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RESEARCH ARTICLE

HOMOCYSTINURIA IN A CHILD WITH CEREBRAL PALSY: A RARE CASE REPORT

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ABSTRACT

Homocystinuria is a rare autosomal recessive disorder with multiple systemic manifestations and is classified into three types(1-3).Classical(type 1)homocystinuria occurs due to deficiency of cystathionine beta- synthase(CBS),an enzyme which converts homocysteine to cystathionine in the trans-sulphuration pathway in the methionine cycle which requires pyridoxal-5-phosphate as a cofactor. The other two cofactors invoved in the remethylation pathway of methionine includes folate and vitamin B12.The four major organ systems involved are the eye, central nervous system, vascular system and skeletal system. The common neurological manifestations include mental retardation, psychiatric disturbances, extrapyramidal signs and less frequently seizures. Here we report a case of homocystinuria in a child with cerebral palsy who presented with focal seizures.

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INTRODUCTION

Homocystinuria is a rare autosomal recessive disorder with a worldwide incidence of 1:2,00,000 live births. Three major types of homocystinuria have been identified and they are caused by three characteristic enzyme defects associated with methionine metabolism(Fig. 1).Type 1(Classical homocystinuria) is caused by the deficiency of the enzyme cystathionine beta-synthase(CBS) or the cofactor pyridoxine which converts homocysteine to cystathionine. Type 2 is due to deficiency of the enzyme tetrahydro folate methyltransferase and type 3 is due to the deficiency of tetrahydrofolate reductase; both of which convert homocysteine to methionine. More than 95% of homocystinuria are type 1.[1,2]

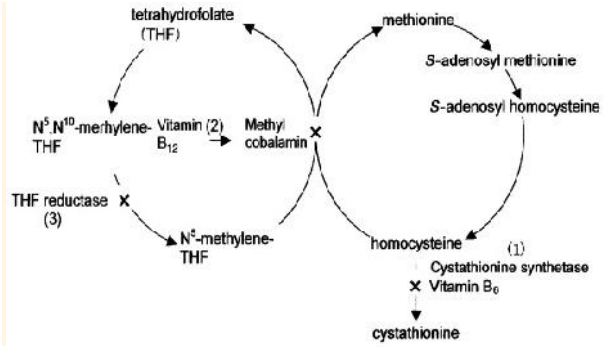

Fig 1. Metabolic pathway of methionine.(1)Classical type1 due to deficiency of CBS and Vit B6(cofactor)(2)Type 2 due to deficiency of tetrahydrofolate methyltransferase(3)Type 3 due to defect of tetrahydrofolate reductase

Classical form of the disease can be suspected in the presence of one or more of the clinical manifestations but the definitive diagnosis is made by certain abnormal biochemical parameters. The typical amino acid profile characteristic of CBS or pyridoxine deficiency leading to the classical variety includes homocystinuria, hyperhomocysteinaemia, hypermethioninaemia and low plasma levels of cystine and cystathionine.

If the disease is diagnosed in the newborn period, the treatment should aim at preventing the development of ocular, skeletal, intravascular thromboembolic complications and to ensure normal development and intelligence. However when the condition is detected at a later stage when complications have already ensued, the clinician should then aim at prevention of life threatening thromboembolic events and to ensure that further escalation of the complications does not occur. This is possible by controlling or eliminating the biochemical abnormalities due to the deficient enzyme. The present report is that of a lately detected case of homocystinuria in a child with cerebral palsy.

