Egyptian Journal of Radiology and Nuclear Medicine

CASE REPORT Open Access

Mitochondrial neurogastrointestinal encephalopathy: a case report

Ghazaleh Jamalipour Soufi[1], Ali Hekmatnia[1], Farzaneh Hekmatnia[2], Andrew Parviz Zarei[3], Farshad Riahi[1*], Shamim Shafieyoon[4] and Sara Azizollahi[1]

Abstract

Background Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive disease associated with alterations in mitochondrial DNA (mtDNA). The typical age of onset of MNGIE is between the first and second decade of life. Diagnosis requires the presence of several key clinical features: sensorimotor neuropathy, external ophthalmoplegia, ocular ptosis, leukoencephalopathy, and gastrointestinal (GI) dysmotility. Unfortunately, MNGIE diagnosis is very challenging, and patients often undergo multiple diagnostic and surgical operations that are unnecessary.

Case presentation This case is of a 51-year-old male presenting with a 2-year history of limb weakness, GI problems and cachexia. There was also a 1-year history of progressive ptosis and ophthalmoplegia. The patient's uncle and brother had both died from GI-related issues prior to the age of 40. On physical examination, ocular motility was impaired in all directions and there was atrophy and reduction in power in both lower and upper extremities. FLAIR and T2-weighted sequences of brain MRI demonstrated diffuse cerebral white matter hyperintensity (leukoencephalopathy). On discharge, the patient was referred for genetic consultation for bone marrow transplantation and had regular follow-up with a gastroenterology specialist.

Conclusion In patients presenting with chronic progressive ophthalmoplegia, severe gastrointestinal complications, sensorimotor neuropathy and white matter lesions on MRI, it is important to consider investigating for MNGIE.

Keywords Mitochondrial neurogastrointestinal encephalopathy, Ophthalmoplegia, Demyelinating neuropathy

Background

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive disease associated with alterations in mitochondrial DNA (mtDNA) [1]. These may present as the accumulation of point mutations at specific places, numerous deletions, or depletion of mtDNA, and their distribution can vary among organs. However, the mtDNA changes are secondary to TYMP gene mutations causing thymidine phosphorylase deficiency. MNGIE typically manifests during the first or second decade of life, with a mean onset age of 17.9–18.5 [2].

Diagnosis requires the presence of several key clinical features: sensorimotor neuropathy, external ophthalmoplegia, ocular ptosis, leukoencephalopathy, and gastrointestinal dysmotility. Visual system dysfunction is uncommon, but there have been reports of retinal pigmentary alterations and optic atrophy. When all of these clinical features are present, it is frequently diagnostic; however, a patient presenting with only one of these features becomes a very challenging diagnosis for any professional. Patients may also end up undergoing unnecessary diagnostic and surgical interventions, such

*Correspondence:
Farshad Riahi
farshadriahi@ymail.com
[1] Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Radiology, St George's Hospital, London, UK
[3] Department of Medicine, The Princes Alexandra Hospital, London, UK
[4] Department of Radiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

as laparotomies, to treat their gastrointestinal complaints [3, 4].

Magnetic resonance imaging (MRI) of the brain almost always detects diffuse symmetric leukoencephalopathy, which is distinguished by confluent T2-hyperintensity in the white matter [5]. In the current study, we present a 51-year-old male with a diagnosis of MNGIE.

Case presentation

A 51-year-old male was referred to the Ayatollah Kashani Hospital of the Isfahan University of Medical Sciences, presenting with progressive ptosis, ophthalmoplegia, and limb weakness. The patient stated that he had been suffering from generalized weakness of the limbs for about two years before visiting our clinic, for which he was administered Mestinon by a neurologist for a suspected diagnosis of myasthenia gravis. He had not recovered, and he has had muscle spasms in his lower limbs for the past 2–3 months. He mentioned that he had bilateral ptosis of the eyes one year ago, which was more severe on the right side. The patient described gastrointestinal issues such as early satiety, nausea, non-bilious vomiting, pseudo-obstruction symptoms (abdominal distention and mild generalized abdominal pain), and cachexia. He had lost 15–20 kg of weight during these two years. Over the last 10 days, he has suffered from fatigue and increased limb weakness.

He has a past medical history of bilateral stapedectomy due to otosclerosis. In the drug history, he has only been taking Mestinon 60 mg for his suspected myasthenia gravis for the past 2 years.

In the patient's family history, his brother and uncle died between the ages of 30 and 40 from similar GI disorders. Unfortunately, they did not undergo a complete diagnostic work-up for a clear diagnosis. This significantly increases the probability of a hereditary disorder.

