Palestinian Medical and Pharmaceutical Journal

A Novel Case of Mitochondrial Neurogastrointestinal Encephalopathy with Growth Hormone Deficiency: *A Case Report*

Ashraf Sawafta[1*], Raya Fuqha[1], Lilyan Jarrar[1], Sara Alqaisi[1], Abdulrahman Hamad[1], Anwar Zahran[1]

Type: Case Report. Received: 24th Jan. 2025, Accepted: 26th Mar. 2025, Published: 1st Jun. 2026,
DOI: https://doi.org/10.59049/2790-0231.11.2.2537

Abstract: **Background:** Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an ultrarare autosomal recessive metabolic disorder caused by mutations in the TYMP gene. The reported endocrine manifestations include diabetes, hyperlipidemia, and hypertriglyceridemia. However, growth hormone deficiency has not been previously described in the literature. **Case presentation:** This case describes a 19-year-old male with genetically confirmed MNGIE who presented with severe malnutrition (BMI 10.9 kg/m²) requiring total parenteral nutrition (TPN). Initially, he was developing normally, then the patient began experiencing chronic abdominal pain, vomiting, and diarrhea at age 11, along with noticeable short stature. Despite normal insulin-like growth factor 1 (IGF-1) levels, growth hormone deficiency was diagnosed through suboptimal responses to glucagon and clonidine stimulation tests. At age 13, he underwent duodenojejunostomy for superior mesenteric artery (SMA) syndrome, but symptoms persisted. Diagnostic workup, including endoscopy, imaging, and serological tests, excluded inflammatory bowel disease and celiac disease. Genetic testing confirmed a homozygous pathogenic mutation in the TYMP gene (p.Gly145Arg). Brain MRI revealed leukoencephalopathy with T2 and FLAIR hyperintensities in the centrum semiovale and parietal regions, which was consistent with MNGIE. Despite TPN therapy, the patient's condition continues to progress, highlighting the need for early diagnosis and multidisciplinary management in MNGIE. **Conclusion:** This case highlights a novel presentation of growth hormone deficiency in MNGIE, offering new insights into its endocrine involvement. Despite treatment with somatotropin and TPN, patients' nutritional improvement has remained limited, underscoring the need for more targeted therapies. Future research should focus on the link between mitochondrial dysfunction and endocrine abnormalities in MNGIE.

Keywords: Mitochondrial Disease, Growth hormone, Malnutrition, Leukoencephalopathies Genetic testing, case report

Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an ultrarare metabolic autosomal recessive multisystem disease with an estimated global prevalence of 1–9 cases per million people (Orphanet, 2018) 1]. It is caused by pathogenic mutations in the TYMP gene, which encodes the enzyme thymidine phosphorylase [2,3]. Severe gastrointestinal, neurological, ophthalmologic, and endocrine features characterize it. These include gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, peripheral neuropathy, leukoencephalopathy, diabetes and abnormal lipid profiles [4,5].

While specific epidemiological data on the prevalence of MNGIE in the Middle East are limited, the high rates of consanguinity in this region, which exceed 50%, suggest that the incidence of autosomal recessive mitochondrial diseases such as MNGIE may be higher than the global average [6]. However, further research is needed to accurately determine the prevalence and genetic characteristics of MNGIE within Middle Eastern populations.

This case report presents a novel case of MNGIE with confirmed growth hormone deficiency, offering valuable insights into the systemic manifestations of mitochondrial disorders.

Case Presentation

A 19-year-old male with genetically confirmed MNGIE presented at our hospital in northern West Bank, Palestine, with severe malnourishment and a body mass index (BMI) of 10.9 kg/m2, necessitating total parenteral nutrition (TPN) management.

