World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Recognizing the rare: A clinical description of mitochondrial neuro-gastro-intestinal encephalopathy

Upadhyay Manal [1,*] and Halani Hiral [2]

[1] *GMERS Medical College and Hospital, Gotri, Department of Medicine, Gujarat, India.*
[2] *Synergy Hospital, Department of Neurology, Gujarat, India.*

World Journal of Advanced Research and Reviews, 2025, 27(03), 176-182

Publication history: Received on 13 March 2025; revised on 14 May 2025; accepted on 16 May 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.27.3.1405

Abstract

This case report describes a patient diagnosed with a rare cause of leukoencephalopathy called Mitochondrial Neurogastrointestinal encephalopathy (MNGIE) syndrome. The patient had cachexia and a childhood history of gastrointestinal symptoms for which he was diagnosed with superior mesenteric artery syndrome. During early adulthood, he developed progressive sensory-motor polyneuropathy and ophthalmoplegia along with skeletal abnormalities. The patient's parents are in a consanguineous marriage and his elder sibling died at a younger age. The combination of multisystem involvement from the patient's history raised the suspicion of a genetic disease involvement and testing revealed MNGIE. This case report highlights the challenges of suspecting and diagnosing rare causes of leukoencephalopathy such as MNGIE when presenting with overlapping symptoms and multisystem involvement since early childhood.

Keywords: Leukoencephalopathy; Polyneuropathy; Ophthalmoplegia; Genetic disease

1. Introduction

Mitochondrial Neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive disorder with a rare prevalence caused by TYMP gene mutation resulting in loss of function of thymidine phosphorylase enzyme [1]. This produces systemic biochemical imbalance as thymidine and deoxyuridine accumulate in blood producing defects in mitochondrial DNA (mtDNA) replication and repair, resulting in improper functioning of mitochondria in various body tissues [2]. It presents with a combination of gastrointestinal and neurological symptoms such as gastrointestinal dysmotility, cachexia, ptosis and ophthalmoparesis, peripheral neuropathy, and diffuse leukoencephalopathy [3]. The prevalence being unknown, a study showed a European incidence of <1 in a million, with Orphanet estimating the prevalence to be 1-9 in 1,000,000 worldwide (Orphanet, 2018). From 1988 to 2011, only 102 documented cases were reported [4]. The disease was first described in 1976 but the current term was coined after a systematic review done by Hirano et al [5]. The mean age of onset of MNGIE is the first two decades of life and the mean age of death is 36.7 years [6].

The diagnosis of MNGIE syndrome can be confirmed from either genetic testing of mutant variants of the TYMP gene or biochemical investigations showing any of the following (a) Raised levels of plasma thymidine and deoxyuridine (b) decreased thymidine phosphorylase enzyme activity [7]. Though a challenging diagnosis, keeping it as a differential for such nonspecific symptoms is crucial for its early diagnosis. It is one of the mitochondrial disorders, which has some treatment options available that can improve the quality of life by slowing down the progression. Interventions such as targeted therapy, stem cell transplantation along symptomatic management can affect the patient's prognosis [8]. Thus the purpose of this case report is to heighten clinical awareness by educating on the importance of considering a rare

* Corresponding author: Upadhyay Manal

diagnosis such as MNGIE in patients presenting with diffuse leukoencephalopathy, with early childhood multisystem involvement, and to provide insights on the effects of early intervention on patient outcomes to effectively manage similar patients.

2. Case presentation

A 23-year-old man presented with complaints of progressive difficulty in walking, which he first noticed a few months back. He also reported imbalance while walking and repeated falls without any precipitating triggers. He also had a feeling of numbness in his legs and slipped out of slippers without awareness. Two years later, he started having difficulty in fine motor activities of his upper limb such as buttoning clothes and writing. He had no history of speech abnormality. The patient had a childhood history of delayed achievement of motor milestones. In his teens, he developed gastrointestinal symptoms of anorexia, frequent vomiting, and failure to gain weight for which he was diagnosed with superior mesenteric artery syndrome and underwent surgery. Notably, the patient's parents are in consanguineous marriage and his elder sibling died at a younger age but the cause of death is unknown.