Due to the history of GI problems, we requested liver functional tests and an ultrasound of the abdomen and pelvis. The tests and ultrasound obtained were normal (Table 1). The patient previously underwent a double-contrast barium enema, upper GI endoscopy and colonoscopy, which only demonstrated gastritis that was confirmed by the pathologist.

Ophthalmologic examination showed bilateral ptosis and ophthalmoplegia, more severe in right side. Ophthalmoplegia was observed in all directions, which had been occurring for about 2–3 months before the visit.

A neurological examination demonstrated a quadriplegia. Atrophy of both the upper and lower limb was seen. Power was 1/5 in both distal and proximal muscles of the upper and lower extremities. Deep tendon reflexes (DTRs) in both upper and lower limbs were significantly decreased.

Table 1 Liver functional tests of our case

Test	Result	Normal
AST (U/L)	32	1–37
ALT (U/L)	26	1–41
PT (s)	12.5	11.5–14.5
PTT (s)	30	25–35
INR	1	1–1.2
ALP (IU/L)	175	75–388
Alb (g/dL)	4.2	3.4–5.4
Direct bilirubin (mg/dL)	0.1	< 0.2
Total bilirubin (mg/dL)	0.4	< 1.2

AST Aspartate aminotransferase, *ALT* Alanine aminotransferase, *PT* Prothrombin time, *PTT* Partial thromboplastin time, *INR* International normalized ratio, *ALP* Alkaline phosphatase, *Alb* Albumin

During electromyography and nerve conduction velocity (EMG-NCV), there was evidence of chronic sensory motor demyelinating polyneuropathy and proximal non-irritable myopathy. Due to the EMG-NCV finding and history of gastrointestinal problems, we suspected MNGIE as a differential diagnosis.

For a more detailed evaluation, an MRI was performed for the patient. FLAIR and T2-weighted sequences of brain MRI demonstrated diffuse cerebral white matter hyperintensity (Leukoencephalopathy) (Fig. 1). Due to a combination of the clinical features, MRI findings and EMG-NCV results, a clinical diagnosis of MNGIE was made. This was later confirmed by whole-exome sequencing analyses. The genetic result demonstrated a homozygous pathogenic nonsense mutation in the TYMP gene defined as NM_001953.5:c.866A > C (p.Glu289Ala) (Table 2).

On discharge, the patient was referred for genetic consultation for bone marrow transplantation and had regular follow-up with a gastroenterology specialist.

Discussion

We present a 51-year-old male with 2-year history of limb weakness, GI problems and cachexia due to weight loss and 1-year history of progressive ptosis, ophthalmoplegia. Also, his uncle and brother had GI problems that were died in range of 30–40 years old. In physical examination, ocular motility impairment in all direction, atrophy and reduction in forces of lower and upper extremities was observed. EMG-NCV demonstrated a chronic sensory motor demyelinating polyneuropathy and proximal non-irritable myopathy. Also, the DTRs in both upper and lower limbs were significantly decreased. Although he reported a history of GI dysfunction, however, abdominopelvic ultrasound and laboratory tests were normal. T2-weighted MRI demonstrated diffuse