The patient was born via normal vaginal delivery with a birth weight of 3 kg following an uneventful pregnancy. He exhibited normal growth and development with good school performance until the age of 11. At that time, the patient began experiencing chronic abdominal pain, nonbloody diarrhea and vomiting. His family observed that he was notably shorter than his peers were; his height was approximately 1.26 m, his weight was 20 kg, and his head circumference was 52 cm. Although insulin-like growth factor 1 (IGF-1) levels fall within the normal range, growth hormone stimulation tests were conducted to assess the functional response of the pituitary gland, as IGF-1 alone may not fully reflect the adequacy of growth hormone secretion. The stimulation tests revealed suboptimal responses to both glucagon and clonidine Table (*1*. These findings led to a diagnosis of growth hormone deficiency, prompting the initiation of somatotropin therapy. Following therapy until 2021, the patient reached a height of 1.68 m and a head circumference of 55 cm, but his weight remained only 32–34 kg. After the patients reached the appropriate height, the therapy was stopped.

Table (1): Growth hormone stimulation test results.

	Glucagon stimulation test, ng/ml	Clonidine stimulation test, ng/ml
Fasting (0 time)	0.24	0.71 ng/ml
30 minutes	5.05	0.24
60 minutes	5.72	2.88
90 minutes	1.38	1.86
120 minutes	0.91	0.54

1 Department of Biology and Biotechnology, Faculty of Science, An-Najah National University, Nablus, Palestine.
* Corresponding authors: asawafta@najah.edu

*Note: A peak serum GH level ≥ 7-10 ng/mL is normal for both tests.

At the age of 13, as the patient's symptoms worsened and he remained unable to gain weight despite appropriate somatotropin therapy, further investigations were performed. The patient was diagnosed with superior mesenteric artery (SMA) syndrome on the basis of CT scan findings showing an aortomesenteric angle of less than 22 degrees Figure (***1***. He subsequently underwent duodenojejunostomy. However, despite surgical intervention, his symptoms persisted, and both his weight gain and growth plateaued. Given that he reached a height of 1.68 m, which is above the average for his age and sex according to the WHO growth charts, and considering the plateau in his growth and weight, it was deemed reasonable to discontinue somatotropin therapy.

In 2021, he was referred to Makassed Hospital in Jerusalem as a case of chronic abdominal pain due to nonbloody, nonbilious vomiting and greasy, foul-smelling stools. A comprehensive diagnostic evaluation, including multiple laboratory tests and imaging studies, was performed.

Upper and lower endoscopies revealed a normal gastrointestinal tract, except for a mildly dilated gastric antrum. Multiple biopsies from the ileum and duodenum revealed normal histological findings, ruling out inflammatory bowel disease (IBD). To further exclude other differential diagnoses, serological testing, including IgA and anti-TTG antibodies, was performed to rule out celiac disease, and all the results returned to normal.

An abdominal CT scan with contrast agent was performed and revealed that the oral contrast agent reached the proximal ileal loops. There is severe dilation of the stomach Figure (***2*** and the first and second parts of the duodenum, and a collapsed third part of the duodenum is present, which is consistent with the patient's history of SMA syndrome. Duodenojejunostomy is noted in the second part of the duodenum, which is consistent with the patient's history of SMA syndrome.

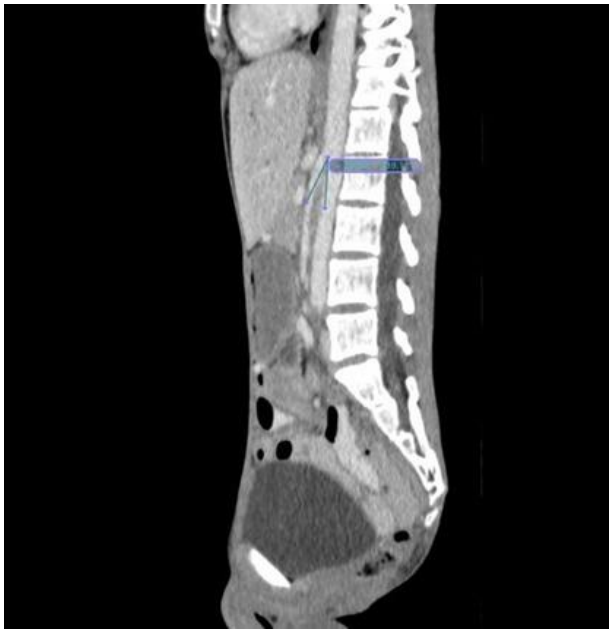

Figure (1): Sagital CT view showing aortomesenteric angle <22° , diagnostic of SMA.

