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Hyperhomocysteinemia and paediatric stroke: A case series

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Abstract: Background: Cerebrovascular disease in children is a rare occurrence with an annual incidence of 2.7/100,000 children. There are limited reports revealing stroke in pediatric population associated with hyperhomocysteinemia. We present a series of cases discussing the clinicolaboratory, radiological findings and management of children presenting with hyperhomocysteinemia and stroke.
Aim and Objective: To study the clinicolaboratory profile, radiological findings and outcome of children with hyperhomocystienemia and stroke.
Methodology: This is a retrospective observational study where case records of paediatric patients (<18 years) who had stroke associated with Hyperhomocysteinemia were studied. Over the last five years, seven were diagnosed with hyperhomocystienemia associated with paediatric stroke.
Results: Out of the seven patients, six of them presented with headache and hemiparesis, one presented with convulsions. Mean age of presentation was 9 ±1.5 years. Neuroimaging in all suggested acute cerebrovascular infracts. All had elevated homocysteine levels and five had documented low vitamin B12 levels. MTHFR gene was positive in one patient. Bilateral lens dislocation was observed in three of them. Intellectual disability was observed in four of these patients, and marfanoid features were seen in three of them. All the patients were started on low dose aspirin and polyvitamin therapy. Four patients had complete recovery, one is still improving and one was lost to follow up. Recurrence was observed in one patient.
Conclusion: Commonest symptoms were headache and hemiparesis. Manifestations of hyperhomocysteinemia can start in infancy. Homocystiene estimation should be included in work up of paediatric stroke and polyvitamin therapy should be included in management.

Keywords: Hyperhomocysteinemia; Stroke; Pediatric stroke.

1. Introduction

Hyperhomocysteinemia is a rare but treatable condition and an important risk factor for stroke in children. The prevalence rates of hyperhomocysteinemia are 5%-7% in the general population and 25% among those with vascular diseases [1,2]. Homocysteine, a sulfhydryl containing amino acid produced by the demethylation of methionine, potentiates oxidation of very low-density lipoprotein, which is toxic to endothelial cells and can cause arterial and venous thrombosis [3,4]. Hyperhomocysteinemia influences the disease in children via its prothrombotic properties [5].

The etiology of hyperhomocysteinemia can be due to dietary and genetic factors. Several genetically inherited enzyme mutations causing elevated homocysteine levels have been described, commonest of which is a cytosine to thymine mutation at nucleotide 677 (C677T) of N^5,N^{10}-methylenetetrahydrofolate reductase (MTHFR). MTHFR deficiency is a heterogeneous presentation, which is inherited in an autosomal recessive manner. The MTHFR gene is susceptible to several mutations, with non-sense mutations being the most common. Other genes associated with hyperhomocystienemia are cystathionine beta-synthase (CBS) and methionine synthase (MS) and their genetic variants. Methionine synthase plays an important role in the homocysteine metabolism as a key enzyme in the remethylation pathway. The methionine synthase gene has several polymorphisms of which A2756G SNP (rs1805087) is prevalent. Abnormal cystathionine beta-synthase activity leads to the manifestation of two major clinical conditions, such as hyperhomocysteinemia and

homocystinuria. Of the large number of mutations identified in human cystathionine beta-synthase gene, a transition mutation, T833C (rs5742905) is common [6].

Normal homocysteine metabolism is dependent upon adequate stores of three dietary vitamins: folic acid, vitamin B_{12} (cobalamin), and vitamin B_6 (pyridoxal phosphate). Therefore a deficiency in these vitamins, either dietary or due to malabsorption can lead to hyperhomocysteinemia. Hyperhomocysteinemia is also reported to be strongly associated with renal diseases possibly because protein bound homocystiene reduces GFR, increasing circulating homocysteine levels. Hypothyroidism and estrogen deficiency states are also known to be associated with hyperhomocysteinemia. Medications such as phenytoin, sulfzalazine, and methotrexate, have also been shown to increase homocysteine levels either by directly depleting folate stores, or impairing synthesis of enzyme cofactors required for normal homocysteine metabolism [6].