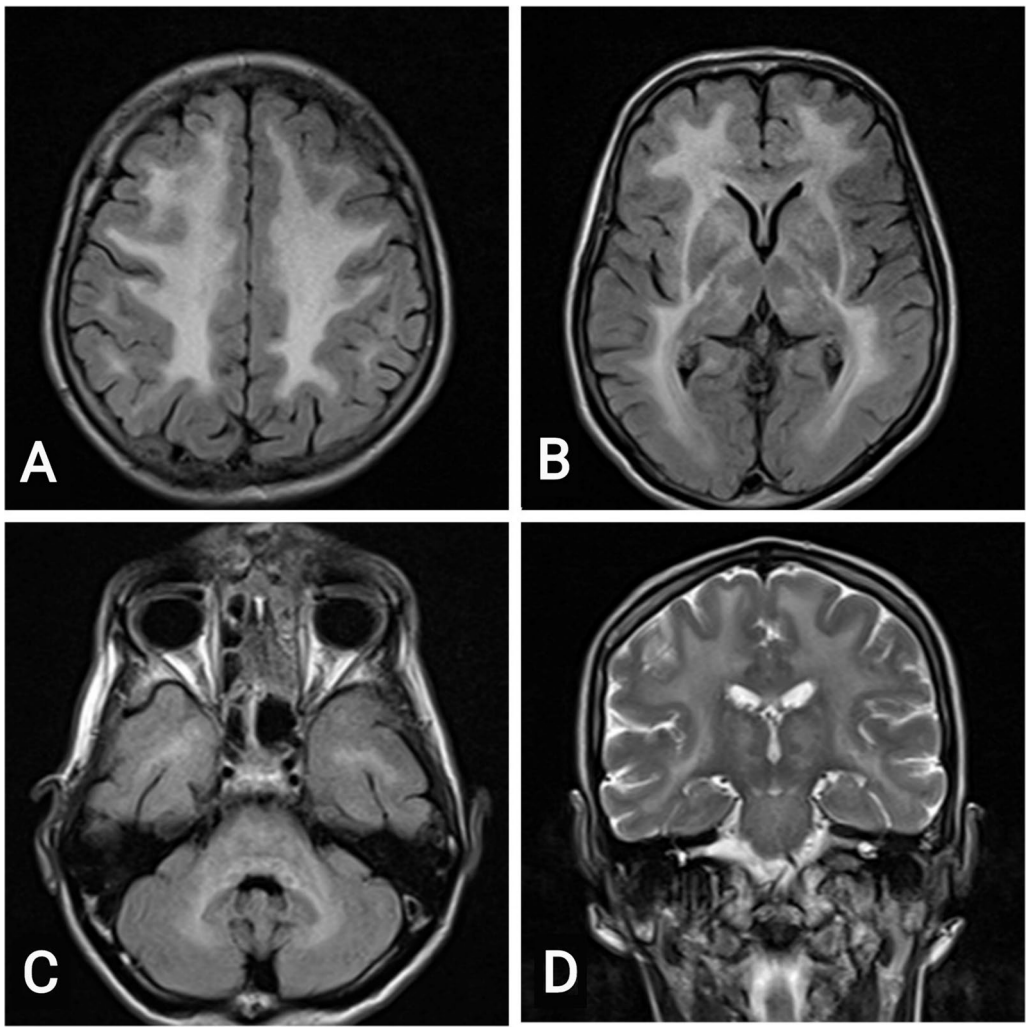

Fig. 1 **A**-**C** Axial fluid-attenuated inversion recovery(FLAIR) images at different levels and (D) coronal T2-weighted image of brain MRI show diffuse symmetrical bilateral supra- and infratentorial white matter (from periventricular to subcortical white matter) high signal change with involvement of corpus callosum, basal ganglia, internal and external capsules, brain stem and cerebellum-no hemorrhage or diffusion restriction is seen

Table 2 Major and secondary findings of whole-exome sequencing analyses of our case

Genetic test	Gene	Protein	cDNA	Zygosity	Class	Matching phenotype
Major finding	TYMP	p.Glu289Ala	NM_001953.5 c.866A > C	Homozygous	Pathogenic	Mitochondrial DNA depletion syndrome 1(MNGIE type)(AR)
Secondary findings	ABCA4	p.Gly1961Glu	NM_000350.3 c.5882G > A	Heterozygous	Likely pathogenic	Cone-rod dystrophy 3 (AR)
	KRT83	p.Pro27AlafsTer 129	NM_002282.3 c.78dup	Heterozygous	Likely pathogenic	Erythrokeratodermia variabilis et progressiva 5 (AR)
	SCN4A	p.Met1367Val	NM_000334.4 c.4099A > G	Heterozygous	VUS	Congenital myopathy 22A, classic (AR)

AR Autosomal recessive, *VUS* variant of unknown significance

cerebral white matter hyperintensity. Finally, MNGIE was diagnosed clinically based on MRI abnormalities, progressive ptosis and ophthalmoplegia, GI issues, and EMG-NCV evidence and confirmed genetically.

MNGIE is a rare mitochondrial genetic disorder that is difficult to detect and frequently goes undiagnosed. This multisystem autosomal recessive disorder primarily affects mitochondrial DNA synthesis and has an incidence of 0.1 per 100,000 people in the Europe. Despite the involvement of mitochondrial dysfunction in the pathogenesis of MNGIE, the condition is caused by a mutation in the TYMP gene, which encodes thymidine phosphorylase. A disruption in thymidine phosphorylase induces the formation of thymidine and deoxyuridine, which disrupts the proper balance of nucleotides necessary for the replication of DNA within mitochondria. MNGIE can thus be diagnosed by detecting biallelic pathogenic mutations in TYMP, significantly decreased thymidine phosphorylase activity, or increased plasma concentrations of thymidine and deoxyuridine.