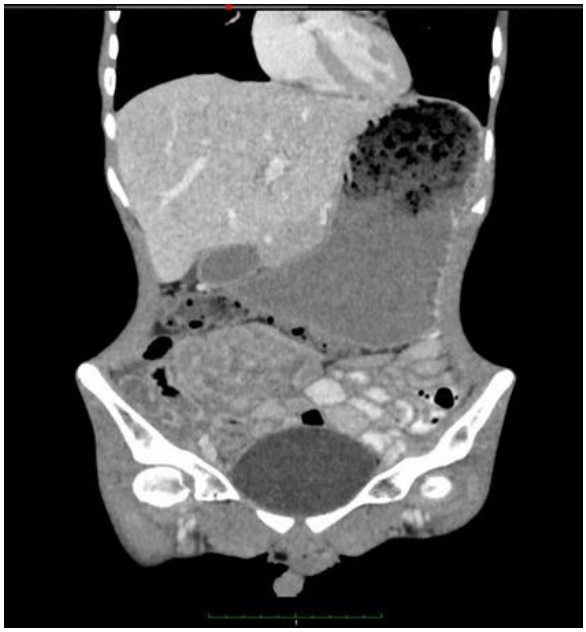

Figure (2): CT coronal view showing severe dilation of the stomach consonant with gastroparesis.

Owing to the combination of his clinical features and after major differential diagnoses were ruled out, a suspicion of MNGIE syndrome was raised among the medical team. This was later confirmed by whole-exome sequencing analyses. The genetic results revealed a homozygous pathogenic nonsense mutation in the TYMP gene, defined as G145R (p.Gly145Arg, c433G>A).

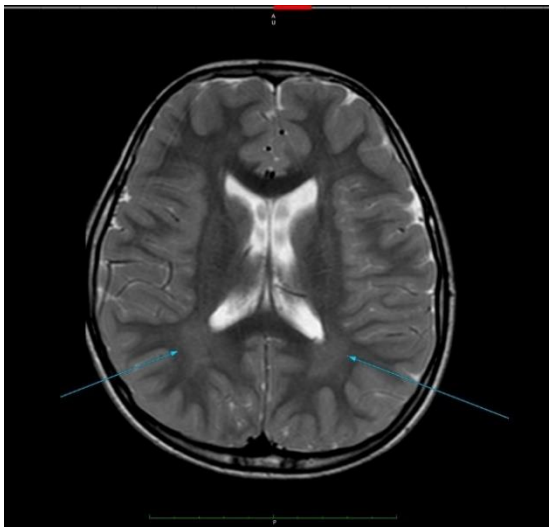

Figure (3): Brain MRI showing bilateral white matter hyperintensities (arrows) in the parietal region blue arrows.

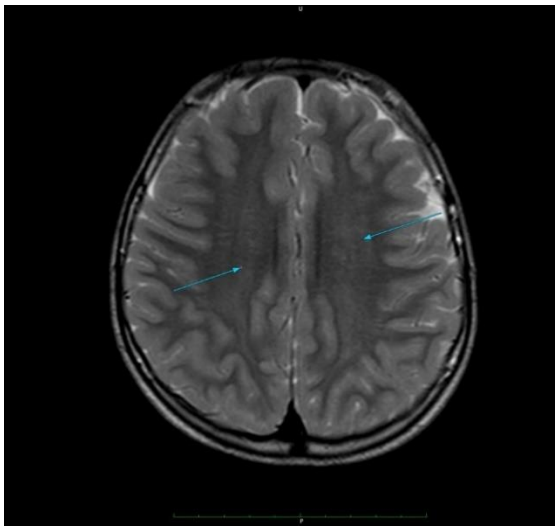

Figure (4): Brain MRI showing bilateral white matter hyperintensities (arrows) in the centrum semiovale blue arrows.

