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Research paper

Homocystinuria presents with generalized tonic-clonic seizure and Broca's aphasia

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Abstract

Homocystinuria follows an autosomal recessive pattern and transpires due to Cystathionine beta-synthase enzyme deficiency. This condition is associated with thrombotic and thromboembolic complications due to an increase in homocysteine and methionine levels in the plasma and urine. We present a case of an Indian adolescent boy who presented to us with generalized tonic clinic seizure and Broca's aphasia he was diagnosed as having homocystinuria type 1, and he responded well to treatment.
Background: Stroke and seizure disorders in young adults have increased substantially and are a relatively common disorder that presents in the emergency department in all age groups. Secondary seizures are more common and manifest as a result of another underlying pathology. This case demonstrates the importance of considering rarer causes of thrombosis such as arterial thrombosis, even in younger patients, with no obvious risk factors or comorbidities. A detailed medical history and thorough investigations need to be taken to identify a potentially treatable underlying cause.
Objective: To increase awareness about this rare etiology and help clinicians to have a higher level of suspicion to diagnose this condition and prevent future life-threatening complications in younger patients with thrombotic and thromboembolic events.

Keywords: *Cystathionine Beta-Synthase; Homocystinuria; Methionine; Thrombosis; Vascular Event.*

1. Introduction

Homocystinuria is an inborn error of metabolism that presents a wide range of signs, symptoms, and clinical manifestations. The biochemical pathway follows the conversion of methionine to cysteine in which homocysteine acts as a crucial intermediate. Homocysteine is remethylated back to methionine. This pathway requires the enzyme methionine synthase, which requires a metabolite of 5-methyltetrahydrofolate and vitamin B12 as a cofactor. As the biochemical pathway proceeds further homocysteine to cystathionine needs pyridoxal phosphate-dependent as well as cystathionine beta-synthase enzymes (1, 2).
Deficiency of cystathionine beta-synthase enzyme results in accumulation of homocysteine. Increased levels of homocysteine convert back into methionine. Homocystinuria -Type 1 is the most common type of inborn error of metabolism causing homocystinuria which occurs due to deficiency of the Cystathionine beta-synthase enzyme (2). It presents with varied signs and symptoms, e.g. ectopia lentis, developmental delay, skeleton abnormalities, mental retardation, Marfan syndrome, and thromboembolic episodes (3). Type II and Type III homocystinuria arise secondary to defects in the methylation pathway (4). We came across an interesting patient who presented with generalized tonic-clonic seizure and Broca's aphasia. After a series of investigations, we concluded the diagnosis of Homocystinuria Type I, and the patient were successfully treated for the same as per the institutional protocol.

2. Case report

A 19-year-old right-handed Indian adolescent presented with a postictal state, reported tongue bite, loss of consciousness along with urinary and stool incontinence. The seizure was witnessed by a friend who reported an abrupt loss of consciousness while studying at the table immediately followed by the generalized tonic-clonic movements lasting for approximately 1-2 minutes. The patient endorsed a headache the day before this convulsive event. Postictally, he fell asleep. He had no past medical history and is up to date with his vaccination, along with that he was academically a bright student, and his dietary history was also normal. The patient does not misuse addictive substances or any drugs. His family history comprised of syringomyelia in his mother who died 5 years ago and his elder sister had a cerebral venous sinus thrombosis 9 months ago.
On physical examination in the emergency department, the patient appeared appropriate to his age with altered mental status, blood pressure of 110/80 mmHg, a pulse of 91 beats per minute, a temperature of 99.8°F, respiratory rate of 18 breaths per minute, and oxygen saturation 99% on room air.

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On neurological examination, cranial nerve examination was normal. Meningeal signs were absent and no abnormal movements of the limbs. Muscle bulk and tone were normal, bilaterally symmetric. The tone was normal in both the upper and lower extremities. Deep tendon reflexes were 2+, symmetric. Planters were down-going bilaterally. No cerebellar signs were present. The skull and spine were normal. The rest of the examination including the cardiovascular system, abdomen, and musculoskeletal system, as well as an eye exam, was unremarkable.

