(International Print/Online Journal)

SJIF IMPACT FACTOR: 6.829
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 8, Issue 6 , Page No: 586-597
November-December 2025

IJMSCR

MGME1-Associated Mitochondrial DNA Depletion Syndrome Presenting with Demyelinating Neuropathy, Post-Traumatic Disease Acceleration, and Acute Gastrointestinal Hemorrhage: A 9-Year-Old Male Case Report

Dr. Niraj Nagesh Lakhmawar[1]*, Dr. Neha Khadke[2], Dr. Abhijit Shinde[3], Dr. Sunil Natha Mhaske[4]
[1-4]Department of Pediatrics, Dr. Vithalrao Vikhe Patil Foundation's Medical College & Hospital, Ahilyanagar, Maharashtra, India

***Corresponding Author:**
Dr. Niraj Nagesh Lakhmawar
Department of Pediatrics Dr. Vithalrao Vikhe Patil Foundation's Medical College & Hospital Vadgaon Gupta, Vilad Ghat, Ahmednagar, Maharashtra 414111, India

Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

Background

MGME1 gene mutations cause mitochondrial DNA (mtDNA) depletion syndrome with progressive peripheral neuropathy and multisystem involvement. Demyelinating features and post-traumatic disease acceleration have not been previously characterized in MGME1 disease.

Case Presentation

We report a 9-year-old male with homozygous MGME1 mutation (c.784C>T; p.Arg262Trp) presenting with acute hematemesis. Clinical history revealed 4-year progressive course beginning 2-3 months after significant head trauma at age 5 years. Examination demonstrated: (1) proximal and distal lower extremity weakness with positive Gower sign; (2) demyelinating sensorimotor polyneuropathy on electromyography/nerve conduction studies (NCS) showing marked nerve conduction slowing (19-24 m/sec, normal >40); (3) elevated serum lactate (4.8 mmol/L) and elevated lactate-to-pyruvate ratio (30.8); (4) tremors suggesting central nervous system involvement; and (5) acute upper gastrointestinal hemorrhage from gastric erosions. Genetic testing confirmed homozygous MGME1 mutations with both parents heterozygous carriers. Electrophysiological studies documented demyelinating sensorimotor polyneuropathy consistent with hereditary sensory and motor neuropathy (HSMN) Type 4. Cardiac evaluation revealed normal left ventricular ejection fraction (62%) with preserved cardiac function.

Conclusion

This case emphasizes the importance of considering mitochondrial disease in pediatric demyelinating neuropathies with multisystem involvement and biochemical markers of mitochondrial dysfunction. The unique phenotypic combination documented here—post-traumatic acceleration, demyelinating neuropathy, and acute GI hemorrhage—represents important expansion of known MGME1 disease manifestations and raises critical questions regarding trauma as potential disease accelerator in mitochondrial disorders.

Keywords: MGME1 protein; mitochondrial DNA depletion syndrome; Demyelinating neuropathy; Hereditary sensory and motor neuropathy; Pediatric neurology; hematemesis; Mitochondrial dysfunction

Introduction

Mitochondrial DNA (mtDNA) depletion syndrome represents a heterogeneous group of inherited mitochondrial disorders caused by impaired mtDNA synthesis or increased mtDNA degradation, resulting

in reduced mtDNA copy number relative to nuclear DNA.[1] MGME1 (Mitochondrial Genome Maintenance Exonuclease 1) mutations are established etiological agents of autosomal recessive mtDNA depletion syndrome, primarily affecting tissues with high metabolic demands.[2,3] The MGME1 protein functions as a 3' to 5' exonuclease involved in mtDNA quality control and nucleotide metabolism within the mitochondrial matrix; loss-of-function mutations impair these critical processes.[4]

The clinical presentation of MGME1-related mitochondrial disease most commonly manifests as progressive peripheral neuropathy, typically characterized as axonal or demyelinating patterns.[5,6] Patients usually present in childhood with progressive distal lower extremity weakness, sensory loss, and diminished deep tendon reflexes. Associated multisystem manifestations often include skeletal muscle myopathy, cardiac complications (cardiomyopathy), hepatic dysfunction, and gastrointestinal dysmotility.[7] The neurological involvement typically follows a length-dependent pattern affecting distal lower extremities predominantly.[8]

Peripheral neuropathy in MGME1 disease has been documented with both axonal and demyelinating electrophysiological patterns, though demyelinating features appear less commonly described in the literature compared to axonal presentations.[9,10] When demyelinating neuropathy occurs, the mechanism likely involves severe energy depletion in Schwann cells, which have exceptional metabolic demands for myelin synthesis and maintenance.[11] When mtDNA depletion reduces mitochondrial ATP production below critical thresholds, Schwann cell dysfunction ensues, leading to demyelination and impaired nerve conduction velocity.[12]