Brain MRI reveals evidence of leukoencephalopathy, characterized by T2 and FLAIR hyperintensities in the white matter of the centrum semiovale and parietal region Figure (***3***, Figure (***4***, which is consistent with MNGIE syndrome. There were no ischemic or hemorrhagic changes. Additionally, no intracranial masses or focal lesions were identified. The patient did not develop other symptoms commonly associated with this syndrome, such as ophthalmoplegia, hearing loss, or polyneuropathy, and he had a normal lipid profile, as shown in Table 2.

At the time of writing, the patient's nutritional status (with a current BMI of 10.9 kg/m2) and functional impairment continue to progress. Laboratory values upon most recent presentation are presented in Table (***2***. A central line was inserted, and parenteral nutrition was started. Daily recommended dosages of vitamins and trace elements were added to all-in-one mixtures with a sufficient caloric content. There was no other method to guarantee that the daily requirements for calories and nutrients were met. The patient's condition is now stable, with no proper weight gain despite the TPN.

Table (2): Laboratory results most recently reported.

Test	Result	Reference
Complete Blood Count		
Hgb	13.8	13.6-17 g/dL
MCV	81	80-96fL
RDW	17.6	12-17%
WBCs count	18.2	(4-11)*10^3
Neutrophils	74.4	40-75%
Lymphocytes	17.6	(20-45)%
Monocytes	7.5	(2-10)%
Eosinophils	0.4	(1-6)%
Basophils	0.1	(0-1)%
Platelets	390	(150-450)* 10^3
Random blood sugar	104	74-110 mg/dl
HbA1c	5.0	%
Liver Function Tests		
ALT/SGPT	16	Up to 41
AST/SGOT	19	Up to 32
Albumin	4.39	(3.5-5.2) g/dL
Lipid profile		
Triglyceride	114	Up to 150 mg/dl
HDL	42	35-65 mg/dl
LDL	50	Up to 150 mg/dl
Kidney function tests		
Creatinine	0.37	0.7-1.2 mg/dl
BUN	.48	6-20 mg/dl

*Note: this table presents the laboratory results from the most recent clinic visit

Discussion

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare multisystem metabolic autosomal recessive disease. It has an estimated incidence of fewer than one in a million in Europe. Orphanet (2018) estimated its global prevalence to be between 1 and 9 cases per million people. Owing to its rarity, most epidemiological data have come from case reports and case series published by various research groups over the past two decades[1]. The mean age at disease onset is 18 years, and more than 60% of patients develop the disease before the age of twenty[4]. MNGIE is a progressive disease with a poor prognosis and high mortality and morbidity, especially between the ages of 30 and 40. The mean age at death is 35 years.[5,7]

This condition is caused by pathogenic mutations in the TYMP gene located on chromosome 22q13.32-qter, which encodes the enzyme thymidine phosphorylase [2]. The resulting enzyme deficiency causes thymidine and 2'-deoxyuridine to accumulate in tissues and body fluids, which consequently results in imbalances in the deoxyribonucleoside pool, leading to impaired mtDNA replication and ultimately mitochondrial failure.[3,8]

The diagnosis of MNGIE relies on two steps: the first is the exclusion of acquired causes [5], and the second is the recognition of the constellation of symptoms and prompt confirmation tests. The diagnosis can be confirmed through genetic testing to detect biallelic mutations in the TYMP gene. Additionally, a significant decrease in thymidine phosphyrlase activity or a significant increase in the plasma concentrations of thymidine and deoxyuridine can aid in diagnosis. [7–9]

Our patient presented with chronic abdominal pain, nonbloody diarrhea, intermittent vomiting, and failure to gain weight. These gastrointestinal manifestations are typical for the presentation of MNGIE, as GI dysfunction is the main cause of morbidity and mortality. [5,7] However, these manifestations can lead to delay or misdiagnosis of the condition, as they are associated with other diseases, such as inflammatory bowel disease, celiac disease, adrenal leukoencephalopathy, anorexia nervosa or another disease.[5,10] Our patient was suspected to have Crohn's disease at the time of clinical presentation, and laboratory values (calprotectin >1000) may indicate Crohn's disease; however, endoscopic findings excluded it.