The most typical manifestation of MNGIE is progressive GI symptoms, which are virtually always present. Generally, GI dysfunction is the leading cause of morbidity and mortality. Peristalsis failure in the small intestine is the most prevalent form of dysmotility observed in MNGIE. This condition can lead to pseudo-obstruction or bacterial proliferation, causing progressive weight loss and cachexia. As a result, gastroenterologists first suspect that these patients have anorexia nervosa, inflammatory bowel disease, or another diagnosis [6]. Ptosis and ophthalmoplegia are common; however, mild ptosis may be the only symptom at first. Slowly progressing ophthalmoplegia, like mitochondrial illnesses, might be asymptomatic in the absence of diplopia [7]. Peripheral neuropathy affects almost all MNGIE patients, with very few exceptions. Clinical manifestation of peripheral neuropathy may be noticeably apparent on clinical presentation, although may also present asymptomatically, where it can then be detected through nerve conduction studies [5].

In 2020, Hammans et al. [2] reported two women with diagnosis of MNGIE that were confirmed genetically. Case one had symptoms of bilateral foot drop and painful foot numbness. She had mild ptosis, stocking distribution sensory loss to all modalities, and areflexia. However, GI problems were not reported. Case two reported symptoms of anorexia, vomiting and weight loss in her teenage years. Ptosis and ophthalmoplegia manifested in her at the age of 28; a muscle biopsy identified symptoms consistent with mitochondrial disease. MRI was performed for both cases that demonstrated the white matter disease.

In 2021, Farahvash et al. [8] described a 31-year-old male who had experienced horizontal diplopia for a year due to a significant exotropia caused by persistent progressive external ophthalmoplegia. He described a 3-year history of severe intermittent diarrhea, cachexia, and diffuse sensory rather than motor peripheral neuropathy. He was diagnosed with MNGIE after an MRI showed diffuse leukoencephalopathy. His younger brother had an identical clinical syndrome and was similarly diagnosed. Similar to our investigation, this significantly increases the probability of a hereditary disorder. MNGIE diagnosis was confirmed later via genetic testing.

Early detection is critical to avoiding unnecessary examinations and therapy for ocular motility impairment, peripheral nerve complaints, and GI problems. Many MNGIE patients undergo unneeded exploratory abdominal procedures, such as laparotomies, before being diagnosed, which carries risks from both the procedure and the anesthesia [4, 9–11]. Genetic and nutritional guidance should be provided to patients with MNGIE diagnoses [10, 11]. Similar to this, before the definitive diagnosis was made, our case also had GI symptoms and cachexia. MRI is critical for diagnosing MNGIE. In patients with MNGIE, brain MRIs of the white matter typically reveal confluent and symmetric T2-hyperintensity [5, 8]. In our study, we used MRI for a more detailed evaluation that showed a diffuse cerebral white matter hyperintensity.

Genetic testing can be used to diagnose MNGIE without the need for MRI imaging [10]. However, because the patient had neurological symptoms and was treated for suspected myasthenia gravis, but it did not improve, it was necessary to undergo an MRI evaluation for further investigation. Also, because this genetic test in our country and almost all other developing countries is considered a specialized test, the ability to perform it is limited, and it takes a lot of time and money for the patient. Therefore, it is better to refer the patient for a genetic test to confirm the diagnosis after performing the MRI and also based on the patient's symptoms if we have a strong suspicion of MNGIE. Also, a study conducted by Scarpelli et al. [12] found that brain MRI should be considered a valuable tool for diagnosing classical and atypical MNGIE. Serial MRIs in untreated and treated MNGIE patients will help establish whether leukoencephalopathy is reversible.

MNGIE is a progressive multisystem disease with a poor prognosis. According to the findings of Garone et al. [13], morbidity and mortality were highest among those aged 20–40, with the mean age of death being 35 years. The prognosis is improved in some patients who have thymidine phosphorylase dysfunction that is not as severe. Aspiration pneumonia, peritonitis resulting from intestinal rupture, electrolyte imbalance and suicide were among the causes of mortality.

MNGIE necessitates a comprehensive approach involving multiple specialties and therapists. Gastroenterologists are critical to medical management. Prokinetic agents may be beneficial; however, medication may be

required for abdominal pain [10]. A study also revealed that pyridostigmine was successfully used in a child with persistent intestinal pseudo-obstruction, which is linked with significant gastrointestinal dysmotility; however, pyridostigmine's efficacy in managing MNGIE is not well established [14]. In some patients, special treatment may be indicated. One of the treatment options includes reducing thymidine and deoxyuridine plasma levels through dialysis or hemodialysis. Additional treatments include gene therapy, hematopoietic stem cell replacement, and platelet infusions (which include thymidine phosphorylase) [15].