Hyperhomocysteinemia can manifest in individuals of varying ages and with different degrees of severity. It can have multisystemic early childhood presentation involving neurological, ophthalmic, skeletal, and hematological manifestations. The condition is categorized as moderate(16-30micromol/l), intermediate(31-100micromol/l), or severe(>100micromol/l) based on the level of plasma homocysteine concentration [7]. The American Heart and Stroke Association recommends treatment with folic acid, vitamin B12, and vitamin B6 for all patients with hyperhomocysteinemia (>10mmol/l) due to its low cost and effectiveness. Normalization of plasma homocystiene concentration typically occurs within 2 to 6 weeks of starting therapy [8].

Herein we present this case series due to the rarity of the association of hyperhomocysteinemia and stroke in paediatric age group.

2. Aim and Objective:

To study the clinicolaboratory profile, radiological findings and outcome of children presenting with hyperhomocystienemia and stroke.

3. Materials and Methods

This is a retrospective observational study conducted in Paediatric department. Case records of paediatric patients (<18 years) who had stroke associated with Hyperhomocysteinemia were studied. Out of twenty six cases of paediatric patients with stroke in the last five years, seven were diagnosed with hyperhomocystienemia. The age, gender, consanguinity, family history, thrombotic risk factors, clinicolaboratory findings and radiological findings were studied.

4. Results

Out of 26 cases of stroke in paediatric patients (<18 years) in the last five years, there were seven cases with hyperhomocysteinemia. The mean age at presentation was 9 ± 1.5 years (range 6 months to 14 years). There were four males and three females. Parental consanguinity was present in four of these cases (57%). Positive family history in a sibling having had stroke was seen in one case (14%). Positive past history of febrile seizures was observed in four of these children (57%). None of the cases had any thromboembolic risk factors. Other parameters like echocardiography, coagulation profile and basic hematological work up of all these patients were normal. Complete thrombotic work up was done in three of them which were normal. The commonest presenting features were headache (85%) and hemiparesis (85%). Four of them had left sided weakness (57%) while one patient had right sided weakness (14%) and one patient had right upper limb monoplegia (14%). Convulsion and vomiting was the presenting feature in one child (14%), who initially presented at 2.5 years of age. She later had recurrence of symptoms at 9 years of age in the form of headache and vomiting. Bilateral lens subluxation (anteroinferior) was seen in three patients (42%) and all three of them underwent lensectomy. Marfanoid habitus was seen four (57%) children. Of the seven patients, four of them were observed to have intellectual disability (57%). Homocysteine levels between 15-50 μmol/L (moderate) was observed in two (28%) patients and >50 μmol/L(intermediate and severe) was seen in five children. Vitamin B12 levels were available in four patients, all of which were low. MTHFR gene defect was confirmed in one patient by detailed genetic work up. Neuroimaging reports showed that five of the patients had arterial infarcts while two of them had venous infarcts. Three of them had right middle cerebral artery (MCA) infarct while two of the patients had right internal carotid artery (ICA) infarct and two patients had sagittal sinus thrombosis as found by MR

Angiography. The child who had recurrence of symptoms initially had sagittal sinus thrombosis, and later during recurrence of symptoms had cortical venous sinus thrombosis of left sigmoid sinus. All the patients were treated with a cocktail of folic acid, vitamin B6 and vitamin B12 and were also on anti-platelet dose of aspirin. Out of the seven patients, four patients had complete recovery of neurodeficit while one is improving and one was lost to follow up. Recurrence of symptoms was observed in one patient who had discontinued treatment.

