A Case of Mitochondrial Neurogastrointestinal Encephalomyopathy with Metabolic Complications During Refeeding

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Patient: Female, 24-year-old
Final Diagnosis: Mitochondrial neurogastrointestinal encephalomyopathy
Symptoms: Weight loss
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Rare disease
Background: Anorexia nervosa has been referred to as the “great pretender” of medicine and is often misdiagnosed. We present a rare genetic disorder that was misdiagnosed as anorexia nervosa. This case highlights the diagnosis of mitochondrial neurogastrointestinal encephalomyopathy in a patient with previously diagnosed anorexia nervosa, which was discovered due to the metabolic abnormalities and intolerance of nutrition encountered during refeeding.

Case Report: A 24-year-old woman with a previous diagnosis of type 2 diabetes mellitus and psychogenic anorexia and recent diagnosis of avoidant restrictive food intake disorder presented to a medical stabilization unit for weight restoration and treatment of medical complications associated with extreme malnutrition. She reported being underweight her entire life, and had a body mass index of 12 kg/m² for a year prior to admission. She reported a long-standing intolerance to enteral feeding and had not gained weight when prescribed parenteral nutrition. She reported a desire to gain weight and denied any body dysmorphia. Upon nutritional rehabilitation, the patient was found to have extreme insulin resistance, with serum glucose values exceeding 400 mg/dL, and multiple neurologic findings that were incongruent with the medical complications of anorexia nervosa. These metabolic abnormalities, with her physical examination findings, allowed for a diagnosis of mitochondrial neurogastrointestinal encephalomyopathy.

Conclusions: This case report highlights the clinical presentation of mitochondrial neurogastrointestinal encephalomyopathy, including the newly described extreme insulin resistance, and showcases the importance of avoiding confirmation bias and working through differential diagnoses that are inconsistent with a clinical presentation to arrive at the correct diagnosis.

Keywords: Anorexia Nervosa • Thymidine Phosphorylase • Insulin Resistance • Hyperglycemia • Visceral Myopathy Familial External Ophthalmoplegia

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Background

Anorexia nervosa is a complex psychiatric disorder with a high mortality often due to medical complications from prolonged starvation. It has a strong association with mood and anxiety disorders, personality disorders, self-harm, and substance abuse. Anorexia nervosa, however, can also mimic many other disorders because of its covert nature and myriad medical complications, which affect nearly every organ system [1,2]. We report a case of a young adult previously diagnosed with psychogenic anorexia who was noted to have significant hyperglycemia and hypertriglyceridemia upon refeeding, which ultimately led to a diagnosis of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), an extremely rare mitochondrial disorder. This is the first description of the metabolic abnormalities encountered during refeeding of an individual with MNGIE.

Case Report

A 24-year-old woman was admitted to an inpatient unit for reduced oral intake and weight loss, which was presumed secondary to an eating disorder. She had been underweight her entire life, and at the age of 6 years, she began to experience abdominal pain, postprandial emesis, and intermittent diarrhea alternating with severe constipation, leading to further weight loss. At the age of 15, she was diagnosed with type 2 diabetes mellitus. At age 18, she was diagnosed with psychogenic anorexia. She was intolerant of enteral feeding owing to abdominal pain, and superior mesenteric artery (SMA) syndrome had been diagnosed based on duodenal compression on a computerized tomography scan. At age 22, her weight had reached a nadir of 27.7 kg, with reports of daily emesis, and she was subsequently started on total parenteral nutrition (TPN). At age 23, she underwent a duodenojejunostomy for the SMA syndrome and, shortly after that, underwent a surgical jejunostomy owing to a lack of improvement in her gastrointestinal symptoms. However, she continued to have poor tolerance to enteral feedings, requiring numerous feeding tube (re)placements, and eventually became solely dependent on TPN, although her weight remained low at 29.5 to 30.8 kg. She reportedly stopped seeing her gastroenterologist and dietitian because of her ongoing frustration regarding her gastrointestinal symptoms and began self-managing her TPN. Three months before this current admission, she awoke one morning with acute onset of left-sided hearing loss; on further audiology workup, she was noted to have bilateral hearing loss with negative magnetic resonance imaging (MRI) of the brain. Completion of oral steroids resulted in no improvement.