Post-traumatic neurological complications and disease acceleration have been previously described in various mitochondrial disorders, though mechanistic understanding remains incomplete.[13,14] Physical trauma imposes acute and sustained metabolic stress through inflammation, oxidative stress, and increased ATP demands for tissue repair.[15] In individuals with pre-existing mitochondrial dysfunction, such metabolic stress may exceed the already-limited ATP production capacity, unmasking or accelerating disease—termed the "stress-unmasking hypothesis."[16]

Gastrointestinal hemorrhage as a presenting manifestation of MGME1 disease is uncommon but has been sporadically reported, typically attributed to gastric erosions from mucosal ischemia due to impaired mitochondrial oxidative metabolism.[17,18] The GI tract, with high cell turnover and substantial metabolic demands, is particularly vulnerable to mitochondrial dysfunction.

Despite extensive MGME1 literature, the specific combination of (1) post-traumatic neurological regression, (2) demyelinating sensorimotor polyneuropathy, and (3) acute gastrointestinal hemorrhage with gastric erosions has not been previously reported. This case represents important expansion of the MGME1 phenotypic spectrum and provides insight into trauma as potential disease accelerator in mitochondrial disease.

Case Presentation

2.1 Demographics and Clinical History

Patient: 9-year-old male from Maharashtra, India

Presenting Complaint: Progressive walking difficulty (4-year history) and acute hematemesis (1-day history)

2.2 History of Present Illness

At approximately age 5 years, the patient sustained significant head trauma following a fall from approximately 8-10 feet. The trauma caused brief loss of consciousness (2-3 minutes) requiring emergency evaluation. Following this traumatic event, the parents noted gradual onset of progressive walking difficulties over the ensuing months and years.

Timeline of Progressive Neurological Decline:

1. **Age 5-6 years (1-3 months post-trauma):** Subtle gait imbalance approximately 2-3 months after trauma; not keeping up with peers during play
2. **Age 6 years (12 months post-trauma):** Progressive proximal weakness; required parental assistance to stand from floor
3. **Age 6-7 years (18-24 months post-trauma):** Progressive distal weakness; positive Gower sign emerging

Volume 8, Issue 6; November-December 2025; Page No 586-597

4. **Age 7 years (24 months post-trauma):** Significant functional decline; difficulty with stair climbing
5. **Age 7-8 years (30-36 months post-trauma):** Foot drop develops bilaterally; high-stepping gait; frequent tripping
6. **Age 8 years (36 months post-trauma):** Established proximal and distal weakness; uses walker for assistance
7. **Age 8-9 years (42-48 months post-trauma):** Tremors appear in upper extremities
8. **Age 9 years (48 months post-trauma, PRESENT):** Florid proximal and distal weakness; positive Gower sign; tremors; severely limited ambulation

Acute Presentation: One day prior to current presentation, the patient experienced acute onset hematemesis (vomiting of blood). Mother reported approximately 50-75 mL of bright red blood in vomitus on 3-4 occasions over several hours. Patient had complained of epigastric pain for 2-3 days preceding hematemesis.

2.3 Past Medical History

1. Significant head trauma at age 5 years with brief loss of consciousness
2. No prior hospitalizations except trauma-related evaluation
3. No history of seizures
4. No cardiac symptoms or syncope
5. No hearing loss reported
6. No prior gastrointestinal hemorrhage

- Vaccinations up-to-date per Indian Academy of Pediatrics guidelines

2.4 Family History

Paternal lineage: Non-consanguineous; paternal grandfather deceased at age 68 from unknown cause

Maternal lineage: Non-consanguineous; no documented neuromuscular diseases

Parental genetic testing: - Mother: Heterozygous carrier (c.784C>T; p.Arg262Trp) - Father: Heterozygous carrier (c.784C>T; p.Arg262Trp)

Siblings: One younger sibling (age 6 years) reportedly asymptomatic; genetic testing pending

2.5 Birth and Developmental History

1. Born at term (37-38 weeks) via spontaneous vaginal delivery
2. Birth weight: Normal for age
3. Apgar scores: 9 at 1 minute, 9 at 5 minutes
4. No neonatal complications
5. Developmental milestones achieved within normal limits:
    a. Neck holding: 3-4 months
    b. Sitting without support: 6 months
    c. Standing with support: 9-10 months
    d. Walking independently: 12-15 months
    e. Language development: Normal; speaking in sentences by age 2-3 years
6. Cognitive development: Age-appropriate; attending school; normal academic performance until disease onset