Upon awakening out of his postictal state, he started to show letter exclusion, agrammatism, and poor formation of words. An MRI of the brain showed an abnormal signal intensity on T2 FLAIR images involving the left frontal region anterior to the motor cortex and above the left insula (see Figure. 1).

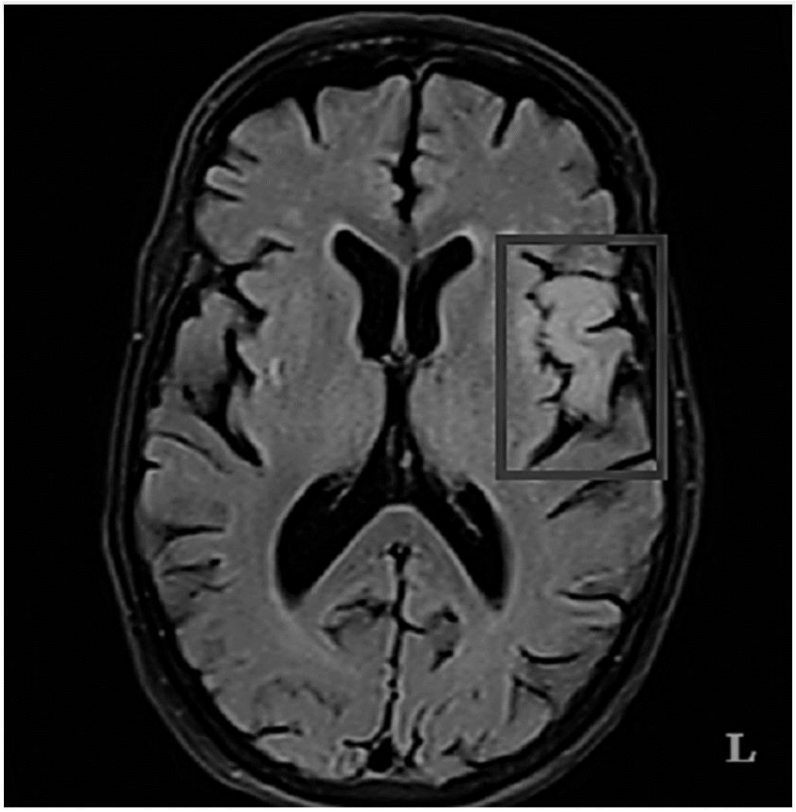


Fig. 1: An Abnormal Signal Intensity Involving in the Left Frontal Region Anterior to the Motor Cortex and Above the Left Insula.

According to the MRI report, the young patient with high specious blood coagulopathy. A blood investigation was ordered and showed hemoglobin of 13 gm%, total and differential leukocyte count was normal. The platelet count was 160 × 10^3/cm. Liver function test, renal function test, serum electrolytes, and blood sugar were also normal. Serum homocysteine level was ordered which resulted in an elevated homocysteine level was 332.43 µmol/L (normal range: 4.60–12.44 µmol/L). The serum vitamin B12 level was 510 pg/ml (normal range: 200–800 pg/ml). The fasting plasma methionine level was elevated to 169.67 µmol/L (normal range: 0–90 µmol/L).

The patient was started on anticonvulsant therapy Valproic acid along with high doses of oral pyridoxine, methylcobalamin, and folic acid. The patient was put on a low protein and methionine diet at the time of discharge. The patient was advised to continue speech and language therapy. Going through the patient family history as well as an elevated level of homocysteine in the plasma genetic testing was carried out on the patient and the diagnosis was confirmed to be homocystinuria. The patient continued with this treatment for 3 months and his serum homocysteine level on follow-up was 9.90 µmol/L (normal range: 4.60–12.44) along with that patient, aphasia improve by speech and language therapy and no seizure episode was imminent after starting of the treatment.

3. Discussion

In a normal biochemical pathway, Homocysteine is not detectable in plasma or urine. However, when the conversion of homocysteine to methionine or cysteine is aborted due to enzyme deficiency this results in the accumulation of homocysteine in the extracellular component. The most common cause of classical homocystinuria (type I) is due to Cystathionine beta-synthase (CBS) gene mutation and type 1 is always associated with the thrombotic and thromboembolic events and absence of megaloblastic anemia which is more common in homocystinuria type-II and III (5). Its prevalence is estimated to be 0.82 per 100,000 worldwide as well as extremely rare in the Asian population (~0.02:100,000). It highlights this condition as being an extremely orphan disease (5).

