

Mitochondrial neurogastrointestinal encephalopathy: A rare case

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Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an exceptionally uncommon metabolic and degenerative disease with progressive multisystem involvement. This autosomal recessive condition is caused by mutations in the nuclear gene encoding the enzyme thymidine phosphorylase (TYMP gene). The disease is distinguished by a series of cumulative and progressive neurological and gastrointestinal manifestations, including leukoencephalopathy, peripheral neuropathy, ophthalmic involvement, such as ptosis and ophthalmoparesis, endocrine disorders, and gastrointestinal dysmotility.^[1]

A 27-year-old male patient was admitted with complaints of dysphagia, occasional episodes of diarrhea, cachexia, and short stature. Neurological examination revealed generalized muscle weakness with Grade 4/5 strength in all extremities. Apart from this mild generalized weakness, no prominent pathological findings were observed, and there was no evidence of ptosis or ophthalmoparesis. Electroneuromyography could not be performed in this patient; therefore, peripheral neuropathy could not be electrophysiologically evaluated. Scrotal ultrasonography revealed bilaterally reduced testicular volumes. Endocrinological evaluation revealed markedly elevated gonadotropin levels (follicle-stimulating hormone: 130 IU/L, luteinizing hormone: 95 IU/L), while total testosterone level was within the normal range (548 ng/dL). Pituitary magnetic resonance imaging (MRI) showed no evidence of adenoma. Brain MRI demonstrated symmetrical and confluent hyperintensities in the

periventricular and supraventricular white matter extending to the U-fibers on Fluid-Attenuated Inversion Recovery (FLAIR) (Figure 1a). White matter hyperintensities were also observed in the splenium of the corpus callosum, basal ganglia, thalamus, pons, and cerebellum (Figures 1b, Figure 2). The imaging findings of the patient, whose brother and cousin had previously been diagnosed with neurogastrointestinal encephalopathy, were consistent with leukoencephalopathy. Genetic analysis confirmed the diagnosis of MNGIE. The patient had a homozygous mutation in the TYMP gene. A written informed consent was obtained from the patient.

Abnormalities in the mitochondrial respiratory chain result in a group of conditions referred to as mitochondrial encephalomyopathies. Alterations in the nuclear DNA gene that encodes the thymidine phosphorylase enzyme, situated on chromosome 22q13.32-qter, cause disruptions in the metabolism of thymidine and deoxyuridine. This results in mitochondrial DNA abnormalities and MNGIE.^[2]

The estimated prevalence of MNGIE is 1 in 1,000,000, as indicated by data from Europe.^[3] The onset of the disease is typically within the first two decades of life.^[4] A previous study showed that symptom onset can occur from 6 months to 21 years of age.^[5] The disease typically manifests with cachexia and abdominal discomfort that lacks an identifiable cause. The initial symptoms in the patient we presented were also abdominal pain, diarrhea attacks, and dysphagia.

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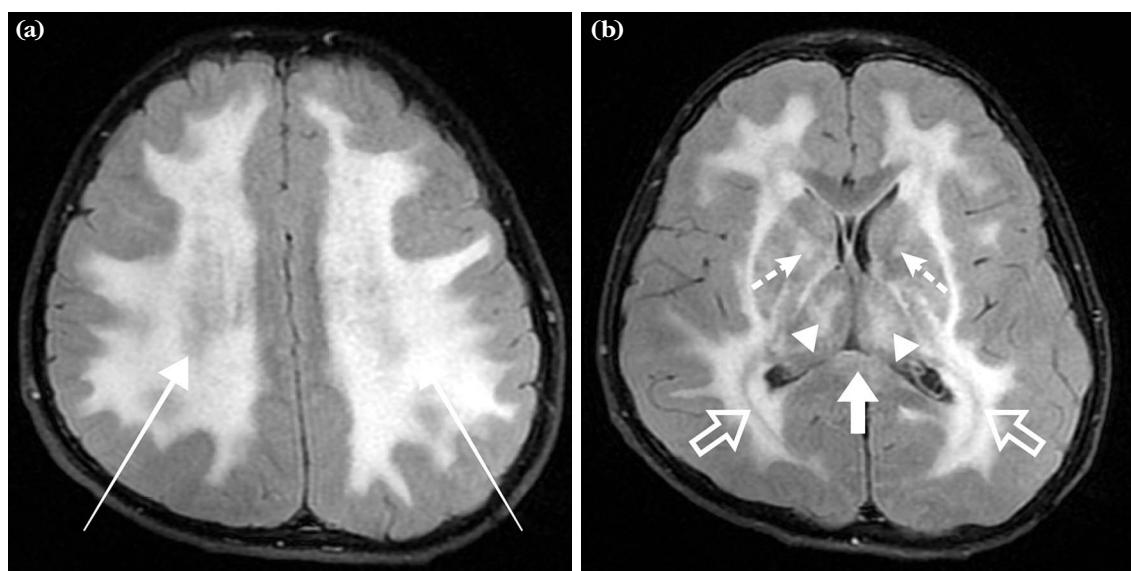


Figure 1. Supratentorial involvement. **(a)** Axial FLAIR image shows symmetric and confluent hyperintensity in the bilateral deep white matter extending to the subcortical U-fibers (arrows). **(b)** Axial FLAIR image demonstrates symmetrical hyperintensities in the bilateral periventricular white matter (filled arrows), as well as in both basal ganglia (dashed arrows) and thalami (arrowheads), with additional hyperintensity at the level of the splenium of the corpus callosum (empty arrow).