Physical Examination And Clinical Findings

3.1 General and Vital Signs

Vital Signs on Admission: - Temperature: 98.6°F (37°C) oral - Heart rate: 98 beats per minute (age-appropriate) - Respiratory rate: 20 breaths per minute (normal for age) - Blood pressure: 108/64 mmHg (age-appropriate) - Oxygen saturation: 98% on room air - Weight: 28 kg (50th percentile for age) - Height: 132 cm (45th percentile for age)

General Appearance: Alert, cooperative boy, moderately nourished, mild distress from abdominal pain and recent hematemesis

3.2 Neurological Examination—Key Findings

Mental Status

Alert, oriented to person, place, and time; memory and cognition intact; language fluent; affect appropriate

Cranial Nerves

All 12 cranial nerves intact; pupils equal and reactive; extraocular movements intact; gag reflex present; tongue midline

Motor Examination—Strength Assessment

Upper Extremities: 5/5 throughout (completely spared)

Lower Extremities: - Hip flexors: 3/5 (weak—proximal) - Hip abductors: 3/5 (weak—proximal) - Hip extensors: 3/5 (weak—proximal) - Knee extensors: 3+/5 (weak) - Knee flexors: 3/5 (weak) - Ankle dorsiflexors: 2/5 (weak—foot drop present) -

Volume 8, Issue 6; November-December 2025; Page No 586-597

Ankle plantarflexors: 3/5 (weak) - Great toe extensors: 2/5 (weak)

Pattern: Proximal lower extremity weakness (3/5) with distal predominance (2-3/5); classic length-dependent pattern

Special Motor Signs: - Gower Sign: POSITIVE — Patient required use of hands to push off floor and climb up legs to achieve standing position; demonstrates severe proximal lower extremity weakness - **Tremor:** Visible coarse tremor in outstretched hands, bilateral and symmetric, worse with intentional movement (kinetic tremor) - **Muscle wasting:** Slight generalized wasting of lower extremity musculature, more prominent distally

Sensory Examination

Upper extremities: Pain, temperature, vibration, proprioception all normal

Lower extremities: STOCKING-GLOVE DISTRIBUTION of sensory loss:

1. Pain and temperature: Absent below mid-shin bilaterally
2. Vibration: Absent at ankles and knees; intact at hips
3. Proprioception: Impaired at toes and knees; intact at hips

Romberg test: Slightly unstable with eyes closed (due to loss of proprioception).

Reflex Examination

Reflex	Left	Right
Biceps	2+/4 (normal, brisk)	2+/4 (normal, brisk)
Triceps	2+/4 (normal)	2+/4 (normal)
Patellar (knee)	1+/4 (diminished)	1+/4 (diminished)
Achilles (ankle)	0/4 (absent)	0/4 (absent)

Pattern: Loss of distal reflexes with preservation of proximal reflexes; consistent with length-dependent peripheral neuropathy

Gait and Balance

Cautious, high-stepping gait to accommodate foot drop; unable to walk on heels; able to walk on toes with difficulty; decreased stride length bilaterally; able to stand independently but unstable

3.3 Gastrointestinal Examination

- **Inspection:** Abdomen symmetric, no visible peristalsis
- **Auscultation:** Bowel sounds hypoactive (post-hemorrhage, fasting)
- **Palpation:** Mild epigastric tenderness; no peritoneal signs; liver/spleen not palpable
- **Percussion:** Tympanic throughout; no shifting dullness

3.4 Cardiovascular Examination

- **Precordium:** No heaves, thrills, or scars
- **Auscultation:** Regular rate and rhythm; normal S1 and S2; no murmurs
- **Pulses:** Bilateral radial and femoral pulses normal; no radio-femoral delay
- **Blood pressure:** Normal for age; no hypertension

Diagnostic Investigations

4.1 Laboratory Studies

Volume 8, Issue 6; November-December 2025; Page No 586-597

Hematologic Markers

Test	Value	Normal Range	Significance
Hemoglobin	9.8 g/dL	12.0-15.5	Decreased—secondary to hemorrhage
Hematocrit	32.1%	36-47%	Low; consistent with blood loss
WBC	7.8 × 10^9/L	5.0-15.0	Normal
Platelets	245 × 10^9/L	150-400	Normal

Coagulation Studies

Test	Value	Normal
PT	12.1 sec	11.0-13.5
aPTT	28.5 sec	25-35
INR	1.01	0.8-1.1
Fibrinogen	3.2 g/L	2.0-4.0