On examination, the patient appeared cachexic with notable overall muscle wasting. Higher functions including speech were normal. The ocular examination revealed extraocular paresis and bilateral partial ptosis with normal pupils. Motor examination revealed hypotonia with bilateral distal motor weakness, more in lower limbs as compared to upper limbs, and generalized areflexia. He also had bilateral foot drop along with the presence of sensory ataxia that resulted in steppage gait and Romberg's test was positive. Musculoskeletal findings include bilateral pes cavus and hallux valgus, common deformities associated with hereditary polyneuropathy. The combination of cachexia, neuromuscular, and skeletal deformities suggested a classic presentation of MNGIE requiring a multidisciplinary approach.

The routine blood work was normal and Nerve conduction studies revealed generalized symmetric demyelinating sensory and motor polyneuropathy. Brain t2w and flair MR images showed bilateral subcortical, deep and periventricular white matter hyperintensities demonstrating diffuse leukoencephalopathy as per FIGURE 1. Due to MNGIE suspicion, exon sequencing was done that showed a pathogenic variant at exon 3 with uncertain significance as per FIGURE 2 and 3 consistent with the diagnosis of MNGIE.

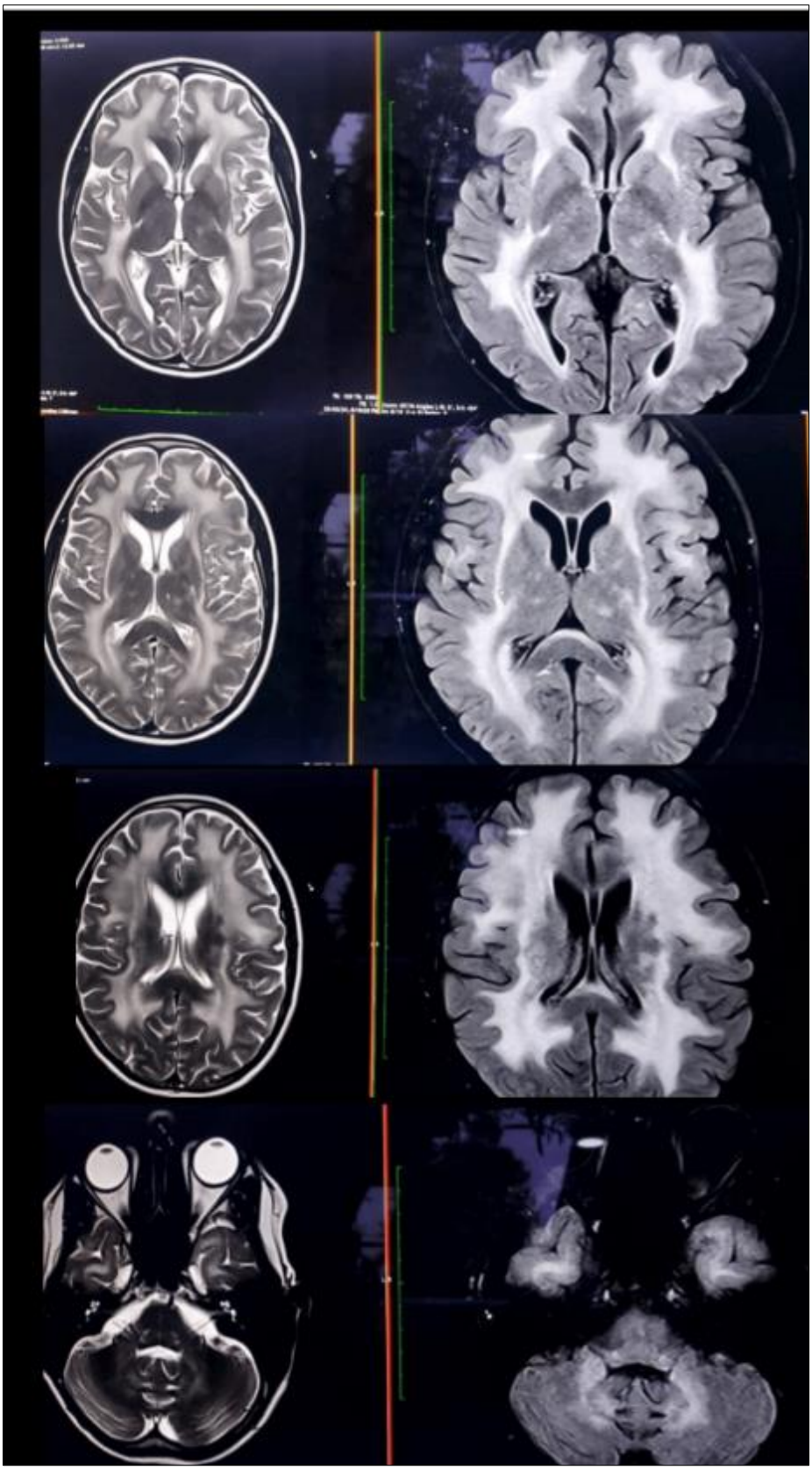
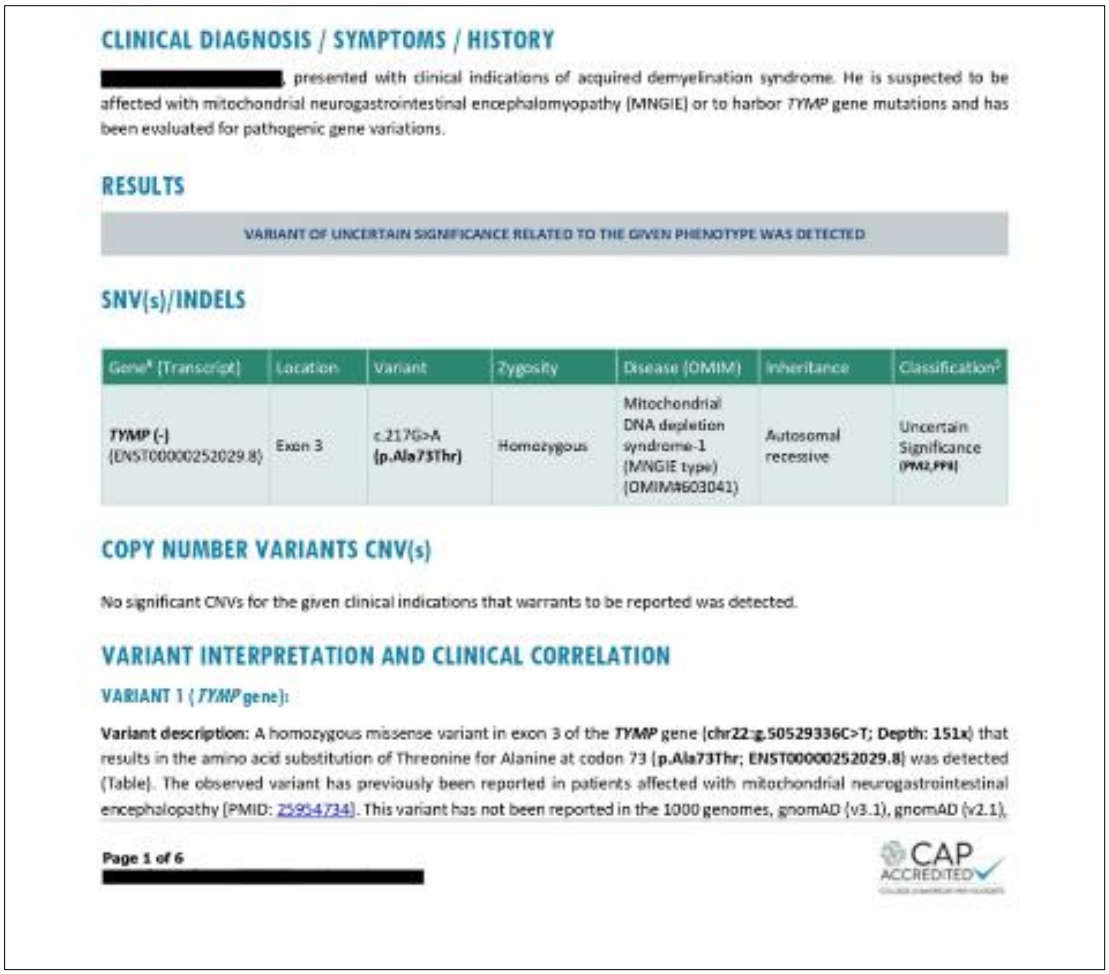


Figure 1 Axial T2-weighted Brain MRI image(left) and Axial FLAIR Brain MRI image(right): showing diffuse leukoencephalopathy



CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

[redacted], presented with clinical indications of acquired demyelination syndrome. He is suspected to be affected with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) or to harbor *TYMP* gene mutations and has been evaluated for pathogenic gene variations.