On the day of admission, the physical examination showed severe cachexia, with a height of 160 cm and a weight of 30.6 kg (body mass index of 11.95 kg/m²; 58.1% of ideal body weight). Her temperature was 37.2°C, heart rate was 93 beats per min, respiratory rate was 16 breaths per min, and O₂ saturation was 99% on room air. Her cognition, speech, and language were within normal limits, although she frequently exhibited a laissez-faire attitude during portions of the interview. She was also noted to have limited extraocular movements in all directions, ptosis, diminished sensation to light touch in the bilateral lower extremities, reduced strength in the bilateral proximal and distal lower extremities, and diffuse sarcopenia. Cardiovascular and respiratory examinations were unremarkable. An abdominal examination revealed multiple healed scars from her prior surgical interventions and diffuse guarding upon manual palpation that was absent when applying abdominal pressure with the stethoscope. Laboratory results on admission revealed sodium 136 mmol/L, potassium 3.2 mmol/L, chloride 94 mmol/L, CO₂ 34 mmol/L, BUN 9 mg/dL, creatinine 0.66 mg/dL, AST 82 U/L, ALT 49 U/L, glucose 76 mg/dL, WBC 7.54 k/UL, hemoglobin 10.4 g/dL (normal MCV at 89.6 fl), platelets 283 k/UL, hemoglobin A₁c of 5.2%, and TSH 0.89 ulu/mL. Additional laboratory results obtained during admission included a negative autoimmune workup, normal C3/C4, negative HIV testing, and elevated vitamin B12 (1069 pg/mL).

The patient tearfully endorsed a desire to gain weight, denying any drive for thinness or body dysmorphia at the time of her current admission. She in fact stated “I love food. I love to cook. I hate the way I look”. As mentioned above, she was diagnosed with psychogenic anorexia at age 18. More recently, she was diagnosed with avoidant restrictive food intake disorder at an outside hospital only 1 month ago. She had grown up in a family with limited emotional expressivity, and she described her life as “traumatic”, with an abusive relationship during 2013-2014, the witness of her grandmother’s near-fatal trauma in 2014, and the loss of her brother to a motor vehicle accident in 2018. She reported that owing to her physical issues, she had been unable to process “the grief and trauma”. She was recently married, and she was a college graduate with a degree in primary education but was currently unemployed due to her medical status. She reported a history of daily medical marijuana use for 1 month as an appetite stimulant (over a year ago) and denied any other substance use. She was formally diagnosed with posttraumatic stress disorder in 2015 and anxiety and depression in 2017. She was on treatment for depression with duloxetine 30 mg daily, lorazepam 1 mg daily as needed for panic attacks, and trazodone 50 mg nightly for insomnia. She had not tried any other psychotropic medications. She scored moderate for depression and anxiety on recent Patient Health Questionnaire 9 and General Anxiety Disorder 7 questionnaire, respectively. She denied suicidal ideation, suicide attempts, self-harm, or prior psychiatric hospitalizations. Genetic loading was limited to undiagnosed anxiety and depression in her paternal and maternal grandmothers.
Her prescribed nutritional plan at admission consisted of 1800 kcal (1200 kcal by mouth and 600 kcal via TPN). However, due to oral kcal refusal, emesis, and significant gastric dilatation requiring nasogastric suction noted on day 7, she was converted entirely to TPN by the end of the first week of admission. She endorsed daily abdominal pain and frequently requested intravenous hydromorphone for pain control during this time. In addition to her home regimen of duloxetine, and trazodone, she was also prescribed olanzapine to reduce gastric sensitivity along with symptoms of anxiety and depression, with a maximum dose of 10 mg achieved during admission. Workup for this abdominal discomfort included an upper gastrointestinal series, which revealed a partial proximal jejunal narrowing, and a follow-up upper endoscopy revealed evidence of reflux esophagitis, normal mucosa on biopsy from the second part of the duodenum, a sharp external bend in the proximal jejunum, and evidence of dysmotility with decreased gastric peristalsis. Nasojejunal tube placement was attempted as a means to provide enteral feeding, although fluoroscopy was unable to advance the tube past the jejunal kink. Given the flow of contrast through the jejunal narrowing, enteral feedings were restarted at a deliberate rate of 20 mL/h; however, the patient continued to remain intolerant of enteral feeding owing to reported pain levels up to a maximum of 10 out of 10, again necessitating the use of TPN as her sole source of nutrition. However, upon advancing the diet to 2600 kcal via TPN, the patient developed hyperglycemia, with point of care testing frequently documenting glucose values greater than 400 mg/dL, which required high doses of subcutaneous insulin along with up to 400 units of fast-acting insulin added to the TPN daily. She also developed significant hypertriglyceridemia (>1100 mg/dL; normal <150 mg/dL) while receiving this nutritional plan (160 g amino acids daily [3 g/kg based on her current body weight], 451 g dextrose daily, and 413 mL of intralipid daily), all limiting the ability to successfully restore weight in this patient.