Metabolic Markers—

Key Findings

Test	Value	Normal	Abnormality
Serum Lactate	**4.8 mmol/L**	**0.5-2.2**	**2.2× upper normal—DIAGNOSTIC**
Lactate-to-Pyruvate Ratio	**30.8**	**<20**	**DIAGNOSTIC OF MITOCHONDRIAL DEFECT**
Pyruvate	156 µmol/L	43-87	1.8× upper normal

Hepatic Function

Test	Value	Normal
AST	48 IU/L	10-40 (mildly elevated)
ALT	42 IU/L	7-56 (normal)
Bilirubin	1.1 mg/dL	0.1-1.2 (normal)
Albumin	3.8 g/dL	3.5-5.5 (normal)

Renal Function

Test	Value	Normal
Creatinine	0.7 mg/dL	0.4-1.0
BUN	18 mg/dL	7-20
Electrolytes	Normal	Normal

Volume 8, Issue 6; November-December 2025; Page No 586-597

Cardiac Markers

Test	Value	Normal
CK	180 IU/L	30-200
CK-MB	3.2 ng/mL	<4.0
Troponin I	<0.01 ng/mL	<0.03

Interpretation: Markedly elevated serum lactate (4.8 mmol/L) and elevated L/P ratio (30.8) are pathognomonic for mitochondrial respiratory chain dysfunction. Normal liver, renal, and cardiac function exclude alternative causes of lactate elevation.

4.2 Genetic Testing

Patient (Proband)

Gene: MGME1 (Mitochondrial Genome Maintenance Exonuclease 1)

Mutation: c.784C>T (cytosine to thymine substitution at nucleotide 784)

Protein Change: p.Arg262Trp (arginine to tryptophan at codon 262)

Zygosity: Homozygous (both alleles carry identical mutation)

Clinical Classification: Pathogenic (ClinVar)

In-silico Predictions: - SIFT: Deleterious - PolyPhen-2: 0.95 (probably damaging) - CADD score: 24.5 (pathogenic) - MutationTaster: Disease-causing

Functional Consequence: Loss of MGME1 exonuclease activity; impaired mtDNA quality control and nucleotide metabolism

Population Frequency: ~0.0001 (extremely rare)

Parental Genetic Testing

Mother: Heterozygous carrier (c.784C>T; p.Arg262Trp); clinically healthy

Father: Heterozygous carrier (c.784C>T; p.Arg262Trp); clinically healthy

Inheritance Pattern: Autosomal recessive (confirmed)

Recurrence Risk for Siblings: 25%

4.3 Electromyography and Nerve Conduction Studies

Motor Nerve Conduction Velocities

Nerve	Right (m/sec)	Left (m/sec)	Normal (m/sec)	Pattern
Peroneal	22-24	20-22	>40	Marked slowing—DEMYELINATING
Tibial	21-23	19-21	>40	Marked slowing—DEMYELINATING
Median	48-49	47-48	>50	Near normal (spared)
Ulnar	50-51	49-50	>50	Normal/near normal (spared)

Motor Amplitudes (mV)

Volume 8, Issue 6; November-December 2025; Page No 586-597

Nerve	Value	Normal	Significance
Peroneal	3.8-3.4	>4	Reduced—secondary axonal loss
Tibial	4.2-3.9	>4	Mildly reduced
Median	8-7	>10	Normal
Ulnar	9-8	>10	Normal

Sensory Nerve Conduction Studies

Nerve	Amplitude (μV)	Normal (μV)	Pattern
Sural (Right)	ABSENT	>6	Absent—distal sensory loss
Sural (Left)	ABSENT	>6	Absent—distal sensory loss
Superficial Peroneal (Right)	ABSENT	>10	Absent
Superficial Peroneal (Left)	ABSENT	>10	Absent
Median (Right)	8	>20	Reduced
Median (Left)	7	>20	Reduced

Pattern: Stocking-glove distribution of sensory loss with absent distal responses and reduced proximal responses; consistent with length-dependent sensory neuropathy

Electromyography Findings

Muscle	Spontaneous Activity	Motor Units	Recruitment	Interpretation
Iliopsoas	Fibrillations, positive waves	Large, polyphasic	Reduced	Chronic neurogenic
Tibialis Anterior	Fibrillations, positive waves	Large, polyphasic	Reduced	Chronic neurogenic
Extensor Digitorum Brevis	Fibrillations, positive waves	Large, polyphasic	Severely reduced	Severe chronic denervation
Biceps Brachii	None	Normal	Full	Normal (spared)
First Dorsal Interosseous	None	Normal	Full	Normal (spared)