RESULTS

VARIANT OF UNCERTAIN SIGNIFICANCE RELATED TO THE GIVEN PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene[1] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[2]
***TYMP* (-)** (ENST00000252029.8)	Exon 3	c.217G>A **(p.Ala73Thr)**	Homozygous	Mitochondrial DNA depletion syndrome-1 (MNGIE type) (OMIM#603041)	Autosomal recessive	Uncertain Significance **(PM2,PP3)**

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

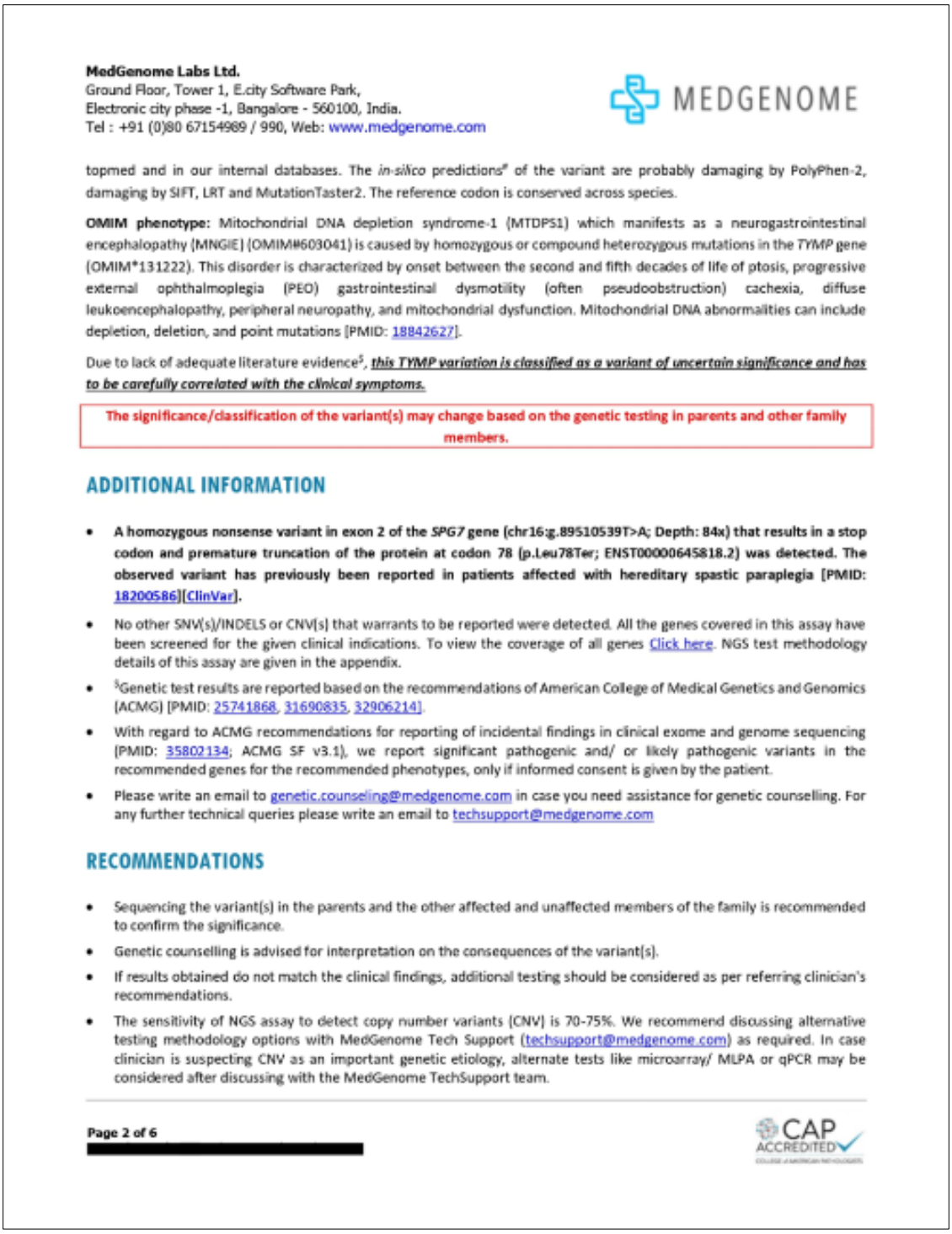
VARIANT 1 (*TYMP* gene):

Variant description: A homozygous missense variant in exon 3 of the ***TYMP*** gene (**chr22:g.50529336C>T; Depth: 151x**) that results in the amino acid substitution of Threonine for Alanine at codon 73 (**p.Ala73Thr; ENST00000252029.8**) was detected (Table). The observed variant has previously been reported in patients affected with mitochondrial neurogastrointestinal encephalopathy (PMID: 25954734). This variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1),

Page 1 of 6 [redacted]

CAP ACCREDITED

Figure 2 Biochem report_page-0001



MedGenome Labs Ltd.
Ground Floor, Tower 1, E.city Software Park,
Electronic city phase -1, Bangalore - 560100, India.
Tel : +91 (0)80 67154989 / 990, Web: www.medgenome.com

MEDGENOME

topmed and in our internal databases. The *in-silico* predictions# of the variant are probably damaging by PolyPhen-2, damaging by SIFT, LRT and MutationTaster2. The reference codon is conserved across species.

