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Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) in a Child with Homozygous TYMP c.928+1G>A Mutation: A Case Report from South India

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Running Title: MNGIE with TYMP Mutation in a Child

Abstract: ***Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) is an ultra-rare autosomal recessive mitochondrial disorder caused by mutations in the TYMP gene. It classically presents with gastrointestinal dysmotility, ptosis, ophthalmoplegia, peripheral neuropathy and diffuse leukoencephalopathy. We report a genetically confirmed case of MNGIE in a 12-year-old boy from South India, born of second-degree consanguineous parents, with a family history of a similarly affected sibling. Genetic testing revealed a homozygous pathogenic variant c.928+1G>A in intron 7 of the TYMP gene. This case underscores the need for heightened clinical suspicion and early molecular diagnosis, especially in regions with prevalent consanguinity.***

Keywords: MNGIE, TYMP mutation, mitochondrial disorder, gastrointestinal dysmotility, pediatric myopathy, consanguinity, leukoencephalopathy

1. Introduction

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) is a multisystemic disorder caused by mutations in the TYMP gene (OMIM #131222) leading to deficiency of thymidine phosphorylase activity. The resultant accumulation of thymidine and deoxyuridine disrupts mitochondrial DNA replication and repair, culminating in mitochondrial DNA depletion and multiple deletions. The disease typically presents before 20 years of age with a constellation of symptoms including severe gastrointestinal dysmotility, external ophthalmoplegia, ptosis, peripheral neuropathy, and white matter changes on neuroimaging. To our knowledge, genetically confirmed reports from the Indian subcontinent remain sparse.

2. Case Report

A 12-year-old boy presented with progressive fatigue, vomiting, early satiety, abdominal distension, and proximal muscle weakness for the past three years. He was born to second-degree consanguineous parents. Developmental milestones were appropriate until age 8, following which symptoms gradually worsened. He had an elder sister who died at age five with similar symptoms, though no definitive diagnosis was made at that time.

Clinical examination revealed:

- Cachexia with BMI <3rd percentile
- Bilateral ptosis with restricted extraocular movements
- Symmetric proximal muscle weakness in both upper and lower limbs
- Hypotonia with preserved deep tendon reflexes
- No cognitive or cerebellar signs
- Abdominal examination revealed visible peristalsis with tympanitic bowel sounds

Laboratory workup:

- Serum lactate: mildly elevated
- Creatine kinase: normal
- Nerve conduction studies: sensorimotor axonal neuropathy
- Brain MRI: diffuse symmetric T2 hyperintensities in periventricular and deep white matter, suggestive of leukoencephalopathy

Genetic testing (PerkinElmer Health Sciences Pvt Ltd, Chennai) revealed a homozygous pathogenic splice-site variant c.928+1G>A in intron 7 of the TYMP gene (NM_001953.4), confirming the diagnosis of MNGIE. The same variant had been identified in his deceased sister in previous testing.

3. Discussion

MNGIE results from mutations in the TYMP gene leading to loss of thymidine phosphorylase activity. The c.928+1G>A splice-site variant is known to be pathogenic and affects splicing of pre-mRNA, likely resulting in a truncated or nonfunctional enzyme. This variant has been previously reported in association with MNGIE and is consistent with autosomal recessive inheritance, especially in populations with high rates of consanguinity.

The clinical features in our patient — gastrointestinal dysmotility, external ophthalmoplegia, peripheral neuropathy, leukoencephalopathy, and muscle weakness — align with classical MNGIE phenotype. The delayed

diagnosis is not uncommon due to its rarity, overlapping features with neuromuscular and metabolic disorders, and lack of awareness.

Currently, there is no curative treatment. Management is largely supportive, including nutritional therapy, prokinetics, and symptomatic relief. Allogeneic hematopoietic stem cell transplantation and orthotopic liver transplantation are under investigation but carry high procedural risks. Gene therapy remains experimental.

4. Conclusion

This case highlights the classical phenotype of MNGIE with a confirmed pathogenic TYMP mutation in a consanguineous family. Awareness of this disorder among pediatricians and neurologists is critical, especially in consanguineous populations. Early recognition and genetic diagnosis are vital for management, prognostication, and genetic counseling.

Declaration of Patient Consent
The authors certify that appropriate patient consent was obtained.

Conflicts of Interest
None declared.

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