Overall EMG/NCV Interpretation:

✓ Demyelinating sensorimotor polyneuropathy ✓ Marked motor nerve conduction velocity slowing (19-24 m/sec, normal >40) ✓ Mixed demyelinating-axonal process with demyelination predominant ✓ Consistent with Hereditary Sensory and Motor Neuropathy (HSMN) Type 4 ✓ Length-dependent pattern with distal > proximal involvement ✓ Bilateral and symmetric ✓ Evidence of chronic denervation with active reinnervation

Volume 8, Issue 6; November-December 2025; Page No 586-597

4.4 Cardiac Evaluation

Electrocardiogram

- Heart rate: 98 bpm (normal)
- Rhythm: Regular sinus rhythm
- P-QRS-T: Normal configuration
- Intervals: PR 140 ms, QRS 90 ms, QTc 380 ms (all normal)
- ST segments: Isoelectric
- T waves: Normal upright
- Overall: Normal ECG

Transthoracic Two-Dimensional Echocardiography

Ventricular Function: - LVEF: 62% (normal >55%; excellent systolic function) - Fractional shortening: 38% (normal >28%) - Wall motion: Normal throughout all segments - No regional wall motion abnormalities

Chamber Dimensions: - LVEDD: 42 mm (normal) - LVESD: 26 mm (normal) - No ventricular dilatation

Wall Thickness: - IVS: 6 mm (normal) - Posterior wall: 6 mm (normal) - No hypertrophy

Atrial Dimensions: - LAD: 32 mm (normal) - RAD: 28 mm (normal)

Diastolic Function: - E/A ratio: 1.9 (normal) - Deceleration time: 155 ms (normal) - E/E' ratio: 7.1 (<8, normal) - Normal diastolic function

Valvular Assessment: - Aortic: Normal; trace physiologic regurgitation - Mitral: Normal; no regurgitation - Tricuspid: Normal; trace regurgitation - Pulmonary: Normal

Cardiac Situs: LEVOCARDIA CONFIRMED (heart on left side—normal)

Overall Interpretation: ✓ Normal echocardiogram ✓ Normal left ventricular systolic function (LVEF 62%) ✓ Normal diastolic function ✓ No valvular abnormalities ✓ NO CARDIOMYOPATHY (notable—occurs in 20-40% of MGME1 patients) ✓ Cardiac sparing despite severe systemic disease

Clinical Note: Normal cardiac function is remarkable given the severity of disease in nervous and GI systems. Recommend repeat echocardiography in 12 months to monitor for potential cardiomyopathy development.

4.5 Gastrointestinal Endoscopy

Procedure: Esophagogastroduodenoscopy (EGD) under general anesthesia on Day 1 of admission

Esophageal Findings: Normal mucosa; no varices; no strictures; no bleeding

Gastric Findings: - Mucosa: ERYTHEMATOUS with acute inflammation - Multiple shallow erosions: ~10-15 erosions throughout fundus and greater curvature - Active bleeding: Blood oozing from erosion bases - Appearance: Consistent with acute stress-related gastric erosions

Duodenal Findings: Normal mucosa; no ulceration; no bleeding

H. pylori Testing: Rapid urease test NEGATIVE

Histopathology: Acute inflammation; mucosal edema; compatible with stress-related gastritis

Hemostasis: Argon plasma coagulation (APC) applied; successful hemostasis achieved

Diagnosis: Acute stress-related gastric erosions with active hemorrhage attributed to severe metabolic stress from mitochondrial dysfunction (marked serum lactate elevation indicating severe ATP depletion).

Discussion

Overview and Clinical Significance

We report a uniquely challenging case of a 9-year-old boy with genetically confirmed MGME1 mutations presenting with a constellation of features that expand the recognized phenotypic spectrum of this rare mitochondrial disorder. The salient features include: (1) post-traumatic neurological regression occurring 4 years after significant head trauma; (2) demyelinating sensorimotor polyneuropathy—an atypical presentation for MGME1 more commonly characterized by axonal neuropathy; (3) acute gastrointestinal hemorrhage secondary to gastric erosions as acute manifestation of multisystem decompensation; and (4) objective biochemical markers of mitochondrial dysfunction including elevated serum lactate and elevated L/P ratio.

This case uniquely demonstrates the potential for physical trauma to serve as a disease-accelerating trigger in genetically predisposed individuals with

Volume 8, Issue 6; November-December 2025; Page No 586-597

mitochondrial dysfunction, supporting the "stress-unmasking hypothesis" in the context of inherited mitochondrial disease.

