



Mitochondrial neurogastrointestinal encephalomyopathy: imaging and clinical findings in three patients

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ABSTRACT

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare multisystemic autosomal recessive disorder characterized by ptosis, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy. We aimed to raise awareness in radiologists regarding this difficult-to-diagnose syndrome, which occurs in the presence of coexistent gastrointestinal dysmotility, cachexia, and neurologic manifestations. We report imaging and clinical findings of three patients with MNGIE. Our findings indicate that early diagnosis of the disease, together with the timely treatment of acute intercurrent illnesses, may retard the progression of MNGIE.

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease associated with multiple deletions and depletion of mitochondrial (mt)DNA in skeletal muscle (1, 2). In 1976, Okamura et al. (3) described the first patient as having congenital oculoskeletal myopathy with abnormal muscle and liver mitochondria. Since then, numerous individuals with MNGIE have been described (1, 2–6). Progressive external ophthalmoplegia, severe gastrointestinal dysmotility, cachexia, and peripheral neuropathy are the clinical manifestations of this disease. Diffuse leukoencephalopathy can usually be found on brain magnetic resonance imaging (MRI). Radiologists should alert other clinicians of the possible presence of MNGIE in patients with leukoencephalopathy on brain MRI in the presence of accompanying cachexia and neurological symptoms. We discuss herein three of our patients who fulfilled the clinical, laboratory, radiological, and genetic criteria for MNGIE.

Case reports

Case 1

A 19-year-old female was admitted to our gastroenterology department with nausea, vomiting, and abdominal pain. She reported a history of monthly attacks of abdominal cramping, chronic diarrhea, and vomiting since the age of 16. She was among seven children of consanguineous parents, and three of her sisters had died because of MNGIE. She was cachectic (height, 165 cm; weight, 39 kg; body mass index [BMI], 14.2 kg/m²). She had generalized muscle weakness, bilateral ptosis, and ophthalmoplegia. Her cognitive functions, vital signs, and other general examinations were normal. Laboratory findings showed an elevated blood leukocyte level (12 500/mm³). Esophagogastroduodenoscopy revealed a hypotonic, dilated stomach, enlarged to the pelvis, with food products and antral gastritis. Barium enema of the colon and radiologic examination of the small intestine were normal, but discharge was delayed. Her echocardiography and electrocardiography were normal. Electromyography (EMG) showed sensorimotor demyelinating polyneuropathy. Brain MRI revealed bilateral widespread cerebellar and cerebral white matter hyperintensities on fluid-attenuated inversion-recovery (FLAIR) and T2-weighted images, and hypointensities on T1-weighted images (Fig. 1). Her corpus callosum and bilateral subcortical U-fibers, head of the caudate nucleus, thalamus, basal ganglia, and brainstem were spared. There was elevated diffusion on the apparent diffusion coefficient (ADC) map, and no enhancement with contrast administration.

Case 2

A 22-year-old male was admitted to our general surgery department with vomiting and abdominal cramping. He reported a history of treat-

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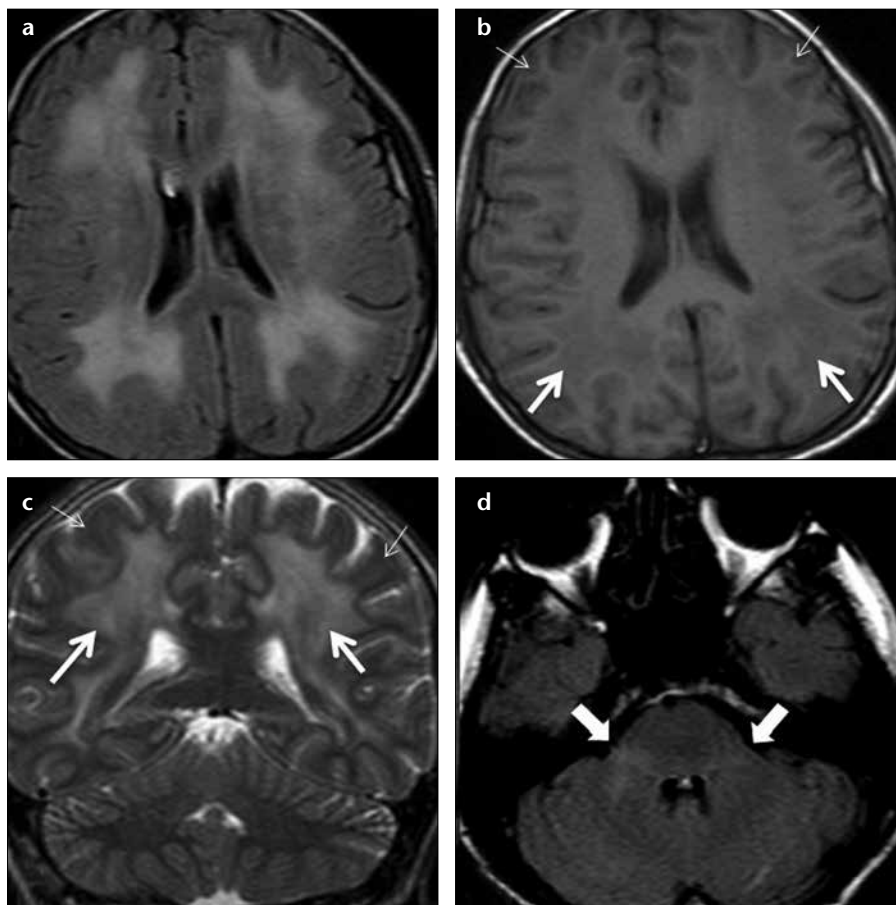


