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A Rare Case of Adult-Onset Leukodystrophy

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Abstract: ***Introduction: Methylene tetrahydrofolate reductase (MTHFR) deficiency is a rare autosomal recessive disorder affecting folate metabolism and homocysteine remethylation, resulting in elevated homocysteine levels and hypomethioninemia. While most cases manifest in infancy or childhood, adult-onset forms are rare and may mimic other neurodegenerative disorders such as leukodystrophies, hereditary spastic paraparesis, or inflammatory demyelinating diseases. Case Report: An 18-year-old male, born of third-degree consanguineous parentage and diagnosed with hypothyroidism, presented with a 1½-year history of progressive decline in scholastic performance, followed by weakness and stiffness of both lower limbs and later upper limb weakness. He also developed generalized tonic-clonic seizures for 6 months. Neurological examination revealed spastic quadriparesis with exaggerated lower limb reflexes and extensor plantar responses, with normal sensory, cerebellar, and cranial nerve functions. MRI brain showed confluent periventricular T2 and FLAIR hyperintensities suggestive of leukodystrophy. Serum vitamin B12 was low (98 pg/ml), and genetic testing confirmed MTHFR deficiency. Treatment And Outcome: The patient was treated with oral betaine (3 g/day), vitamin B12, and pyridoxine, resulting in mild clinical improvement. Conclusion: MTHFR deficiency, although rare in adults, should be suspected in cases of unexplained spastic paraparesis, seizures, or cognitive decline. Early identification and metabolic therapy can halt progression and improve outcomes.***

Keywords: Leukodystrophy, MTHFR deficiency, Adult-onset leukodystrophy, Hyperhomocysteinemia, Betaine therapy

1. Introduction

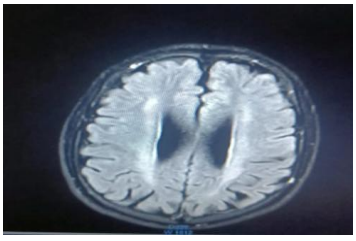
Leukodystrophies represent a group of genetic disorders primarily affecting white matter of the CNS. Among these, MTHFR deficiency is an autosomal recessive metabolic disorder impairing the remethylation of homocysteine to methionine.[2] The resultant hyperhomocysteinemia and hypomethylation disrupt myelin synthesis, leading to progressive neurological dysfunction.[3] Although usually seen in childhood, adult-onset variants may mimic multiple sclerosis or hereditary spastic paraparesis[4]

2. Case Report

An 18-year-old male, born of third-degree consanguineous parents, presented with 1½ years of scholastic decline, progressive weakness of all four limbs, stiffness of both lower limbs, and seizures for 6 months. He was known hypothyroid since age 11 years on regular thyroxine therapy. Neurological examination revealed spastic quadriparesis, exaggerated reflexes in lower limbs, and extensor plantar responses without sensory or cerebellar deficits. MRI brain showed confluent periventricular T2/FLAIR hyperintensities suggesting leukodystrophy. Whole exome sequencing confirmed MTHFR mutation. Serum vitamin B12 was low (98 pg/ml) and homocysteine elevated.

3. Materials and Methods / Investigations

Routine labs were normal. CSF analysis showed protein 35 mg/dL, sugar 44 mg/dL, no cells, OCB negative. EEG normal. MRI spine normal. MRI brain showed confluent T2 and flair hyper intensities not showing diffusion restriction involving periventricular white matter likely leukodystrophy.



Thyroid profile: TSH 20.02 µIU/mL. Anti-TPO antibody 66 IU/mL. Vitamin B12 98 pg/mL, raised to 1950 pg/mL after supplementation. Whole exome sequencing revealed MTHFR gene mutation confirming diagnosis.

4. Final Diagnosis

S. No	Gene, Variant details	Zygosity Depth (Alt allele %)	In silico tools	MAF	Literature	OMIM Disease	Inheritance	Classification
1	***MTHFR* (-)** c.459C>G p.Ile153Met Exon-3 ENST00000376590.9	Homozygous 83x (100%)	SIFT - D LRT - D PolyPhen - PrD MT2 - D	1000 G - NA gnomAD (V2.1) - 0.01% gnomAD (V3.1) - NA MedVar - 0.1%	PUBMED - 35322348 CLINVAR ID - 996033	Homocystinuria due to methylenetetrahydrofolate reductase deficiency (OMIM#236250)	Autosomal recessive	Uncertain Significance *

Abbreviation: D: Damaging; Prd: Probably damaging; BN: Benign; T: Tolerated; MAF: minor allele frequency; MedVar: MedGenome Internal database: MT2: MutationTaster2

Adult-onset leukodystrophy secondary to MTHFR deficiency.

Treatment and Follow-Up

Patient was treated with betaine (3 g/day), vitamin B12 injections, and pyridoxine. He showed mild improvement and stabilization of symptoms after therapy.

5. Discussion

Methylene tetrahydrofolate reductase (MTHFR) deficiency is a rare metabolic disorder impairing remethylation of homocysteine to methionine, leading to hyperhomocysteinemia and hypomethylation of myelin phospholipids.[2] The resultant demyelination produces characteristic white matter changes and progressive neurological dysfunction.[3] Although classically seen in infancy, adult-onset forms present with spastic paraparesis, cognitive decline, and seizures, often mimicking hereditary or inflammatory leukodystrophies.[4] MRI typically shows symmetric periventricular and deep white matter hyperintensities without contrast enhancement.[5] Hyperhomocysteinemia with normal folate and low methionine strongly suggests the diagnosis, confirmed by genetic testing.[6] Treatment with betaine, vitamin B12, folinic acid, and pyridoxine helps remethylation and may halt disease progression.[6] Early recognition is crucial, as delayed therapy leads to irreversible neurological damage.[7] MTHFR deficiency represents one of the few treatable causes of adult-onset leukodystrophy.[7],[8]

6. Conclusion

Adult-onset MTHFR deficiency should be suspected in young adults with unexplained spastic paraparesis, cognitive decline, or epilepsy, especially when MRI shows white matter abnormalities. Early diagnosis through serum homocysteine and vitamin B12 levels followed by genetic testing allows timely initiation of therapy and prevents irreversible neurological damage.

Ethical Considerations

Written informed consent was obtained from the patient's family for use of clinical data and imaging in this publication.

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