Mitochondrial Neurogastrointestinal Encephalomyopathy Presenting with Peripheral Neuropathy and Hearing Loss

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ABSTRACT

Introduction: Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare and often fatal genetic disorder caused by mutations in the thymidine phosphorylase gene (*TYMP*), leading to mitochondrial dysfunction. Symptoms include severe gastrointestinal and neurological issues, such as dysmotility, ophthalmoplegia, leukoencephalopathy, and peripheral neuropathy. Diagnosis typically is delayed until the second decade of life, with an average lifespan of 37 years.

Case Presentation: The patient is a 20-year-old female who initially presented with progressive bilateral peripheral lower extremity neuropathy. She was treated symptomatically for years prior to the onset hearing loss, which prompted further imaging and genetic workup revealing MNGIE. She then opted to undergo liver transplant and is awaiting a donor.

Discussion: Currently, MNGIE treatment options include hematopoietic stem cell transplantation, orthotopic liver transplantation, hemodialysis, and platelet infusion. Hematopoietic stem cell transplantation treatments help restore *TYMP* gene activity, but carry with them increased risk of transplant-related morbidity and mortality. Orthotopic liver transplantation appears to have a more favorable safety profile when compared to hematopoietic stem cell transplantation.

Conclusions: This case highlights the importance of adequate monitoring and interdisciplinary thinking, especially when caring for diseases with wide clinical manifestations. A thorough review of symptomology that includes various specialists may translate to improved diagnosis and care of MNGIE.

INTRODUCTION

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare and frequently deadly autosomal recessive disorder caused by pathogenic mutations in the thymidine phosphorylase gene (*TYMP*) located on the chromosome 22q13.33.[1] Mutations in the *TYMP* gene lead to a deficiency of the thymidine phosphorylase enzyme, causing an excess of thymidine and deoxyuridine leading to mitochondrial dysfunction.[2] MNGIE presents with progressive, severe gastrointestinal (GI) and neurological manifestations, including gastrointestinal dysmotility, ophthalmoplegia, leukoencephalopathy, and peripheral neuropathy. Recently, a case of MNGIE involving the reproductive system was reported, suggesting a broad scope of clinical disease with a host of unique presentations.[3] This vast heterogeneity of presenting symptoms and the rarity of MNGIE often leads to diagnosis late into the disease course—typically in the second decade of life—and early death, on average 37 years of age.[4] Temporizing treatment options, including hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), erythrocyte encapsulated thymidine phosphorylase (EE-TP), and platelet infusion, have been shown to be effective before a long-term alternative can be performed. Current durable treatment options include hematopoietic stem cell transplantation (HSCT) and orthotopic liver transplantation (OLT) and are aimed at restoring thymidine phosphorylase resulting in the long-term clearance of dUrd and dThd.[4,5]

At the time of writing, less than 200 cases have been reported in the scientific literature. We present the case of MNGIE with unique presentation of bilateral lower extremity neuropathy, bilateral hearing loss, and gastrointestinal dysmotility originally attributed to primary dysmenorrhea.

CASE PRESENTATION

A 20-year-old female with past medical history pertinent for polythelia, hyperhidrosis of bilateral lower extremities, menorrhagia/

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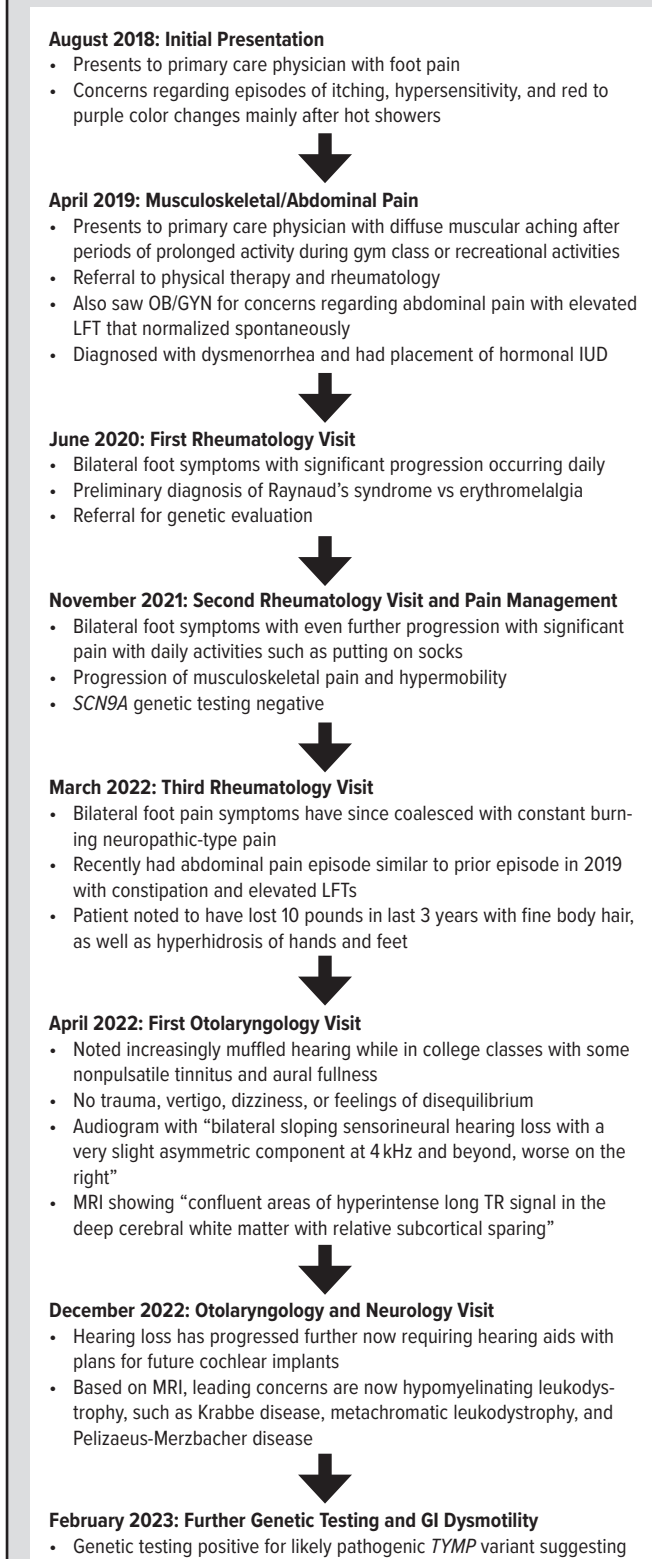
Figure. Timeline of Pertinent Diagnostic Evaluation and Symptom Progression