Conclusions

In conclusion, patients who present with chronic progressive ophthalmoplegia, gastrointestinal symptoms, sensorimotor neuropathy and white matter lesions on MRI should be evaluated for MNGIE. Since gastrointestinal issues related to cachexia are a common cause of mortality in patients with MNGIE, treatment focuses on alleviating symptoms of ocular motility impairment, providing dietary counselling, regular monitoring by gastroenterology specialists and genetic consultation for bone marrow transplantation.

Abbreviations

MNGIE	Mitochondrial neurogastrointestinal encephalopathy
mtDNA	Mitochondrial DNA
MRI	Magnetic resonance imaging
DTR	Deep tendon reflex
EMG	Electromyography
NCV	Nerve conduction velocity
TYMP	Thymidine phosphorylase

Acknowledgements

Not applicable.

Author contributions

GJS carried out the literature review, created the study's idea and design, and wrote the first draft of the manuscript. AH helped with data collecting, gave the article a careful evaluation, and offered insightful commentary. FH revised the text, summarized the important elements, and contributed to the interpretation of the findings. To ensure the manuscript was accurate, coherent, and clear, APZ and FR examined and corrected it. SS and SA helped understand the data, and edited the article. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Received: 21 March 2024 Accepted: 1 July 2024
Published online: 09 July 2024

References

1. Hirano M (2016) Mitochondrial neurogastrointestinal encephalopathy disease
2. Hammans SR (2020) Mitochondrial neurogastrointestinal encephalopathy disease (MNGIE). Pract Neurol. https://doi.org/10.1136/practneurol-2020-002558
3. Mizel ML, Serota M, Cantor J, Russell-Fritch JA (2023) Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE) Disease. Wisconsin Law Review, pp 287–343
4. Bax BE (2020) Mitochondrial neurogastrointestinal encephalomyopathy: approaches to diagnosis and treatment. J Translat Genet Gen 4:1
5. Gramegna L, Pisano A, Testa C, Manners DN, D'Angelo R, Boschetti E, Giancola F, Pironi L, Caporali L, Capristo M (2018) Cerebral mitochondrial microangiopathy leads to leukoencephalopathy in mitochondrial neurogastrointestinal encephalopathy. Am J Neuroradiol 39:427–434
6. Patel R, Coulter LL, Rimmer J, Parkes M, Chinnery PF, Swift O (2019) Mitochondrial neurogastrointestinal encephalopathy: a clinicopathological mimic of Crohn's disease. BMC Gastroenterol 19:1–5
7. Wang H, Ruan G, Yang S, Li H, Sun Z, Tian B, Yan P, Li Y, Yang H, Zhong Y (2023) Ocular manifestations of mitochondrial neurogastrointestinal encephalomyopathy: a case report and literature review. Am J Med Genet A 191:2819–2824
8. Farahvash A, Kassardjian CD, Micieli JA (2021) Mitochondrial neurogastrointestinal encephalopathy disease: a rare disease diagnosed in siblings with double vision. Case Reports in Ophthalmology 12:174–181
9. Szarka L (2015) Dysmotility of the small intestine and colon. Yamada's textbook of gastroenterology. Wiley, Hoborken, pp 1154–1195
10. Hirano M, Carelli V, De Giorgio R, Pironi L, Accarino A, Cenacchi G, D'Alessandro R, Filosto M, Marti R, Nonino F (2021) Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network. J Inherit Metab Dis 44:376–387
11. Filosto M, CottiPiccinelli S, Caria F, Gallo Cassarino S, Baldelli E, Galvagni A, Volonghi I, Scarpelli M, Padovani A (2018) Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE-MTDPS1). J Clin Med 7:389
12. Scarpelli M, Ricciardi GK, Beltramello A, Zocca I, Calabria F, Russignan A, Zappini F, Cotelli MS, Padovani A, Tomelleri G (2013) The role of brain MRI in mitochondrial neurogastrointestinal encephalomyopathy. Neuroradiol J 26:520–530
13. Garone C, Tadesse S, Hirano M (2011) Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Brain 134:3326–3332
14. Turcotte M-C, Faure C (2022) Pediatric intestinal pseudo-obstruction: progress and challenges. Front Pediatr 10:837462
15. Lara M, Valentino M, Torres-Torronteras J, Hirano M, Martí R (2007) Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): biochemical features and therapeutic approaches. Biosci Rep 27:151–163

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.