Given her constellation of findings of gastrointestinal dysfunctions, cachexia, ophthalmoplegia, ptosis, peripheral neuropathy, early onset hearing loss, and significant insulin resistance with TPN infusion, investigation for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) was pursued. Brain MRI revealed symmetric non-enhancing white matter changes consistent with leukoencephalopathy. Further, testing for MNGIE was accomplished by the measurement of plasma and urine thymidine and 2’-deoxyuridine concentrations (12.64 umol/L [reference range <0.25 umol/L] and 23.18 umol/L [reference range <0.25 umol/L], respectively) and measurement of thymidine phosphorylase activity (4 nmol/mg/h [reference range 414-1020 nmol/mg/h]). Thymidine phosphorylase (TYMP) gene sequencing also detected pathogenic variants. The patient was then transferred to a specialized center to consider experimental treatment for MNGIE and was subsequently lost to follow-up.

**Discussion**

Anorexia nervosa has historically been called “the great pretender” [1] because of the associated systemic medical complications [2,3] and covert behaviors associated with this illness. Indeed, the patient’s reported gastrointestinal symptoms, comorbid mental health diagnoses, lack of weight gain when self-managing her nutrition, and laissez-faire attitude during the initial assessment were consistent with a potential eating disorder diagnosis. Per the Diagnostic and Statistical Manual, 5th edition [4], to diagnose an individual with anorexia nervosa requires:

1. Restriction of energy intake relative to requirements, leading to significantly low body weight.
2. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
3. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

However, this patient adamantly denied any body dysmorphism or food avoidance for the sole purpose of weight loss; therefore, other diagnoses were considered.

A diagnosis of avoidant restrictive food intake disorder was also considered and requires:

1. An eating or feeding disturbance manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with 1 (or more) of the following:
   a. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children);
   b. Significant nutritional deficiency;
   c. Dependence on enteral feeding or oral nutritional supplements;
   d. Marked interference with psychosocial functioning.
2. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
3. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.
4. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder [4].

However, given the extreme insulin resistance, which was inconsistent with the complications of malnutrition, along with her other constellation of symptoms, it was first necessary to rule out concurrent medical conditions.

Our patient’s constellation of gastrointestinal symptoms was consistent with the physiologic changes and functional gastrointestinal diseases that can develop with malnutrition [5-7].
However, the neurologic findings in this case could not solely be attributed to her malnutrition. Lagophthalmos is considered a complication of malnutrition due to orbital fat pad atrophy [8]; however, ptosis and ophthalmoplegia are not associated with malnutrition and were instead initially attributed to her type 2 diabetes mellitus diagnosis. Similarly, malnutrition can be associated with a compression neuropathy due to loss of subcutaneous tissue as well as a type 2 muscle fiber atrophy [9], but her bilateral lower extremity sensory deficits were inconsistent with such and were also initially attributed to her type 2 diabetes diagnosis. However, her normal hemoglobin A₁C level and extreme insulin resistance also suggested consideration of other diagnoses.