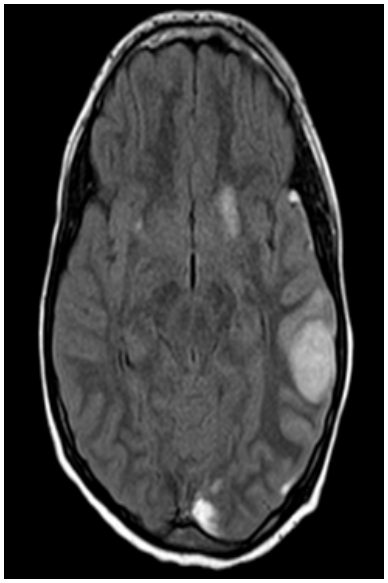

Figure 1. MRI Image of Case 2: Cortical Venous Thrombus, Sagital Sinus Thrombosis

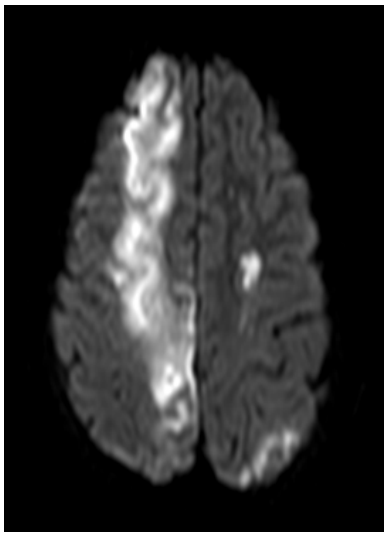

Figure 2. MRI Image of Case 5: Right Internal Carotid Artery infarct

Table 1. Patient characteristics, clinical presentation and outcome

Case No.	1	2	3	4	5	6	7
Patient details:	12y/ male	5 y/ female	6 m/ female	4 y/male	15 y/ female	10 y/ male	12 y/ male
Presentation during 1st admission	Headache, vomiting, left side hemiparesis, left facial palsy	Left side hemiparesis, headache	Left side hemiparesis	Convulsions, vomiting	Headache, left hemiparesis	Slurring of speech, hemiparesis right side	Right upper limb monoparesis
Consanguinity	No	3rd degree	3rd degree	3rd degree	No	No	3rd degree
Past history/Febrile seizures	Yes	Yes	No	Yes	No	No	Yes
Positive family history	No	Yes	No	No	No	No	No
Bilateral lens dislocation	No	Yes (7 years)	No	Yes(at 8 years)	No	Yes (11 years)	No
Intellectual disability	No	Mild	No	Mild	No	Mild	Mild
Marfanoid habitus	No	No	No	No	Yes	Yes	Yes
Neuroimaging	Right mca acute infarct	Cortical venous thrombus, sagital sinus thrombosis	Bilateral tca thrombosis	Superior sagittal portion thrombosis, sagittal sinus complete thrombosis	Right tca thrombosis	Left mca infarct	Left mca infarct
Homocysteine levels(4.3 - 13.3 micromol/l)	25.4	82	42	65	65	50	56
Vitamin b12 level (200-1500)	140	112	Not done	186	145	Not done	Not done
Thrombotic work up	Normal	Normal	Not done	Normal	Normal	Normal	Normal
Treatment	Folic acid, pyridoxine, cyanocobalamine supplements and low dose aspirin	Folic acid, pyridoxine, cyanocobalamine supplements and low dose aspirin	Folic acid supplements and low dose aspirin	Sodium valproate, folic acid, pyridoxine, cyanocobalamine supplements and low dose aspirin	Folic acid, pyridoxine, cyanocobalamine supplements and low dose aspirin	Folic acid supplements and low dose aspirin	Folic acid, pyridoxine, cyanocobalamine supplements and low dose aspirin
Repeat homocysteine level	16	80	52	98	Not done	Not done	No
Recurrence	No	Yes (9 years)	No	No	No	No	No

5. Discussion

The association between hyperhomocysteinemia and stroke in adults has been well documented in the literature. However, the prevalence of hyperhomocystienemia among paediatric stroke patients is not known.