Abbreviations: OB/BYN, obstetrician/gynecologist; LFT, liver function test; IUD, intrauterine device; MRI, magnetic resonance imaging; GI, gastroenterology.

dysmenorrhea with regular cycle, body mass index less than 5th percentile, and chronic bilateral foot pain presented to her primary care physician at the age of 14 for recurrent discoloration and hyperhidrosis of her feet. She described 8 to 10 episodes per month of well demarcated bilateral erythema and edema extending to her malleoli, with associated burning and itching pain as well as hyperhidrosis. She was referred to dermatology, who discussed treatment with topical aluminum chloride as well as oral anticholinergic therapy. Workup including ferritin and thyroid panel was unremarkable.

Approximately a year and a half later, the patient reported again to her primary care physicians for progression of the same symptoms and was given a rheumatology referral. She noted at this time that the extent of the erythema and edema extended to her upper ankle/lower leg with new associated symptoms of tingling and numbness. While still generally associated with hot temperatures such as in the shower, she also noted sporadic episodes in the absence of any obvious triggers. The episodes began to increase in frequency at this time, and she reported 2 to 3 episodes per day lasting about 5 minutes at a time. She was referred to genetics for erythromelalgia *SCN9A*, *SCN10A*, and *SCN11A* gene evaluation, which was negative.

The patient was seen a year later in the rheumatology clinic with significant progression of her lower extremity discomfort. At this point, she was having pain with simple activities of daily living, such as putting on socks, which was hindering her sleep. This was in conjunction with worsening lower back pain determined to be caused by lumbar hypermobility hindering her posture, hamstring function, and core stability and affecting her ability to participate in sports or ambulate for long periods of time. She was seen by physical therapy in conjunction with pain management and was started on a course of gabapentin, diclofenac gel, and meloxicam as needed for pain. Laboratory panel at this time showed transiently elevated liver function tests that normalized without intervention.

On follow-up 3 months later, the patient noted that the diclofenac gel had minimal effect, she was starting to notice hearing loss, and she had lost 10 pounds over the course of 3 years. During the previous 2 months, she had begun to notice symmetric aural fullness and muffled hearing, as well as bilateral, nonpulsatile tinnitus. Audiogram showed bilateral sloping sensorineural hearing loss with slight asymmetric component at 4 kHz and beyond, worse on the right. Magnetic resonance imaging to evaluate for retrocochlear pathology was remarkable for confluent areas of hyperintense long repetition time (TR) signal. This was noted throughout the cerebral white matter, though prominent in the frontal and parietal lobes involving the deep white matter to a greater degree than the peripheral white matter. There were some subtle hyperintense foci in the lower pons. With these findings, a tentative diagnosis was made for a leukodystrophy vs Susac syndrome.

At this time, the patient began using hearing aids with a plan for follow-up in the neurology clinic for further evaluation of various leukodystrophies that present with peripheral myelinating defects, including Krabbe disease, metachromatic leukodystrophy, and Pelizaeus-Merzbacher disease. Additionally, mitochondrial disorders, such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), which have associated hearing loss, also were considered. Genetic testing was positive for a likely pathogenic *TYMP* variant, suggesting MNGIE. Over the coming months, her hearing continued to deteriorate, with her right side requiring eventual cochlear implant and treatment with high-dose oral and local steroids.

