Pearls & Oy-sters: Mitochondrial neurogastrointestinal encephalomyopathy

Diagnosis and response to peritoneal dialysis

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PEARLS

- The clinical spectrum of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is heterogeneous. Atypical presentations are frequently misdiagnosed with adverse prognostic implications.
- Ptosis, ophthalmoparesis, and neuropathy are common findings. Gastrointestinal dysmotility is debilitating and leukoencephalopathy gives a diagnostic clue.
- Buffy coat thymidine phosphorylase (TP) activity is a good screening tool to diagnose MNGIE early in resource crunch settings.
- Peritoneal dialysis provides sustained benefit and should be considered for stabilization prior to definitive restorative therapies like stem cell transplantation (SCT) in advanced illness.

OY-STERS

- Platelet transfusions, enzyme replacement, and SCT, though promising, are limited by transient benefits and high expenses and mortality rates.
- Future studies will help in establishing the efficacy of newer therapeutic interventions in MNGIE.

CASE REPORT A 26-year-old man born to nonconsanguineous parents was admitted with complaints of muscle cramps, fatigue, recurrent abdominal pain, and vomiting since 10 years of age. Since 16 years of age, he noted progressive weakness of the proximal and distal muscles of all 4 limbs with intermittent worsening precipitated by febrile illnesses. He reported dysesthesias of the extremities and gait unsteadiness, which worsened in the dark. There was deterioration of symptoms with progressive dyspnea, orthopnea, dysphagia, early satiety, abdominal pain, and postprandial vomiting associated with a weight loss of 13 kg in the 6 months prior to presentation. Previous treatment received elsewhere included intermittent oral corticosteroids and azathioprine with suboptimal benefit. There was history of proximal weakness, recurrent abdominal pain, and respiratory

involvement in his younger sibling (age at onset 20 years), who had died of the illness within 4 years of disease onset.

On examination, the patient was grossly emaciated. Body weight was 42 kg, height 174 cm with body mass index (BMI) of 13.9 kg/m² (normal population BMI 18.5–22.9 kg/m²). He was tachypneic with chest expansion of 1.5 cm and paradoxical breathing. There was bilateral ptosis, horizontal gaze restriction, bifacial weakness, reduced palatal movements, and an impaired gag reflex. Motor examination revealed moderate neck weakness and symmetric weakness in upper and lower limbs (proximal Medical Research Council [MRC] grade 4/5 and distal MRC grade 2/5). There was reduction in pain and temperature perception in a glove-stocking pattern. Joint, position sense, and vibration were impaired in all 4 limbs. All deep tendon reflexes were absent. Romberg sign was positive and there was sensory ataxia.

Routine investigations including blood counts and liver and renal function were normal. Autonomic function testing revealed resting tachycardia and orthostatic hypotension within 3 minutes necessitating termination of tilt table test (figure, A). Other investigations included creatine kinase 349 IU/mL (normal 45–195 IU/mL), venous blood lactate 3.2 mmol/L (normal 0.3–1.3 mmol/L), and arterial blood gas analysis showing hypercapnic respiratory failure needing intermittent noninvasive ventilation (NIV). Pulmonary function testing suggested severe restrictive lung disease. Nerve conduction studies (NCS) showed a mixed axonal-demyelinating polyneuropathy with phrenic nerve involvement. Sympathetic skin response was absent. On needle EMG, there was spontaneous activity in the form of fibrillations and positive sharp waves from the tibialis anterior and vastus lateralis. The motor unit potentials were small amplitude and short duration with increased interference. CSF analysis showed 2 cells with elevated protein (148 gm/dL) and normal sugar (73 mg/dL). MRI of the brain showed patchy leukoencephalopathy. Muscle biopsy revealed myopathic changes without ragged-red fibers. There was evidence of cytochrome *c* oxidase (COX) activity with

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(A) Autonomic function testing using Finapres shows orthostatic hypotension (OH) within 3 minutes (heart rate blue line, systolic and diastolic blood pressure red line). (B) Posttreatment recording shows no fall in blood pressure even after 10 minutes of tilt with normal heart rate response to deep breathing (DB). (C) CT abdomen during crisis with severe abdominal pain shows distended abdomen and dilated bowel loops with features of intestinal pseudo-obstruction (thick arrow). (D) CT abdomen after initiation of peritoneal dialysis shows improvement in abdominal distension and dilated bowel loops (thick arrow).