Endocrine and metabolic dysfunctions have been sporadically reported in patients with MNGIE. These include endocrine/exocrine pancreatic insufficiency, diabetes, elevated amylase levels, and glucose intolerance, as reported by Garone et al.[5]. Alterations in plasma lipid profiles, such as severe hyperlipidemia and hypertriglyceridemia, have also been observed[2]. Furthermore, hypeogonadotropic hypogonadism was reported in MNGIE patients by Carod-Artal et al., whereas hypergonadotropic hypogonadism was reported by Kalkan et al.[11,12]. However, growth hormone deficiency has not been previously reported in the literature. In our case, the patient was diagnosed with growth hormone deficiency at the age of 11, on the basis of abnormal growth hormone stimulation tests using both glucagon and clonidine. The patient was subsequently treated with somatotropin.

The management of MNGIE requires a comprehensive approach and a multidisciplinary team, as seen in our case where nutritional deterioration necessitated immediate intervention with total parenteral nutrition (TPN). While TPN has stabilized the patient's condition, it does not address the underlying metabolic defect. Other therapeutic strategies have been explored for MNGIE management. An improvement in symptoms such as vomiting and abdominal pain was reported with peritoneal dialysis [13]. Liver transplantation (LT) and allogeneic hematopoietic stem cell transplantation (AHSCT) can restore thymidine phosphorylase activity and normalize nucleoside levels in MNGIE, leading to stabilization or partial clinical improvement, although full recovery remains limited owing to irreversible tissue damage[14,15]. Given our patient's persistent nutritional decline despite TPN, considering definitive treatments such as transplantation is crucial for long-term management and improved outcomes. However, financial constraints present a significant barrier to accessing these therapies, highlighting a critical challenge in the management of rare metabolic disorders.

Conclusion

This case report highlights the rare association between MNGIE and growth hormone deficiency, offering valuable insights into the systemic manifestations of mitochondrial disorders. Exploring this unique presentation could improve the understanding of the clinical variability of MNGIE, promote early recognition of atypical cases and reduce unnecessary diagnostic

procedures, facilitating future research into the mechanisms linking mitochondrial dysfunction and endocrine abnormalities.

Abbreviations

MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), TPN (total parentral nutrition), SMA (superior mesenteric artery), GH (growth hormone), LT (liver transplant), AHSCT (allogeneic hematopoietic stem cell transplantation).

Disclosure Statement

- **Ethics approval and consent to participate:** Informed consent was obtained from the patients. The patient was also informed that his name and identification information would not be published.
- **Consent for publication:** Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient's legal guardian. A copy of the consent form is available for review by the journal's editorial office upon request.
- **Availability of data and materials:** All data generated or analyzed during this study are included in this published article. Additional data, such as laboratory values and the patient consent form, are available from the corresponding author upon reasonable request.
- **Competing Interest:** The authors have no competing interests to declare that are relevant to the content of this article.
- Funding: The authors did not receive support from any organization for the submitted work.
- **Acknowledgments:** The authors acknowledge the assistance of the medical team at Jenin Governmental Hospital, Makassed Hospital, and Islamic Hospital. We also appreciate the efforts and time of the patient's family.
- **Author contributions:** All authors contributed equally as co-first authors to the writing of this case report, provided feedback on earlier drafts, reviewed and approved the final manuscript, and agreed to its submission to the journal.

Open Access

References

1] Prevalence and incidence of rare diseases: Bibliographic data. [cited 2025 Mar 5]; Available from: www.orpha.net

2] Pacitti D, Levene M, Garone C, Nirmalananthan N, Bax BE. Mitochondrial Neurogastrointestinal Encephalomyopathy: Into the Fourth Decade, What We Have Learned So Far. Front Genet [Internet]. 2018 Dec 21 [cited 2024 Dec 3];9. Available from: https://pubmed.ncbi.nlm.nih.gov/30627136/

3] Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. Science [Internet]. 1999 Jan 29 [cited 2024 Dec 19];283(5402):689–92. Available from: https://pubmed.ncbi.nlm.nih.gov/9924029/