Pathophysiology: An increased level of homocysteine is associated with an increased risk of stroke, coronary artery disease, and venous thromboembolism. There are many proposed mechanisms by which homocysteine causes this including endothelial dysfunction, increases platelet reactivity, increased thrombin production as well as decreased action of the antithrombotic factors (6).Thromboembolic episodes as well as thrombosis occurring in both large and small vessels of the brain are commonly seen in type-I homocystinuria and can occur at any age (2). In our patient, an increased level of homocysteine caused thrombotic occlusion of the inferior temporal branch of the left middle cerebral artery resulting in Broca's aphasia and seizure. Treatment of Homocystinuria Type-I requires high doses of pyridoxine, which work as a coenzyme for the Cystathionine beta-synthase and increases its affinity for binding with the substrate (7). Gradual improvement was noted in our patient through this therapy as we noticed through his follow-up results.

4. Conclusion

Although it is rare homocystinuria should always be considered when young age patients presenting not only with stroke symptoms but even with any acute neurological symptoms including seizures, especially when there is a family history of thrombo-embolic conditions. The patient may not always exhibit classical features of homocystinuria as noted in our case. Genetic counseling of the family and early age screening plays an important role in accurate diagnosis and prevention of complications of this disease. This case allows us to increase awareness about the diagnosis amongst physicians in other specialties as well as may help with early detection of the condition. The treatment of homocystinuria type 1 with high doses of pyridoxine and folate plays a significant role in the prevention of thromboembolic complications as well as in halting the progression of the disease and associated complications.

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References

[1] Grieco AJ. Homocystinuria: pathogenetic mechanisms. Am J Med Sci. 1977 Mar-Apr;273(2):120-32. [PMID: 324277]. https://pubmed.ncbi.nlm.nih.gov/324277/. https://doi.org/10.1097/00000441-197703000-00001.

[2] Rezvani I. Defects in metabolism of amino acids. Methionine. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics, 16th ed. Philadelphia: Saunders; 2000. p. 350-2.

[3] Fatima S, Hafeez A, Ijaz A, Asif N, Awan A, Sajid A. Classical Homocystinuria in a Juvenile Patient. J Coll Physicians Surg Pak. 2018 Jun; 28(6):488-489. [PMID: 29848432]. https://pubmed.ncbi.nlm.nih.gov/29848432/. https://doi.org/10.29271/jcpsp.2018.06.488.

[4] Sulochana KN, Amirthalakshmi S, Vasanthi SB, Tamilselvi R, Ramakrishnan S. Homocystinuria with congenital/developmental cataract. Indian J Pediatr. 2000 Oct; 67(10):725-8. [PMID: 11105422]. https://pubmed.ncbi.nlm.nih.gov/11105422/. https://doi.org/10.1007/BF02723928.

[5] Weber Hoss GR, Sperb-Ludwig F, Schwartz IVD, Blom HJ. Classical homocystinuria: A common inborn error of metabolism? An epidemiological study based on genetic databases. Mol Genet Genomic Med. 2020 June; 8(6):e1214. Epub 2020 Mar 30. [PMID: 32232970]; PMCID: PMC7284035. https://pubmed.ncbi.nlm.nih.gov/32232970/. https://doi.org/10.1002/mgg3.1214.

[6] Undas A, Brozek J, Szczeklik A. Homocysteine and thrombosis: from basic science to clinical evidence. Thromb Haemost. 2005 Nov; 94(5):907-15. [PMID: 16363230]. https://pubmed.ncbi.nlm.nih.gov/16363230/. https://doi.org/10.1160/TH05-05-0313.

[7] Sunil G, Pooja D, Tarun D. Homocystinuria: A rare cause of megaloblastic anemia. Indian Pediatr 2004; 41:9413. https://pubmed.ncbi.nlm.nih.gov/15475638/.