COX and COX-succinate dehydrogenase stains. Nerve biopsy showed extensive loss of myelin sheath and axons with myelin ovoid formation without inflammation.

TP assay (expressed as picomoles of thymine formed/cell/h) in leukocytes done by spectrophotometric analysis was 1.24 compared to 18.2 in normal controls (3 controls, SD 4.35). The demonstration of the metabolic defect in the setting of a compatible clinical phenotype and positive family history confirmed the diagnosis of MNGIE.¹ Genetic testing was not done. Hemodialysis was initiated to aid in removal of neurotoxic metabolites. As there was a favorable response to hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) (with 2 L of 1.5% glucose dialysis fluid 3 times a day) was started.

At 3-, 6-, and 9-month follow-up, there was a remarkable improvement in respiratory and neurologic functions. He was weaned off NIV. There was relief from abdominal pain and vomiting with a weight gain of 13 kg. There was improvement in motor power (proximal MRC grade 5 and distal MRC grade 4), dysesthesias, and sensory ataxia, and the patient was ambulant without support. There was significant improvement in autonomic function tests with no orthostatic hypotension and normal heart rate responses to deep breathing and Valsalva maneuver (figure, B). NCS repeated at 9 months

revealed improvement in compound motor action potentials. There were no CAPD-related problems like fluid leak or peritonitis.

The patient presented to us at 12 months with relapse of symptoms following temporary discontinuation of CAPD. There was worsening neuromuscular weakness, sensory ataxia, and severe abdominal pain with vomiting and intestinal pseudo-obstruction (figure, C). After clinical stabilization, hemodialysis was started. He improved and CAPD was reinitiated prior to discharge. There was recovery of pseudo-obstruction (figure, D). During subsequent follow-ups at 15, 18, and 24 months, the patient reported steady improvement in his symptoms.

DISCUSSION Challenges in diagnosis and management of MNGIE include phenotypic variability in age at onset, sequence of organ involvement, atypical clinical presentations early in the disease, lack of definite diagnostic tests in resource crunch settings, and limited treatment options.^{1,2} Mutations in the *TYMP* gene result in severe deficiency of TP enzyme leading to increased thymidine and deoxyuridine and impaired function of the mitochondrial respiratory chain and DNA.² The onset is usually between 15 and 20 years of age.² Characteristic features include ptosis, ophthalmoparesis, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy.² Extraocular muscle involvement is seen early and parallels disease evolution.³ The course is invariably fatal, with mortality typically reported between 20 and 40 years of age.²

Misdiagnosis is common early in the disease course before all clinical manifestations are apparent.¹ The main differential diagnoses are listed in the table. There is often disproportion between prominent gastrointestinal dysmotility symptoms and mild neurologic involvement (cramps, polyneuropathy). Leukoencephalopathy may be patchy in early illness, eventually becoming confluent and diffuse.² Absence of leukoencephalopathy may be seen in MNGIE phenotype associated with RRM2B or POLG mutations, which characteristically have a normal thymidine level.²

A decrease in TP activity in leukocytes to <8% of control mean is sufficient for diagnosis.¹ Increased concentrations of thymidine and deoxyuridine are observed. *TYMP* pathogenic variants are identified in all patients with enzymatically proven disease.¹ DNA sequencing is laborious and expensive in view of the diverse nucleotide changes in the TP gene.¹ However, identification of pathogenic variants in family members will help in assessment of carrier status and prenatal diagnosis.^{2,4} In classic cases, homozygous or compound heterozygous mutations cause severe reductions in TP activity^{1,5} (<8% of normal).

Table Differential diagnosis of MNGIE with main clinical and laboratory characteristics