Figure 1. a–d. MR images in a 19-year-old female with MNGIE (case 1). Axial FLAIR image (TR/TE, 6000/100; TI, 2000) (a) shows an abnormally high signal intensity in the bilateral periventricular white matter. Axial T1-weighted image (TR/TE, 462/11) (b) shows an abnormal hypointensity in the bilateral deep white matter (*thick arrows*). Note the sparing of subcortical U-fibers (*thin arrows*). Coronal T2-weighted turbo spin echo (TSE) image (TR/TE, 4500/100) (c) shows an increased signal intensity in the bilateral periventricular white matter (*thick arrows*) and spared subcortical U-fibers (*thin arrows*). Axial FLAIR image (TR/TE, 6000/100; TI, 2000) (d) shows an abnormally high signal intensity in the bilateral middle cerebellar peduncle (*arrows*).

ment for Crohn's disease over five years in an outside center. His first diagnosis was an intestinal obstruction from severe vomiting attacks. He was cachectic (height, 171 cm; weight, 35 kg; BMI, 12.2 kg/m²). He had hearing loss, generalized muscle weakness, and bilateral ptosis. His cognitive functions, vital signs, and other general examinations were normal. Laboratory findings showed an elevated blood leukocyte level (17 400/mm³) and serum lactate dehydrogenase level (398 U/L). Barium enema of the colon and radiologic examination of the small intestine were normal. Mechanical obstruction was not present in any segment. Left-sided sensorineural hearing impairment was evident on pure tone audiometry. EMG showed sensorimotor demyelinating polyneuropathy. Brain MRI revealed bilateral, widespread, and symmet-

rical periventricular and supraventricular white matter hypointensities on T1-weighted images, and hyperintensities on FLAIR and T2-weighted images. His corpus callosum and bilateral subcortical U-fibers, head of the caudate nucleus, thalamus, basal ganglia, and brainstem were spared (Fig. 2). There was no enhancement with contrast administration, and there was elevated diffusion on the ADC map.

Case 3

A 25-year-old male was admitted to our emergency department with severe nausea, vomiting, and fever. He was a member of a consanguineous family of four children, and two of his brothers had died of unknown causes. His physical examination revealed a blood pressure of 60/35 mmHg and a heart rate of 150 beats per minute; he

was cachectic (height, 169 cm; weight, 35 kg; BMI, 12.3 kg/m²) and had diminished turgor tonus. Laboratory findings showed an elevated blood leukocyte level (17 300/mm³) and serum lactate dehydrogenase level (310 U/L), and mild anemia. Other laboratory tests were in normal limits. He was referred to the gastroenterology department. Central venous catheter was inserted for hyperalimentation treatment. His parents reported that he had a history of abdominal cramping, chronic diarrhea, and vomiting attacks for three years. He had hearing loss, generalized muscle weakness, and bilateral ptosis. His cognitive functions and other general examinations were normal. Bilateral sensorineural hearing impairment was evident on pure tone audiometry. EMG showed sensorimotor demyelinating polyneuropathy. He could not tolerate a barium enema for colonography because of severe vomiting. Esophagogastroduodenoscopy revealed esophagitis and antral gastritis, and hypotonic and dilated stomach with food products. Brain MRI revealed right cerebellar and symmetric periventricular and supraventricular white matter, and widespread hyperintensities on FLAIR and T2-weighted images. His corpus callosum and bilateral subcortical U-fibers, head of the caudate nucleus, thalamus, basal ganglia, and brainstem were spared. There was no restriction on diffusion-weighted imaging (DWI), and there was elevated diffusion on the ADC map.

All patients were hospitalized, and a central venous catheter was placed for hyperalimentation treatment.