Case Report

A 14 year old male ,a known case of cerebral palsy, was brought to the Paediatric Out-Patient department with chief complaints of low grade fever for 1 day;3 episodes of abnormal involuntary movements(tonic-clonic)involving the left half of

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the body on the next day of fever followed by loss of consciousness for a period of 30 minutes. Each of the seizure episodes lasted for 20-30min.There was no history of loose stools , vomiting ,cough, jaundice, head injury or epistaxis. Past history revealed that the child had been admitted multiple times with complaints of vomiting and there were previous 3 episodes of focal seizures involving the left side. The first episode occurred at the age of 3 months for which no antiepileptic drugs were prescribed. The 2nd episode which was a right sided focal seizure occurred at 7 years of age and the child took carbamazepine for 2 years. The third episode(left focal) occurred at 12 years of age and Valproic acid was prescribed. Meanwhile the child had multiple hospital admissions with complaints of vomiting; in suspicion of an inborn error of metabolism, Tandem Mass Spectrometry for Inborn Metabolic Disorder panel(Quantitative) was sent which revealed low carnitine levels and high methionine and homocystine levels(Table).

The low level of carnitine was attributed to the drug Valproic acid which was then stopped and was replaced by oral Levetiracetam. The child had been on levetiracetam at the time of the present episode but was on irregular treatment. The child was born by normal term vaginal delivery and cried immediately after birth. There was history of delay in all developmental milestones and the child was unable to sit without assistance. He was immunised for age. He had a male sibling who did not have similar complaints and was thriving well. Examination revealed a tall stature with thin and slender extremities with a marfanoid habitus(Fig.2), the upper to lower segment ratio being 65:75 with arm span>length of the child measured bedside, mild pallor and bilateral dislocation of the lens(Fig4,5), pigeon shaped chest(pectus carinatum)(Fig.3).

Systemic examination showed generalised hypertonia and grade 0 power in all 4 limbs with exaggerated deep tendon reflexes, demonstrable ankle and patellar clonus and a positive babinski's sign. Other systems were within normal limits. Neuroimaging(CT brain) was done which revealed hyperdensity in the sulci of right cerebral hemisphere, along the course of the sigmoid sinus with relative atrophy of the left cerebral hemisphere(Fig.6). The child was treated with antiseizure medications, pyridoxine with vitamin B12 and folate supplementation and the child is on regular follow with initial signs of improvement. Counselling the caretakers to ensure the drug compliance and physiotherapy also formed a part of the treatment.