FLAIR, Fluid-Attenuated Inversion Recovery.

The disease is rare and presents with complex clinical findings due to its effects on multiple organ systems. This leads to diagnostic delays

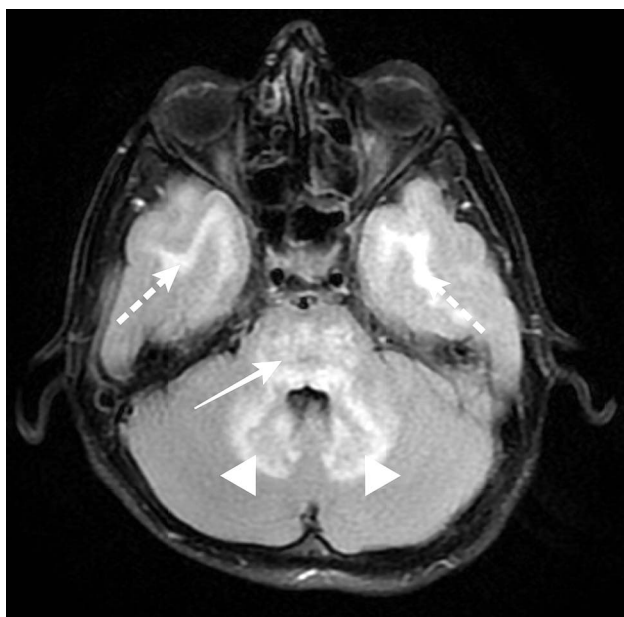


Figure 2. Infratentorial involvement. Axial FLAIR image reveals hyperintensity in the pons (arrow) and dentate nuclei (arrowheads), along with bitemporal subcortical FLAIR hyperintensities (dashed arrows).

FLAIR, Fluid-Attenuated Inversion Recovery.

of between five and 10 years. Mitochondrial neurogastrointestinal encephalopathy patients are frequently misdiagnosed as malabsorption, inflammatory bowel disease, or anorexia nervosa. Positive family history and brain MRI findings were key to diagnosis in the present case. The average age of death is generally between 35 and 37 years due to the progressive nature of the disease. Frequent causes of mortality often include cachexia, metabolic acidosis, pulmonary infections, peritonitis, and sepsis.

Peripheral neuropathy is one of the most important indicators of nervous system involvement in MNGIE. Ocular findings, including ptosis and progressive external ophthalmoplegia, support the diagnosis. Peripheral neuropathy most commonly presents with sensory impairment and reduced or absent tendon reflexes, while distal limb weakness may be less frequently observed. In the present case, clinical signs suggestive of peripheral neuropathy were not prominent, and the absence of electrophysiological evaluation constitutes a limitation of this report. Progressive leukoencephalopathy is the most significant hallmark of central nervous system involvement, with a prevalence approaching 100% in affected patients. Magnetic resonance imaging is crucial in detecting the presence of progressive

leukoencephalopathy.^[5] The leukoencephalopathy pattern is characterized by symmetric and confluent hyperintensities on T2-weighted images, particularly at the level of the centrum semiovale. This pattern involves both periventricular and supraventricular white matter while generally sparing the subcortical U-fibers. In MNGIE, signal abnormalities in white matter are attributed to myelin rather than axonal involvement. The corpus callosum, thalamus, basal ganglia, midbrain, and pons may also be involved.^[2] Cognitive function is preserved despite extensive central nervous system involvement. In the current case, FLAIR sequence showed symmetric and confluent hyperintensities extending to subcortical U-fibers in both periventricular and supraventricular white matter. Similarly, hyperintense signal abnormalities were seen in the pons, cerebellum, splenium of the corpus callosum, bilateral basal ganglia, and thalami. Bilateral symmetrical FLAIR hyperintensities are not specific for MNGIE; radiation-induced encephalopathy, toxic encephalopathy, metabolic disorders such as lysosomal storage diseases, Canavan disease, and congenital muscular dystrophies may also present with bilateral periventricular white matter involvement as hyperintensities in T2-weighted images. Other mitochondrial disorders may also present with atypical and misleading clinical or radiological features, sometimes mimicking infectious or inflammatory diseases.^[6] Given the family history, multisystem clinical findings, and MRI involvement pattern, MNGIE was suspected in the presented case. Genetic analysis confirmed the diagnosis by identifying a homozygous mutation in the TYMP gene.

Although MNGIE is exceptionally uncommon, it should be included in the differential diagnosis of patients with unexplained cachexia, abdominal pain, dysphagia, and episodes of diarrhea, particularly in conjunction with neurological symptoms and brain MRI findings.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: E.Ç.: Data collection and processing, analysis and interpretation, literature review, writing the article, references and fundings, materials; İ.Ö.: Idea/consept, design, control/supervision, critical review; H.D.: Supervision, analysis and interpretation, critical review. All authors read and approved the final manuscript.

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