OMIM phenotype: Mitochondrial DNA depletion syndrome-1 (MTDPS1) which manifests as a neurogastrointestinal encephalopathy (MNGIE) (OMIM#603041) is caused by homozygous or compound heterozygous mutations in the *TYMP* gene (OMIM*131222). This disorder is characterized by onset between the second and fifth decades of life of ptosis, progressive external ophthalmoplegia (PEO) gastrointestinal dysmotility (often pseudoobstruction) cachexia, diffuse leukoencephalopathy, peripheral neuropathy, and mitochondrial dysfunction. Mitochondrial DNA abnormalities can include depletion, deletion, and point mutations [PMID: 18842627].

Due to lack of adequate literature evidence[5], ***this TYMP variation is classified as a variant of uncertain significance and has to be carefully correlated with the clinical symptoms.***

The significance/classification of the variant(s) may change based on the genetic testing in parents and other family members.

ADDITIONAL INFORMATION

- **A homozygous nonsense variant in exon 2 of the *SPG7* gene (chr16:g.89510539T>A; Depth: 84x) that results in a stop codon and premature truncation of the protein at codon 78 (p.Leu78Ter; ENST00000645818.2) was detected. The observed variant has previously been reported in patients affected with hereditary spastic paraplegia [PMID: 18200586][ClinVar].**
- No other SNV(s)/INDELS or CNV(s) that warrants to be reported were detected. All the genes covered in this assay have been screened for the given clinical indications. To view the coverage of all genes Click here. NGS test methodology details of this assay are given in the appendix.
- [5]Genetic test results are reported based on the recommendations of American College of Medical Genetics and Genomics (ACMG) [PMID: 25741868, 31690835, 32906214].
- With regard to ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (PMID: 35802134; ACMG SF v3.1), we report significant pathogenic and/ or likely pathogenic variants in the recommended genes for the recommended phenotypes, only if informed consent is given by the patient.
- Please write an email to genetic.counseling@medgenome.com in case you need assistance for genetic counselling. For any further technical queries please write an email to techsupport@medgenome.com

RECOMMENDATIONS

- Sequencing the variant(s) in the parents and the other affected and unaffected members of the family is recommended to confirm the significance.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.
- The sensitivity of NGS assay to detect copy number variants (CNV) is 70-75%. We recommend discussing alternative testing methodology options with MedGenome Tech Support (techsupport@medgenome.com) as required. In case clinician is suspecting CNV as an important genetic etiology, alternate tests like microarray/ MLPA or qPCR may be considered after discussing with the MedGenome TechSupport team.

Page 2 of 6

CAP ACCREDITED

Figure 3 Biochem report_page-0002

3. Discussion

This case illustrates the importance of considering rare differentials of leukoencephalopathy such as MNGIE, especially in patients with a history of early childhood gastrointestinal symptoms and mild developmental delay in motor functions. The strengths of this case are the classic presentation of MNGIE and the illustration of a diagnostic challenge because of the disease's rarity and overlapping symptoms. The importance of clinical suspicion of a hereditary cause combined with the targeted diagnostic testing adds additional strength to the case.

However initial diagnosis of superior mesenteric artery syndrome clouded the suspicion of MNGIE which led to a delay in the diagnosis. Existing literature has shown an association of MNGIE with IBD and pseudo-obstruction, but its association with superior mesenteric artery syndrome like anatomical syndromes and consequent surgery has not been reported [9,10]. Sometimes patients undergo unnecessary surgery due to gastrointestinal involvement [11]. This patient also underwent surgery for superior mesenteric artery syndrome. In clinical practice, this case can be a reminder that when presented with leukoencephalopathy with a previous history of GI symptoms, MNGIE must remain on differentials. Misdiagnosis or delay in diagnosis can significantly affect the morbidity and mortality of MNGIE which already has a poor prognosis with the mean age of death 35 years [12]. Thus, it is crucial for diagnosticians to actively pursue relevant investigations when the suspicion is high.