With the tentative diagnosis of MNGIE, the patient's previous symptoms of dysmenorrhea consisting of vomiting, diarrhea, abdominal pain, and anorexia suggested the need for further evaluation of gastric motility. She was seen by gastroenterology, with labs showing elevated liver function tests and elevated total protein. She endorsed episodes of alternating constipation and diarrhea with episodes of feeling like she was choking on her food. These episodes would occur when she ate large quantities of food and were described as retrosternal fullness requiring her to eat smaller portions. Further workup, including liver biopsy, esophageal manometry, and gastric emptying, was ordered. Liver biopsy was largely unremarkable, with the most significant finding being the presence of scattered intracytoplasmic PAS-D-positive (periodic acid Schiff with diastase) globules in hepatocytes. Esophageal manometry and gastric emptying studies showed concerns for gastric dysmotility. Over the next 3 months, she had worsening earlier satiety that culminated with jejunal perforations requiring resection and anastomosis. Since surgery, she has been relatively well and is pending liver transplantation (Figure).

DISCUSSION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an exceedingly rare and often fatal disease, with fewer than 200 patients currently diagnosed across the globe.[1] Its diverse and often misleading presentation involving multiple organ systems makes early diagnosis extremely difficult, leading to a widely diverse presentation upon initial diagnosis. The most observed clinical features involve severe gastrointestinal dysmotility, dysphagia, nausea, diarrhea, external ophthalmoplegia, and leukoencephalopathy. Patients with MNGIE occasionally have been reported to present with neurodegenerative changes, such as peripheral neuropathy and sensorineural hearing loss, as is the case with our patient.[6] Additionally, while rare, intestinal perforations have been reported, which are likely attributable to the poor gastrointestinal motility causing regions of relatively high pressure and predisposing the patient to perforations.[7-9]

The current gold standard for MNGIE diagnostics is testing for elevated levels of dUrd and dThd in the urine and serum, as well as genomic sequencing to identify mutations in the *TYMP* gene.[10] Despite the relative availability of diagnostics, the complex clinical presentation of MNGIE often leads to unnecessary—and sometimes invasive—testing and overall diagnostic delays. In the absence of genomic testing capabilities, thymidine phosphorylase activity must be evaluated to gain insight into the presence and severity of disease.

Management of MNGIE is typically symptomatic and requires an interdisciplinary approach. Hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), erythrocyte-encapsulated thymidine phosphorylase (EE-TP), and platelet transfusion have been used to temporarily lower nucleoside levels.[4] Long-term treatment options, including hematopoietic stem cell transplantation (HSCT) and orthotopic liver transplantation (OLT), aim to restore thymidine phosphorylase activity, resulting in sustained metabolic correction.[5] However, both HSCT and OLT are invasive procedures with significant risk and variable success rates.[5]

After thorough and thoughtful discussion with the multidisciplinary team involved in our patient's care and our patient and her family, an OLT was decided to be the best course of action moving forward. Despite this, these treatments are inadequate for the treatment of the GI manifestations of MNGIE, as those with already severe GI manifestations are unlikely to see significant improvement in these symptoms. The current pathogenesis is thought to be the result of mitochondrial disfunction in the interstitial cells of Cajal in the small intestine.[11] Further research into the underlying mechanism of the gastric dysmotility is needed to allow for more definitive management of MNGIE.

MNGIE also poses anesthetic challenges due to mitochondrial DNA dysfunction that may predispose the patient to acidosis by glucose loads and stressors during surgery, as well as cardiac abnormalities.[12] As such, patients should receive cardiopulmonary workup prior to surgery, as well as labs evaluating baseline glucose levels and lactic acid. Also prior to surgery, the patient's fasting glucose should be monitored closely and replenished with intravenous (IV) dextrose. The use of volatile and IV anesthetics have been shown to inhibit the electron transport chain, though short-term use of these agents are generally well tolerated despite the increased anesthetic sensitivity secondary to pathology and lower overall body weight in this patient population. The use of local anesthetics and regional anesthetics also may be an alternative in high risk or emergency cases, though they too impair the electron transport chain and carry some risk.[8,12] To date, there have been no cases of malignant hyperthermia with MNGIE.

MNGIE has an incredibly broad presentation often leading to delayed diagnosis despite evident symptomology. In our case, from presentation of the patient's symptoms of peripheral neuropathy until diagnosis was about 5.5 years. Throughout her care, she presented to us with symptoms characteristic of MNGIE, including gastric dysmotility originally thought to be dysmenorrhea,

leukodystrophy, anorexia, and progressive sensorineural hearing loss. While GI and ocular symptoms are often the most common, peripheral neuropathy and sensorineural hearing loss are often the most initial presenting symptoms.[1]

The diagnosis of MNGIE is difficult, as the patient can present with a host of symptoms that present a diagnostic hurdle. Therefore, it is important to notice early symptoms, such as hearing loss and peripheral neuropathy, in addition to more classic symptoms, such as cachexia, leukoencephalopathy, and gastrointestinal dysmotility. With symptoms being so diverse, clinicians are encouraged to explore this diagnosis in individuals with unexplained multisystem dysfunction as there is potential for these patients to be written off as having psychiatric disorders.

CONCLUSIONS

This case highlights the importance of adequate monitoring and interdisciplinary thinking, especially when caring for diseases with wide clinical manifestations. A thorough review of symptomology that includes various specialists may result in improved diagnosis and care of MNGIE.

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