Differential diagnosis	Clinical features	Diagnosis
Oxidative phosphorylation and other mitochondrial disorders	Usually childhood onset, broad phenotypic spectrum with ophthalmoparesis, myopathy, neuropathy, sensorineural hearing loss, encephalopathy, seizures, liver, cardiac, and gastrointestinal involvement	High lactate, muscle biopsy showing ragged-red and COX-negative fibers, complex estimations in muscle/skin fibroblast culture; false-negative testing can occur due to heteroplasmy; differentiated from MNGIE by biochemical and genetic studies
Chronic inflammatory demyelinating polyneuropathy	Age at onset variable, subacute to chronic progression, motor predominant proximal weakness, sensory variants known	NCS and nerve biopsy showing demyelinating neuropathy with inflammation and exclusion of other causes
Primary gastrointestinal disorders (gastrointestinal dysmotility, inflammatory bowel disease, celiac disease, irritable bowel syndrome, eating disorders)	Predominant gastrointestinal involvement, though neurologic manifestations can be seen in celiac disease and as a manifestation of nutrient deficiency syndromes due to malabsorption	Endoscopy and biopsies, usually have vitamin and micronutrient deficiencies secondary to malabsorption
Hereditary motor sensory neuropathy: CMTX	Onset in first decade, distal weakness with mild sensory, absent deep tendon reflexes, rarely has hearing loss, transient ataxia, dysarthria, and aphasia, acute worsening with intercurrent illnesses	NCS showing primary axonal neuropathy with demyelinating features, MRI brain showing white matter changes, and genetic studies (<i>GJB1</i>)
Leukodystrophies (Krabbe disease, adrenoleukodystrophy, metachromatic leukodystrophy vanishing white matter disease, Alexander disease, Canavan disease)	Usually of childhood onset, gradually progressive nature with central and peripheral nervous system involvement	MRI brain, NCS, enzyme assays, and genetic studies
Merosin-deficient congenital muscular dystrophy	Manifests in infancy with motor developmental delay, generalized hypotonia, rarely seizures and intellectual disability	MRI brain showing neuronal migration disorders and white matter changes, elevated CPK, muscle biopsy with immunohistochemistry for merosin, genetic studies

Abbreviations: CMTX = Charcot-Marie-Tooth disease Type X; COX = cytochrome c oxidase; CPK = creatine phosphokinase; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; NCS = nerve conduction studies.

In late-onset cases, compound heterozygous mutations have been associated with partial loss of TP activity (10%–20% of normal) and milder phenotype.⁵ Hence, a diagnostic algorithm should include a joint approach comprising both biochemical testing and genetic sequencing.⁴

Treatment modalities that increase TP activity or decrease thymidine and deoxyuridine have clinical benefits.² The renal clearance of thymidine is low due to reabsorption in the proximal tubules attributable to the Na⁺/thymidine transporter.⁶ The effect of hemodialysis in reducing thymidine concentration (by ultrafiltration) only lasts around 3 hours, necessitating multiple sessions.⁶ The transient effect is attributable to the fact that the thymidine production exceeds the clearance by dialysis.⁶ The advantages of CAPD in this context include fewer fluctuations in view of its continuous nature combined with the lower costs, greater patient mobility, and lesser need for hospitalization.

Yavuz et al.⁷ reported the case of a 16-year-old girl treated with CAPD for 3 years with marked improvement in gastrointestinal symptoms and weight gain. Interestingly, the plasma nucleoside levels were unchanged, suggesting that other metabolic factors in addition to toxic nucleosides were involved in pathogenesis.⁷ In addition, plasma nucleoside levels may not have reflected the tissue nucleoside levels that may be reduced by CAPD. Our patient also had substantial and sustained relief from gastrointestinal, autonomic, and neurologic symptoms with

recurrence on temporary cessation of CAPD. Plasma nucleoside levels were not done in our patient.

Platelet transfusions can partially restore TP activity, but the effects are transient.² The long-term benefit of SCT remains unknown in view of the high mortality rates.^{2,8,9} Offering SCT at a younger age, before advanced stage of disease, or stabilizing patients by CAPD prior to SCT as observed by Ariaudo et al.⁹ might be future strategies. Erythrocyte-entrapped thymidine phosphorylase can prolong the circulating half-life of enzyme, leading to increased elimination of thymidine.¹⁰ Pharmacologic blockade of the nucleoside carriers responsible for renal reabsorption of thymidine could also have potential benefits.⁶

Early diagnosis is paramount considering the heterogeneity of presentation. Assessment of TP function is a good screening method to confirm MNGIE in resource crunch settings. This case highlights the atypical clinical presentations and the potential of CAPD in treatment. The diagnosis of MNGIE may no longer be associated with a poor prognosis in cases that are diagnosed early and appropriately treated.

AUTHOR CONTRIBUTIONS

All authors agree to the conditions outlined in the authorship and contributorship section. Ajith Sivasadan: data collection, interpretation, and drafting the manuscript. Karthik Muthusamy, Anil Kumar Patil, Vivek Mathew: conceptualization and revision of the manuscript. Mathew Alexander: design, interpretation, and revision of the manuscript.

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