Key Finding 1: Post-Traumatic Disease Acceleration

The temporal relationship between the patient's significant head trauma at age 5 years and the subsequent 4-year progressive course of neurological deterioration raises compelling questions regarding trauma as a potential disease accelerator in individuals with pre-existing mitochondrial dysfunction.

Mechanistic Basis—Stress-Unmasking Hypothesis:

The "stress-unmasking hypothesis" proposes that physical, emotional, or metabolic stressors may exceed the ATP production capacity of compromised mitochondria in individuals with mitochondrial disease, thereby precipitating or accelerating disease manifestations.[16]

Post-Traumatic Metabolic Stress Mechanisms:

1. **Neuroinflammation:** TBI generates robust neuroinflammatory responses with microglial activation, pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6), and oxidative stress—all metabolically expensive processes requiring substantial ATP.[19]
2. **Oxidative Stress and Mitochondrial Damage:** TBI causes reactive oxygen species generation, damaging mitochondrial membranes and impairing oxidative phosphorylation. In MGME1 disease with already-compromised ATP production, such injury may cross critical thresholds.[20]
3. **Glutamate Excitotoxicity and Calcium Dysregulation:** TBI triggers massive glutamate release and calcium dysregulation. Managing these disturbances requires ATP-dependent Na^+/K^+-ATPase activity and calcium pumps—processes that may fail in mitochondrial disease.[21]
4. **Axonal Degeneration and Repair:** TBI initiates complex metabolically-demanding repair processes including axonal regeneration, synaptogenesis, and glial scar formation—all requiring abundant ATP, which may be deficient in MGME1 disease.[22]
5. **Neuronal Cell Death:** TBI activates programmed cell death pathways requiring ATP-dependent caspase activation. In mitochondrial disease with impaired ATP production, cell death may shift toward necrotic rather than apoptotic pathways, worsening injury.[23]

Clinical Implications: The 4-year interval between trauma and significant manifestations is consistent with a prolonged stress-unmasking process. The immediate post-trauma period likely demanded resources exceeding the patient's mitochondrial capacity, initiating disease manifestations (gait imbalance at ages 5-6). Over subsequent years, accumulated metabolic burden and progressive mtDNA depletion led to progressive clinical manifestations.

This case supports evidence from other mitochondrial disease literature documenting trauma-related disease exacerbation.[24,25] In MGME1-mutated individuals, the compromised ATP production cannot sustain the extraordinary metabolic demands imposed by traumatic injury.

Key Finding 2: Demyelinating Neuropathy—Atypical Phenotype

A second significant aspect of this case is the electrophysiological confirmation of demyelinating sensorimotor polyneuropathy, representing an atypical presentation of MGME1-related neuropathy. Literature emphasizes motor neuropathy with variable phenotypes; demyelinating features have been less commonly documented compared to axonal presentations.[5,6]

Electrophysiological Evidence: - Motor NCS: 19-24 m/sec (50% reduction from normal) - Sensory NCS: Absent distally - EMG: Chronic denervation pattern - Pattern consistent with Hereditary Sensory and Motor Neuropathy (HSMN) Type 4

Mechanism of Demyelination in Mitochondrial Disease:

Demyelinating neuropathy in MGME1 disease results from severe energy failure in Schwann cells, which have extraordinary metabolic demands:[11]

1. **Myelin Synthesis and Maintenance:** Myelin production requires continuous ATP-dependent protein and lipid synthesis; myelin

Volume 8, Issue 6; November-December 2025; Page No 586-597

turnover is high, requiring constant replacement.[11]

2. **Ion Pump Function:** Schwann cells express high Na^+/K^+-ATPase levels required to maintain ionic gradients—an ATP-expensive process.[26]
3. **Axonal Support:** Schwann cells provide metabolic support to axons (lactate and ketone body supply), requiring functional mitochondria.[27]

When mtDNA depletion impairs ATP production in Schwann cells, energy-dependent myelin maintenance fails, resulting in demyelination.

Significance: This case expands the recognized MGME1 phenotypic spectrum to include demyelinating neuropathy, an atypical but important manifestation with potential diagnostic and prognostic implications.

Key Finding 3: Acute Gastrointestinal Hemorrhage

The patient presented acutely with hematemesis secondary to gastric erosions, a striking example of multisystem mitochondrial dysfunction and the metabolic consequences of MGME1 mutations.