Discussion

Radiologists should consider MNGIE when leukoencephalopathy is associated with neurological symptoms, cachexia, and chronic intestinal symptoms. MNGIE is caused by mutations in the gene encoding thymidine phosphorylase (*ECGF1*). Thymidine phosphorylase is a cytosolic enzyme that regulates pyrimidine nucleoside levels by phosphorolytic catabolism of deoxyuridine and thymidine to uracil, thymine, and 2-deoxy-D-ribose 1-phosphate. *ECGF1* mutations cause severe loss of enzyme function in patients with MNGIE, resulting in very high concentrations of the nucleosides thymidine and deoxyuridine in extracellular fluids (4, 5).

Gastrointestinal symptoms are common in patients with mitochondrial disease. Gastrointestinal dysmotility is caused by the combined effects of neuromuscular dysfunction and autonomic dysfunction (1). Nausea and vomiting from intestinal pseudo-obstruction are the main gastrointestinal symptoms. The main neurological symptoms are peripheral neuropathy and leukoencephalopathy. All individuals with MNGIE have peripheral neuropathy. In some, the first symptoms are paresthesias and weakness. The weakness is usually symmetric and distal. Audiology examinations of all of our patients showed sensorineural hearing impairment (1). All three had vomiting, chronic diarrhea, abdominal cramping, ptosis, peripheral neuropathy, leukoencephalopathy, and leukocytosis. Two had hearing loss and elevated lactate dehydrogenase levels.

Patients with MNGIE have diffuse and abnormally increased signal intensities in cerebral and cerebellar white matter on FLAIR and T2-weighted images, but this is not specific for MNGIE. Toxic encephalopathy, lysosomal storage disorders, metachromatic leukodystrophy, congenital muscular dystrophies, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Krabbe disease, and Canavan's disease have similar symptoms on brain MRI. Symmetric white matter abnormalities can occur in toxic encephalopathies (2, 4).

MRI findings may show abnormally increased T2-weighted signal intensities in the periventricular white matter, corpus callosum, posterior limbs of the internal capsules, cerebellar white matter, and brainstem in lysosomal storage disorders, such as metachromatic leukodystrophy and Krabbe disease. As metachromatic leukodystrophy progresses, these signal abnormalities become more extensive and confluent with associated atrophy. Distinguishing features of metachromatic leukodystrophy include the absence of contrast enhancement, frequently involving cerebellar white matter and not involving deep gray matter. In late-infantile metachromatic leukodystrophy, a "tigroid and leopard skin" pattern of demyelination in periventricular white matter and centrum semiovale has been described (7). DWI shows increased signals within these white matter abnormalities,