Fig.2 Marfanoid habitus

Fig.3 Pectus carinatum

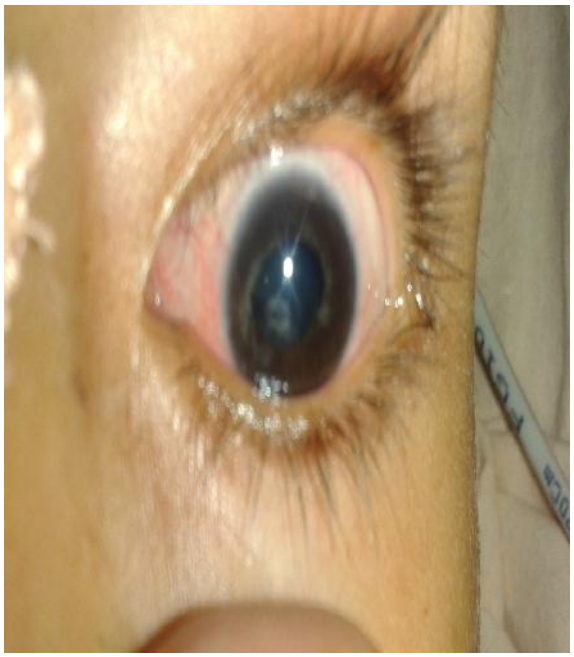

Fig.4 Ectopia lentis left eye

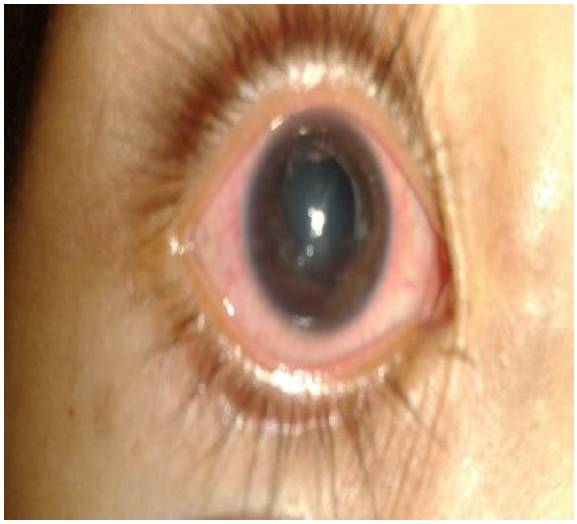

Fig.5 Ectopia lentis right eye

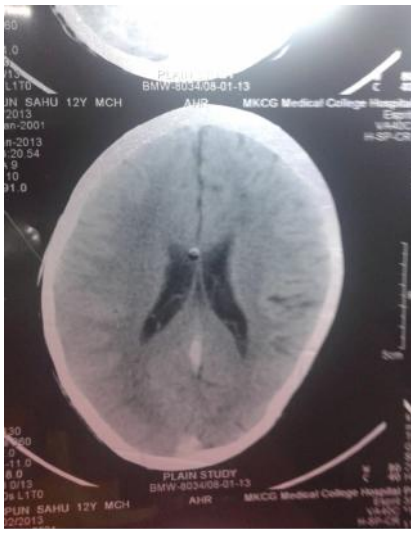

Fig.6 CT brain:Hyperdensity along sulci of right cerebral hemisphere with relative left cerebral atrophy.

DISCUSSION

Du Vignead *et al* first coined the term "homocysteine" and "homocystine" in 1932 to represent the sulphydryl(reduced) and disulphide(oxidised)forms of the next higher homologues of cysteine and cystine. The term homocystinuria describes an increased excretion of the thiol amino acid homocysteine in urine (and incidentally, also an increased concentration in plasma). The source of this increase may be one of many metabolic factors, only one of which is CBS deficiency. Others include the re-methylation defects (cobalamin defects, methionine sythase deficiency, MTHFR) and vitamin deficiencies (cobalamin (vitamin B12) deficiency, folate (vitamin B9) deficiency, pyridoxal phosphate deficiency (vitamin B6)).

Classical homocystinuria is characterised by a wide range of clinical and pathological abnormalities with major involovement in 4 organ systems-eye, skeletal, central nervous system and the vascular system. Other organs including the liver, skin and hair are also found to have been involved.[3]This wide range of clinical manifestations clearly depicts the abound heterogeneity of the mutant enzyme. Elevated levels of homocysteine interferes with the normal cross linkage of collagen, which plays an important role in the multisystemic manifestations. Table 1 enlists the clinical manifestations.

Ectopia lentis and high myopia(<5 dioptres)are the most common ocular manifestation in classical form[4]. Disruption of the thickened zonulae fibres causes the lens to dislocate inferiorly or nasally or both and is usually bilateral. The disruption also leads to increased curvature of the lens leading to high myopia and astigmatism. Skeletal manifestations are not evident at birth and usually not seen in infants and young children. The appearance of genu valgum and pes cavus are usually the first signs[5].

As puberty approaches, anterior chest wall deformities appear in the form of pectus excavatum, carinatum, kyphosis or scoliosis. The facial appearance may be altered due to prominence and overcrowding of upper teeth and the palate is almost always high arched. The skeletal manifestations resemble that of Marfans syndrome. Osteoporosis especially of spine is another characteristic feature. Thromboembolism of both small and large arteries and veins occur and is the most common cause of severe morbidity and mortality. Thrombophlebitis is the most common complication often leading to fatal pulmonary emboli or cor pulmonale. Mental retardation is the most common central nervous system abnormality and is often the first recognisable sign of CBS deficiency. When walking begins a waddling or a 'Charlie Chapplin' gait is often present.

