before the neurological system involvement, so it is very important to think MNGIE in the differential diagnosis of a patient with gastrointestinal symptoms and neurological symptoms like progressive external ophthalmoplegia and peripheral neuropathy because there is some potential new emerging therapies like allogeneic stem cell transplantation. Hirano et al. reported two patients whose biochemical abnormalities in the blood and some clinical symptoms were corrected with allogeneic stem cell transplantation (10). Early diagnosis will offer a

better response to the therapy as the disease has a progressive course in following years.

Another interesting point about our patient is the cranial MRI findings as the leukoencephalopathy is localized mainly to the frontal lobes at his first admission (Figure 1). One year later the leucoencephalopathy had spread to other periventricular areas (Figure 2). In patients with MNGIE brain MRI usually shows diffuse leukoencephalopathy affecting predominantly the periventricular white matter of the cerebral hemispheres, corpus callosum, and brainstem (2,6,11,12). Gamez et al. reported a 29-year-old woman diagnosed with MNGIE, who presented with marked ophthalmoparesis and ptosis. Her T2-weighted brain MRI showed multiple small areas of increased signal affecting the periventricular white matter of the frontal lobes and corpus callosum (11). So it can be hypothesized that leucoencephalopathy may begin at the frontal lobes in MNGIE. As our patient's age is early teens we could be able to see the initial phases of the leukoencephalopathy. There are few neuroradiology studies about the MNGIE patients. Miller et al. showed that involvement of the corpus callosum as well as the capsular white matter, basal ganglia, thalami, midbrain, pons, and cerebellar white matter is not rare and does not preclude the diagnosis of mitochondrial neurogastrointestinal encephalomyopathy (13).

The presumed pathogenesis of white matter lesions in MNGIE can be related to the enzyme thymidine phosphorylase which is chemically and immunochemically identical to the ''gliostatin''. Gliostatin is a polypeptide which can evoke neuronal survival and neuritogenic actions on central neurons and plays an essential role in the neuron-glial interaction during development or regeneration of the central and peripheral nervous system both inhibiting glial growth and promoting endothelial cell proliferation (14). Although white matter changes are diffuse ın MNGIE, interestingly, no one had any overt symptoms attributable to leukoencephalopathy, such as gross dementia or spasticity (15). Van Goethem et al. reported a family with features of MNGIE but no leukoencephalopathy in which two patients carry three missense mutations in POLG, of which two are novel mutations. The presence of pseudo-MNGIE patients without typical leukoencephalopathy indicates that brain MRI is useful to confirm the diagnosis (16).

The brain MRS of our patient did not show any lactate-peak. Also NAA/cholin, cholin/creatinin ratios were within normal limits (Figure 3). This situation may be related to the early stages of the disease in our patient. Schüpbach et al. reported that, MRS of patients with MNGIE revealed a reduction of NAA and choline in the severely affected areas. This might indicate loss of neurons, axons, as well as glial cells. The lack of a reduction in the less affected white matter indicates that MRS is not able to detect metabolite changes earlier than conventional MRI detects white matter abnormalities indicative of leukoencephalopathy (12).

As a result, a MNGIE patient can have an unexpected presentation related to GIS involvement like an iron and zinc deficiency anemia unresponsive to the therapy because of malnutrition. Brain MRI findings can change with time, therefore, these changes may be useful in follow up examinations.

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