There are only a few isolated case reports available in literature. We hereby report this case series due to the rarity of this association.

This case series presents seven cases of hyperhomocysteinemia in pediatric stroke patients. The mean age of the patients was 9 years, with a range of 6 months to 13 years. One of the larger studies by ven Beynum et al reported hyperhomocysteinemia in 8 out of 45 paediatric patients of ischemic stroke, the observed range of age group ranged from 16 months to 15 years [5].

There was no significant sex preponderance. The most common presenting features were hemiparesis and headache, which is consistent with previous case reports [5,9].

The study found a positive family history of hyperhomocysteinemia in one child, whose sibling JIA, Intan was also diagnosed with the condition. Four of the patients were born out of consanguineous marriages, which is consistent with previous research that suggests a genetic component to hyperhomocysteinemia. It has been reported in a Norwegian study on adolescent children that a modest elevation in serum homocysteine is related to premature cardiovascular death in male relatives, which may account for the contribution of family history to risk of cardiovascular disease [10].

Hyperhomocysteinemia can be due to genetic causes or due to dietary deficiencies or malabsorption of vitamin B12 and folic acid [6]. Genetic causes should be ruled out in all children with hyperhomocysteinemia. Out of the seven children in our study, MTHFR gene defect could be confirmed only in one child. Febrile seizures were observed in four of the patients in this series. This is consistent with previous research that has found homocysteine to act as an excitatory neurotransmitter that competes with gamma-aminobutyric acid, causing seizures. Seizure control was achieved in patients with hyperhomocysteinemia by vitamin B12 supplementation as observed in a study by Taskesen et al [11].

Intellectual disability was observed in four of the seven patients in this series. Previous research that has documented that hyperhomocysteinemia is a sensitive indicator of vitamin B12 deficiency in patients presenting with neuropsychiatric manifestations as reported by Lindenbaum et al [12].

Three of the patients in this series developed bilateral anterior subluxation of the lens on follow-up, while one patient developed secondary glaucoma as a complication. Similar observations have been made in a few isolated case reports. All three of our patients underwent lensectomy and vitrectomy. Lens dislocation reportedly occurs in 70% of patients with hyperhomocysteinemia by 8 years of age, and in 60% of cases, it is bilateral [13].

Marfan syndrome is one of the closest differential diagnoses in hyperhomocysteinemia patients due to their similar features like long limbs, pectus deformity and dislocated lenses. However hyperhomocystienemia does not have joint laxity or the cardiac manifestations associated with Marfan syndrome, and the lens dislocation is usually downward, not upward as in Marfan syndrome. Also, intellectual disability is only seen hyperhomocysteinemia [14].

Serum homocysteine levels can be lowered by polyvitamin therapy, which is inexpensive and well-tolerated. All seven patients in this series were started on a cocktail of folic acid, vitamin B12, and vitamin B7. Repeat homocystiene levels were done in five patients, all of who showed reduction in serum homocystiene levels, values of which have been mentioned in the summarizing table attached. This case series highlights the need for further research on hyperhomocysteinemia among pediatric stroke patients and the long-term effects of polyvitamin therapy on their outcomes.

Due to paucity of published data on the association of stroke and hyperhomocysteinemia in paediatric population, not much is known about the overall outcome. However, out of the seven patients in this case series, four patients had complete recovery while one is still improving and one was lost to follow up. Recurrence of symptoms was observed in one patient, who had discontinued medication and was lost to follow up for two years.

This case series highlights the clinical presentation, biochemical and radiological profile and outcome of children who presented with hyperhomocysteinemia.

6. Conclusion

Headache and hemiparesis were the commonest presenting feature. It can manifest even as early as infancy. Greater clinical awareness and high index of suspicion is important in the early recognition and

prevent catastrophic manifestations. A cocktail of vitamin B6, vitamin B12 and folic acid lowers serum homocystiene levels and should be considered an important part of management of the same.

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Conflicts of Interest: "The authors declare no conflict of interests."

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