Diagnosis and diagnostic methods

1. ***Urine:*** The most consistent biochemical abnormality is homocystinuria, qualitatively screened by the sodium nitroprusside test("Brand test"),though neither sensitive nor specific.
2. ***Blood:*** There is increased levels of homocysteine and methionine with low levels of cysteine.
3. ***Direct Enzyme Assays:*** Definitive confirmation of a diagnosis of CBS deficiency is by assaying the CBS enzyme activity in liver biopsy, cultured skin fibroblast, phytohaemagglutinin-stimulated lymphocytes or long term cultured lymphocytes. Less than 15% of enzyme activity confirms the diagnosis.
4. ***Molecular Diagnosis:*** CBS mutational analysis.
5. ***Antenatal Diagnosis*:** Extracts of cells from cultured amniotic fluid contains readily detectable activity of CBS. Both the homozygous and heterozygous states can be detected. The first prenatal diagnosis of CBS deficiency was made by Fowler *et al* in 1982.

Table 1 Clinical Manifestations

System	Frequent	Less Frequent
Skeletal	Osteoporosis, Biconcave("codfish")vertebrae, Scoliosis, Pes cavus, High arched palate, Increased length of long bones, Metaphyseal spicules	Arachnodactyly, Pectus carinatum or excavatum, Enlarged carpal bones, Genu valgum, Kyphosis, Short fourth metacarpal, Abnormal bone age
Ocular	Ectopia lentis, Iridodenesis, Myopia	Glaucoma, Optic atrophy, Retinal degeneration, Cataracts, Corneal abnormalities
Cns	Mental retardation, Psychiatric diseases, Extrapyramidal signs	Seizures, Abnormal EEG
Vascular	Vascular occlusions, Malar flush, Livedo reticularis	
others	Fair, brittle hair; Thin skin, Fatty liver, Inguinal hernia, Myopathy, Endocrine abnormalities, Reduced clotting factors.	

Treatment: There are currently three recognised modalities of treatment[6]:

A. ***Pyridoxine:*** Approximately 50% of CBS deficient patients respond to pharmacological doses of pyridoxine and the responsiveness correlates to the presence of residual CBS activity in the cultured fibroblast. Pyridoxine responsiveness is not due to the overcoming of a depletion or defective metabolism of B6 in these patients. All newly diagnosed cases must be given a pyridoxine trial while remaining on a normal diet. Pyridoxine 50mg thrice a day in neonates and 100-200mg thrice daily in older children is prescribed to assess vitamin responsiveness with deproteinised amino acids monitoring every three days initially until stabilised. Biochemically, response is indicated by falling homocysteine(<5mmol/L) and methionine levels while remaining on pyridoxine in the presence of adequate vit B12 and folate. If the levels remain elevated or rises while on pyridoxine, the patient is biochemically pyridoxine non responsive and is started on a methionine restricted diet.

B. ***Methionine Restricted Cysteine Supplemented Diet:*** The parameters to be monitored duringdietary treatment are normal growth rate, methioninaemia(<40mmol/L) and normal plasma homocysteine.

C. ***Betaine:*** It is a methyl donor(trimethyl glycine)and acts by increasing the remethylation of homocysteine to methionine. The resultant hypermethioninemia does not affect the pathophysiology of the disease and so far has not produced any side effects. It is useful in pyridoxine non responsive patients who cannot tolerate methionine restriction or as an adjunct to such a diet. The dosage schedule is 4-6grams/day as 3 divided doses.

If left untreated the classical variety carries a bleak prognosis with progressive morbidity and mortality. However it has been established that treating the condition prevents the development of complications and ameliorates the pretreatment insult but complete reversal is not possible. Hence we can conclude that classical homocystinuria is a potentially treatable condition especially if detected early and the homocysteine levels should always be assessed in any patient presenting with ectopia lentis, mental retardation or premature vascular events especially affecting the central nervous system.

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