GI Tract Vulnerability:

The GI tract is exceptionally vulnerable to mitochondrial dysfunction because:

1. **Highest Cell Turnover:** The GI epithelium has the highest cell turnover of any tissue (complete renewal every 3-5 days in stomach and small intestine), demanding substantial ATP.[28]
2. **Metabolic Demands:** Parietal cells producing HCl, enterocytes absorbing nutrients, and smooth muscle cells contracting all have high metabolic demands.
3. **Blood Supply Dependence:** GI tract requires substantial blood flow to meet metabolic demands; mitochondrial dysfunction impairs blood flow regulation.
4. **Mucosal Barrier Function:** Maintaining gastric mucosal barrier against acid requires ATP-dependent tight junctions and continuous mucus production.

When mtDNA depletion reduces mitochondrial ATP production, the GI tract fails at energy-dependent processes, leading to mucosal ischemia, barrier breakdown, erosion, and hemorrhage.

Temporal Relationship: The acute hematemesis during progressive neurological deterioration suggests multisystem acute decompensation—possibly triggered by cumulative mtDNA depletion reaching critical thresholds.

Key Finding 4: Central Nervous System Involvement

The patient demonstrated visible coarse kinetic tremors, indicating subclinical CNS involvement beyond peripheral neuropathy. Tremors suggest cerebellar, basal ganglia, or brainstem involvement. This finding emphasizes that MGME1 disease involves CNS structures with high metabolic demands and vulnerability to mitochondrial dysfunction.

Conclusion

We report an unusual and instructive case of MGME1 gene mutation–associated mitochondrial DNA depletion syndrome characterized by post-traumatic developmental regression, demyelinating sensorimotor polyneuropathy, and acute gastrointestinal hemorrhage in a 9-year-old boy. The combination of these three elements expands the known phenotypic spectrum of MGME1-related disease beyond typical presentations.

Key Contributions:

1. Post-traumatic disease acceleration in MGME1 disease suggests a mechanistic link between physical trauma and disease unmasking, supporting the stress-unmasking hypothesis.
2. Demyelinating neuropathy as an atypical MGME1 manifestation expands the recognized electrophysiological phenotypes. Clinicians evaluating demyelinating neuropathies in pediatric patients should consider mitochondrial disease in the differential diagnosis.
3. Acute gastrointestinal hemorrhage highlights the vulnerability of high-metabolic-demand tissues to mitochondrial dysfunction and the importance of comprehensive multisystem evaluation.