4. Conclusion

This case report is written to emphasize on the possibility of rare genetic causes for diffuse encephalopathy like MNGIE in young individuals, particularly demonstrating gastrointestinal symptoms and an early childhood history of some developmental delays. The classic MNGIE presentation in this case underscores the diagnostic challenge it poses because of its rare prevalence and overlapping symptoms with other diseases. This case also highlights importance of clinical suspicion and diagnostic testing even when initial diagnosis of an anatomical syndrome was made and treated that can obscure the true underlying disorder.

Unique diseases like MNGIE, with poor prognosis need early identification to improve the quality of life of patients and a personalized approach to slow down the progression. This case report serves as a reminder to the clinicians to keep a broader range of differentials on the list for improved outcomes of patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. Neurologist. 2004 Jan; 10(1):8-17. Doi: 10.1097/01.nrl.0000106919.06469.04. PMID: 14720311.

[2] Lara MC, Valentino ML, Torres-Torronteras J, Hirano M, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): biochemical features and therapeutic approaches. Biosci Rep. 2007 Jun; 27(1-3):151-63. Doi: 10.1007/s10540-007-9043-2. PMID: 17549623.

[3] Filosto M, Cotti Piccinelli S, Caria F, Gallo Cassarino S, Baldelli E, Galvagni A, Volonghi I, Scarpelli M, Padovani A. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE-MTDPS1). Journal of clinical medicine. 2018 Oct 26; 7 (11):389.

[4] Kareem, Shabana; Mathai, Reemy Sara. An Indian Case Study on Mitochondrial Neurogastrointestinal Encephalomyopathy. Archives of Medicine and Health Sciences (): 10.4103/amhs.amhs_295_23, June 28, 2024. | DOI: 10.4103/amhs.amhs_295_23

[5] Pacitti D, Levene M, Garone C, Nirmalananthan N, Bax BE. Mitochondrial Neurogastrointestinal Encephalomyopathy: Into the Fourth Decade, What We Have Learned So Far. Front Genet. 2018 Dec 21; 9669. Doi: 10.3389/fgene.2018.00669. PMID: 30627136; PMCID: PMC6309918.

[6] Bax BE. Mitochondrial neurogastrointestinal encephalomyopathy: approaches to diagnosis and treatment. Journal of translational genetics and genomics. 2020 Mar 30; 4:1.

[7] Khan ZR, Karam A, Ul Haq MA, Aman A, Karam AS: Mitochondrial neurogastrointestinal encephalomyopathy in a Pakistani female: a case report. J Med Case Rep. 2022161, 363-2022. 10.1186/s13256-022-03582-6

[8] Yadak R, Sillevis Smitt P, Van Gisbergen MW, Van Til NP, De Coo IF. Mitochondrial neurogastrointestinal encephalomyopathy caused by thymidine phosphorylase enzyme deficiency: from pathogenesis to emerging therapeutic options. Frontiers in cellular neuroscience. 2017 Feb 15; 11: 31.

[9] Cousyn L, Boehm V, Shor N, Treton X, Benamouzig R, Gaignard P, Nadjar Y. Brain White Matter Lesions and Presumed Crohn's Disease: Did You Consider MNGIE? Can J Neurol Sci. 2020 Jul; 47(4):572-575. Doi: 10.1017/cjn.2020.41. Epub 2020 Mar 3. PMID: 32122424.

[10] Yadak R, Breur M, and Bugiani M. Gastrointestinal Dysmotility in MNGIE: from thymidine phosphorylase enzyme deficiency to altered interstitial cells of Cajal. Orphanet J Rare Dis. 2019 Feb 8; 14(1):33. Doi: 10. 1186/ s13023-019-1016-6. PMID: 30736844; PMCID: PMC6368792.

[11] Jamalipour Soufi G, Hekmatnia A, Hekmatnia F, Zarei AP, Riahi F, Shafieyoon S, Azizollahi S. Mitochondrial neurogastrointestinal encephalopathy: a case report. Egyptian Journal of Radiology and Nuclear Medicine. 2024 Jul 9; 55(1):137.

[12] Barisic A, Ljubas Kelecic D, Vranesic Bender D, Karas I, Brinar M, Miletic V, Krznaric Z. Case report: A patient with mitochondrial neurogastrointestinal encephalomyopathy and chronic intestinal failure. Front Nutr. 2022 Nov 7;9: 983873. Doi: 10.3389/fnut.2022.983873. PMID: 36419558; PMCID: PMC9676446.