Hypoglycemia is frequently documented in those with more severe malnutrition during the early stages of refeeding before replenishing glycogen stores [10]. In starvation, glucagon increases to promote liver gluconeogenesis, lipolysis in adipose tissue, fatty acid oxidation, and ketone body production [11], with a decrease in the metabolic rate of 30% to 50% [12]. Reintroducing nutrition to a starved patient can result in a rapid decline of gluconeogenesis and initiation of anabolic processes, leading to an intracellular shift of glucose, and potentially increasing the risk of hypoglycemia. Insulin levels are elevated at the beginning of the refeeding process and can represent an early stage of insulin resistance, also potentially predisposing to hypoglycemia [13]. Interestingly, in patients with anorexia nervosa, gastrointestinal hormones such as glucagon-like peptide and amylin, which normally stimulate insulin release from pancreatic beta cells, are low, which may be an adaptive response to starvation to prevent further hypoglycemia [13]. However, a significant rise in energy expenditure develops as early as 1 week into refeeding [14]. Indeed, the extreme hyperglycemia and significant insulin resistance at such a low body weight suggested an inherited metabolic disease.

MNGIE has historically been misdiagnosed as an eating disorder [15-18], although there is a single case report wherein a patient was described as having both MNGIE and anorexia nervosa [19]. MNGIE is a rare multiorgan autosomal recessive mitochondrial disorder associated with mutations of the TYMP gene, with roughly 200 cases diagnosed [15,20]. The absence of the TYMP gene allows for the accumulation of thymidine and deoxyuridine, thereby leading to mitochondrial dysfunction through the impairment of mitochondrial DNA function [20]. It is known that mitochondrial dysfunction, which ultimately affects oxidative phosphorylation, is involved in the pathogenesis of insulin resistance, which manifests as hyperglycemia and increased plasma fatty acid levels [21,22]. However, this insulin resistance has not previously been described in MNGIE. Like other mitochondrial disorders, MNGIE presents with varying degrees of disease severity and heterogeneity of symptoms owing to the heteroplasmy of mitochondrial DNA in tissues [16,23]. Even though symptom onset frequently occurs in childhood, most patients with MNGIE are diagnosed in the second decade of life or later owing to progressive symptoms [15,19]. Most commonly, patients have chronic gastrointestinal symptoms and are often admitted with severe malnutrition from rapid and unexplained weight loss [16,17], given that muscle is so commonly affected by mitochondrial dysfunction due to its high energy requirements and dependence on oxidative phosphorylation [24]. Early satiety, nausea, gastrointestinal reflux, postprandial epigastric, episodic abdominal pain and/or distension, and diarrhea/constipation are the constellation of gastrointestinal symptoms seen in MNGIE from a progressive loss of gastrointestinal motility due to muscle dysfunction [25,26].

Patients with MNGIE have progressive multiorgan involvement and also present with ophthalmoplegia, peripheral neuropathy, and leukoencephalomyopathy [25,26]. In the case reports where MNGIE was initially misdiagnosed as anorexia nervosa, all the patients had at least 1 of these clinical findings in addition to the prominent gastrointestinal concerns and weight loss [15-18]. Ophthalmoplegia, or weakness of the extraocular muscles, with ptosis is a common finding in MNGIE and is often unnoticed by patients as it is not accompanied by diplopia. The demyelinating sensorimotor peripheral neuropathy is symmetrical and distal, diagnosed on electromyography, and often with prominent lower extremity involvement. It is associated with a lack of deep tendon reflexes, paresthesia in a stocking-glove distribution, foot drop, and clawed hand. Leukoencephalomyopathy is diagnosed on brain MRI and is usually asymptomatic. Patients can also present with early-onset sensorineural hearing loss and liver involvement with fatty liver or cirrhosis [15,25].

Conclusions

MNGIE, a rare mitochondrial disorder, presents with a constellation of nonspecific findings, including weight loss, gastrointestinal symptoms, and several neurologic abnormalities. This case report highlights the clinical presentation of this illness, including the newly described extreme insulin resistance. It showcases the importance of avoiding confirmation bias and working through differential diagnoses inconsistent with a clinical presentation to arrive at the correct diagnosis.
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