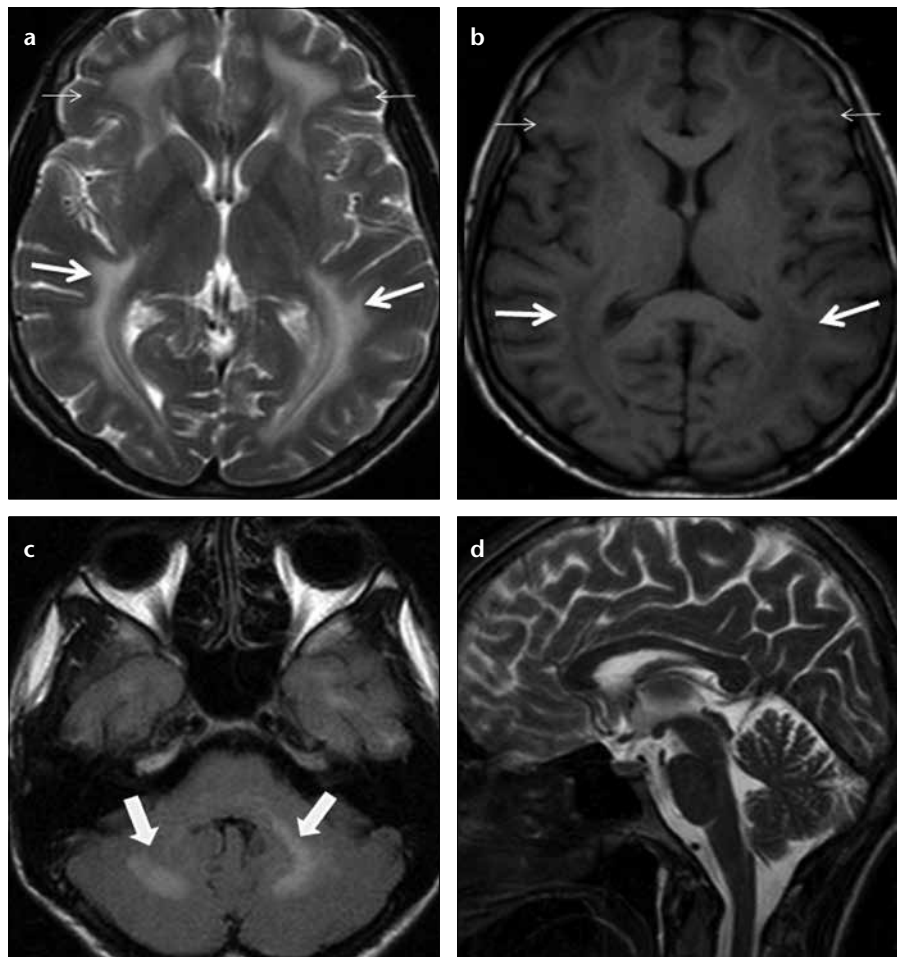


Figure 2. a–d. MR images of MNGIE in a 22-year-old male (case 2). Axial T2-weighted TSE image (TR/TE, 4500/100) (a) shows an abnormally high signal intensity in bilateral periventricular white matter (*thick arrows*). Note the sparing of the bilateral internal capsules, thalamus, head of caudate nucleus, globus pallidus, and subcortical U-fibers (*thin arrows*). Axial T1-weighted image (TR/TE, 462/11) (b) shows an abnormal hypointensity in the bilateral parietal deep white matter (*thick arrows*) with sparing of subcortical U-fibers (*thin arrows*). Axial FLAIR image (TR/TE, 6000/100; TI, 2000) (c) shows an abnormally high signal intensity in the bilateral cerebellar white matter (*arrows*). Sagittal T2-weighted TSE image (TR/TE, 4500/100) (d) shows normal signal intensity in the corpus callosum.

with a "tigroid" pattern and decreased ADC-map signals, secondary to myelin edema (8). Characteristic MRI patterns, in the late-onset form of Krabbe disease include abnormally increased T2-weighted signal intensities along the corticospinal tracts, and predominant involvement of the posterior portion of the corpus callosum, and bilateral parieto-occipital white matter. However, the cerebellar white matter and deep gray nuclei (dentate, basal ganglia, thalamus) are not involved in the late-onset form. Optic nerve atrophy and occasional bilateral optic nerve hypertrophy have been described (9). DWI shows increased signals along the "progression line" of active demyelination during the early stage, related

to myelin edema, with eventual normalization and decreased signals with advancing demyelination (10).

Congenital muscular dystrophies have diffuse symmetric cerebral white matter hypomyelination and many structural encephalic malformations, such as cortical dysplasia, cerebellar hypoplasia, cerebellar cysts, and ventriculomegaly (2, 4). The main MRI findings are lacunar infarcts in the basal ganglia, internal capsule, thalamus, and pons; less well-demarcated and/or confluent subcortical white matter lesions, which are hyperintense on T2-weighted and FLAIR sequences, are also observed in CADASIL (11). In the literature, centrum semiovale, basal ganglia, thalamic, midbrain, and

pons involvement have been reported in MNGIE (2, 4). In our patients, diffuse and abnormally increased signal intensities in cerebral and cerebellar white matter were seen on FLAIR and T2-weighted images, but the corpus callosum, bilateral thalamus, basal ganglia, head of caudate nucleus, globus pallidus, and subcortical U-fibers were all spared.

Although Petcharunpaisan et al. (12) reported multiple cranial nerve contrast enhancements on MRI in a patient with MNGIE, there were no cranial nerve contrast enhancements in our three patients. In another report, brain magnetic resonance spectroscopy demonstrated reduced regional N-acetylaspartate and choline in three siblings with MNGIE (13).

Some studies have discussed treatments with hemodialysis and continuous ambulatory peritoneal dialysis (14, 15). Likewise, studies have shown partial correction of excessive plasma nucleoside levels in patients with MNGIE by either infusing platelets from healthy subjects or by performing allogenic stem cell (bone marrow) transplantation (16, 17). These interesting treatments can reduce nucleosides, but the clinical effects are unknown. We applied hyperalimentation therapy in our patients. All three exhibited weight gain after the treatment.

In MNGIE syndrome, the causes of death reported in the literature are peritonitis due to intestinal rupture, aspiration pneumonia, cardiac arrest, suicide, postcolostomy complications, and esophageal variceal bleeding related to cirrhosis. The average age for disease onset is the late teens, and death

usually occurs by 40 years of age (4). Our patients are alive and have had recurrent abdominal pain, nausea, and vomiting attacks, but no complications. As acute medical events such as infections may provoke worsening of symptoms, early treatment and careful monitoring of intercurrent illnesses may be beneficial.

In conclusion radiologists should alert other clinicians of the possible presence of MNGIE in patients with leukoencephalopathy on brain MRI in the presence of accompanying cachexia and neurological symptoms.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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