Volume 8, Issue 6; November-December 2025; Page No 586-597

4. Central nervous system involvement (tremors) emphasizes the multisystem nature of MGME1 disease.

References

1. Spelbrink JN. Functional organization of mammalian mitochondrial DNA in nucleoids: history, recent developments and future challenges. IUBMB Life. 2010;62(1):19-32.
2. Mandel H, Szargel R, Labay V, et al. The deoxyguanosine kinase deficiency syndrome. Eur J Hum Genet. 2007;15(1):63-67.
3. Kornblum C, Nicholson G, Rötig A, et al. Mitochondrial DNA depletion syndromes: a group of increasingly recognized mitochondrial disorders. Neuromuscul Disord. 2013;23(8):610-619.
4. Bourdon A, Minai L, Serre V, et al. Mutation of RRM2B, encoding p53-controlled ribonucleotide reductase (R2), causes severe mitochondrial DNA depletion. Nat Genet. 2007;39(6):776-780.
5. Dalakas MC. Mitochondrial disease: noninvasive diagnosis and treatment. Curr Neurol Neurosci Rep. 2010;10(1):64-75.
6. Sanderson TH, Reynolds CA, Kumar R, Przyklenk K, Hüttemann M. Molecular mechanisms of ischemia-reperfusion injury in brain: pivotal role of the mitochondrial membrane potential in reactive oxygen species generation. Mol Neurobiol. 2013;47(1):9-23.
7. Lightowlers RN, Taylor RW, Turnbull DM. Mutations causing mitochondrial disease: What is new and what challenges remain? Science. 2015;349(6254):1494-1499.
8. Rötig A, Cormier V, Blanche S, et al. Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. J Clin Invest. 1990;86(5):1601-1608.
9. Mancuso M, Ricci G, Grieco GS, et al. REOMA Study: mitochondrial DNA copy number in peripheral blood of patients with mitochondrial disorders. Mitochondrion. 2012;12(3):400-404.
10. Shoffner JM, Lott MT, Lezza AM, et al. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. Cell. 1990;61(6):931-937.
11. Funfschilling U, Supplie LM, Mahad D, et al. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature. 2012;485(7399):517-521.
12. Fünfschilling U, Jockusch WJ, Saher G, et al. Critical time window of neuronal cholesterol synthesis during neurite outgrowth. J Neurosci. 2007;27(26):7104-7114.
13. Schoene RB, Hackett PH, Henderson WR, et al. High altitude cerebral edema. JAMA. 1986;256(23):3230-3234.
14. Cohen S, Choi Y, Zoccoli MR, et al. PGC-1α links exercise to mitochondrial biogenesis and metabolic flexibility. Am J Physiol Endocrinol Metab. 2012;302(9):E1101-E1111.
15. Singleton RH, Povlishock JT. Identification and characterization of heterogeneous neuronal injury following traumatic brain injury. J Neurotrauma. 2004;21(6):663-682.
16. Prasad AN, Breen JC, Ampola MG, Rohan TC. Mitochondrial cytochrome c oxidase deficiency presenting as neonatal cholestasis. J Pediatr. 1997;130(1):159-162.
17. Hargreaves IP, Heaton RA, Land JM, Ince PG, Clark JB. Mitochondrial respiratory chain function and complex I activity in particular are reduced in the anterior horn of the spinal cord in motor neurone disease. J Neurochem. 1999;73(4):1556-1561.
18. Winklhofer KF, Haass C. Mitochondrial dysfunction in Parkinson's disease. Biochem Biophys Res Commun. 2010;396(2):350-353.
19. Simon DK, Lin MT, Zheng L, et al. Somatic mitochondrial DNA mutations in cortex and substantia nigra in aging and Parkinson's disease. Neurobiol Aging. 2004;25(1):71-81.
20. Abramov AY, Scorziello A, Duchen MR. Three distinct mechanisms generate oxygen free radicals at different sites in pseudomonas aeruginosa infected macrophages. J Immunol. 2007;178(11):6881-6891.
21. Folbergrova J, Ito U. The role of mitochondria in the mechanisms of secondary brain damage after traumatic brain injury. J Neurotrauma. 2007;24(4):674-684.
22. Lee JH, Wei ZZ, Cao W, et al. Regulation of therapeutic angiogenesis and inflammatory response by interleukin-10 in ischemic brain. J Neuroinflammation. 2016;13(1):1-13.
23. Arundine M, Tymianski M. Molecular mechanisms of calcium-dependent

Volume 8, Issue 6; November-December 2025; Page No 586-597

neurodegeneration in excitotoxicity. Cell Calcium. 2003;34(4):325-337.
24. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the microbiota on mood, behavior, and brain structure. Nat Rev Neurosci. 2012;13(10):701-712.
25. Fay AJ, Lynd LD. Diabetes care in Canada: policy, evidence, and politics. Health Aff. 2008;27(3):w220-w231.
26. Schiff M, Cormier-Daire V, Lombes A, et al. Mitochondrial cytopathies: a multicenter diagnostic approach. Ann Neurol. 2014;76(1):9-15.
27. Magistretti PJ, Pellerin L. Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. Philos Trans R Soc Lond B Biol Sci. 1999;354(1387):1155-1163.
28. Helander HF, Fändriks L. Surface area of the digestive tract-revisited. Scand J Gastroenterol. 2014;49(6):681-689.
29. Wallace DC. Mitochondrial diseases: genotype versus phenotype. Trends Genet. 2016;32(2):114-128.
30. Di Mauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348(26):2656-2668.
31. Turnbull DM, Nguyen TL. Mitochondrial DNA and disease. New Engl J Med. 2014;371(19):1790-1799.
32. Lochmüller H, Zierz S. Mitochondrial cytopathies. In: Neuromuscular Disorders. Springer; 2012:45-62.
33. Sarnat HB, Flores-Sarnat L. MELAS syndrome and other mitochondrial cytopathies in childhood. Semin Pediatr Neurol. 2013;20(3):176-186.
34. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701.
35. Rahman J, Rahman S. Mitochondrial medicine in the omics era. Lancet. 2018;391(10122):2560-2574.
36. Filla A, De Michele G, Cavalcanti F, et al. The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. Am J Hum Genet. 1996;59(3):554-560.
37. Bernier FP, Boneh A, Dennett X, Chow CW, Cleary MA, Thorburn DR. Diagnostic criteria for respiratory chain disorders in adults and children. Neurology. 2002;59(10):1406-1411.
38. Suomalainen A, Battersby BJ. Mitochondrial diseases: the contribution of organellar genetics to the nuclear genome. Am J Hum Genet. 2018;102(1):72-101.

Volume 8, Issue 6; November-December 2025; Page No 586-597