4] Barisic A, Ljubas Kelecic D, Vranesic Bender D, Karas I, Brinar M, Miletic V, et al. Case report: A patient with mitochondrial neurogastrointestinal encephalomyopathy and chronic intestinal failure. Front Nutr [Internet]. 2022 Nov 7 [cited 2024 Dec 19];9. Available from: https://pubmed.ncbi.nlm.nih.gov/36419558/

5] Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Brain [Internet]. 2011 [cited 2024 Dec 19];134(Pt 11):3326–32. Available from: https://pubmed.ncbi.nlm.nih.gov/21933806/

6] Mitochondrial disorders in the Arab Middle East population: the impact of next generation sequencing on the genetic diagnosis. | Journal of Biochemical and Clinical Genetics [Internet]. [cited 2025 Mar 7]. Available from: https://jbcgenetics.com/?mno=27765

7] Jamalipour Soufi G, Hekmatnia A, Hekmatnia F, Zarei AP, Riahi F, Shafieyoon S, et al. Mitochondrial neurogastrointestinal encephalopathy: a case report. Egyptian Journal of Radiology and Nuclear Medicine [Internet]. 2024 Dec 1 [cited 2024 Dec 19];55(1):1–5. Available from: https://ejrnm.springeropen.com/articles/10.1186/s43055-024-01310-2

8] Case Reports: Mitochondrial Neurogastrointestinal Encephalopathy - Practical Neurology [Internet]. [cited 2024 Dec 19]. Available from: https://practicalneurology.com/articles/2020-nov-dec/case-reports-mitochondrial-neurogastrointestinal-encephalopathy

9] Hirano M. Mitochondrial Neurogastrointestinal Encephalopathy Disease. Pagon RA, Adam MP, Ardinger HH et al., editor. GeneReviews(®) [Internet]. 2016 Jan 14 [cited 2025 Mar 7]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK1179/

10] Patel R, Coulter LL, Rimmer J, Parkes M, Chinnery PF, Swift O. Mitochondrial neurogastrointestinal encephalopathy: a clinicopathological mimic of Crohn's disease. BMC Gastroenterol [Internet]. 2019 Jan 15 [cited 2024 Dec 19];19(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30646848/

11] Kalkan İH, Tayfur Ö, Öztaş E, Beyazit Y, Yildiz H, Gastroenterology BT, et al. A novel finding in MNGIE (Mitochondrial Neurogastrointestinal Encephalomyopathy): hypergonadotropic hypogonadism. Hormones. 2012(3):377–9.

12] Carod-Artal FJ, Herrero MD, Lara MC, López-Gallardo E, Ruiz-Pesini E, Martí R, et al. Cognitive dysfunction and hypogonadotrophic hypogonadism in a Brazilian patient with mitochondrial neurogastrointestinal encephalomyopathy and a novel ECGF1 mutation. Eur J Neurol [Internet]. 2007 May [cited 2024 Dec 19];14(5):581–5. Available from: https://pubmed.ncbi.nlm.nih.gov/17437622/

13] Yavuz H, Özel A, Christensen M, Christensen E, Schwartz M, Elmaci M, et al. Treatment of mitochondrial neurogastrointestinal encephalomyopathy with dialysis. Arch Neurol [Internet]. 2007 Mar [cited 2025 Mar 7];64(3):435–8. Available from: https://pubmed.ncbi.nlm.nih.gov/17353390/

14] D'Angelo R, Boschetti E, Amore G, Costa R, Pugliese A, Caporali L, et al. Liver transplantation in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): clinical long-term follow-up and pathogenic implications. J Neurol [Internet]. 2020 Dec 1 [cited 2025 Mar 7];267(12):3702–10. Available from: https://pubmed.ncbi.nlm.nih.gov/32683607/

15] Case Reports: Mitochondrial Neurogastrointestinal Encephalopathy - Practical Neurology [Internet]. [cited 2024 Dec 19]. Available from: https://practicalneurology.com/articles/2020-nov-dec/case-reports-mitochondrial-neurogastrointestinal-encephalopathy.