Homocystinuria with Early Thromboembolic Episodes and Rapid Response to High Dose Pyridoxine

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Homocystinuria is an autosomal recessive disorder resulting in defective function of the eye, skeletal, central nervous and cardiovascular systems. The defect lies in the enzyme cystathione (3 synthetase (CBS) which is a pyridoxal 5' phosphate requiring enzyme that converts homocysteine to cystathionine. The genetic linkage studies have confined the CBS locus on chromosome 21q 22.3(1,2). Patients with homocytstinuria are categorized as pyridoxine responsive or non responsive depending on the results of *in vivo* pyridoxine therapeutic trials. Pyridoxine responsive patients usually have milder clinical phenotypes than pyridoxine non responsive patients. The compound heterozygote patients who have the missense mutation 1278T in the CBS gene are likely to retain some degree of pyridoxine responsiveness(3,4). We report one such case with the early thromboembolic manifestations who responded well with pyridoxine therapy.

Case Report

A 7-year-old boy, a product of a nonconsanguineous marriage was born to a primigravida mother by full term normal vaginal delivery. Antenatal and perinatal periods were uneventful. He presented with recurrent right focal seizures since 3 years of age, right sided weakness of body, slurring of speech and abnormal behavior. A history of global developmental delay was present. There was no history of fever, head injury or ear discharge. Family history of early deaths due to strokes or myocardial infarction was absent and there was no history of contact with tuberculosis. On examination, the child had microcephaly with right sided hemiplegia with upper motor neurone signs present bilaterally. Right sided upper motor neurone type of seventh cranial nerve palsy, bilateral optic atrophy and slurring of speech were present. The child did not have Marfanoid habitus, dislocation of lens, abnormal color of skin or hair and other systemic examination were within normal limits.

Investigations revealed a normal hemogram, coagulogram and serum electrolytes and renal function tests. CT scan of the head revealed right caudate head infarct and left hippocampal infarct with cortical atrophy and ventriculomegaly (*Fig. 1).* EEG revealed a normal awake record. Work up for tuberculosis was negative. Antinuclear factor, rheumatoid factor and LE cell were absent. To decipher the cause of bilateral infacts, urine test with cyanide nitroprusside as well as by paper chromatography was undertaken(5). Both were positive for homocysteinuria. This was confirmed further with silver nitroprusside test which is specific for this condition. Substitution of silver diamine ion for cyanide as the reducing agent makes the test specific for homocysteine. The IQ of the patient was 28. The child was treated with high dose pyridoxine, folic acid and anticonvulsants. Six months into

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merit in his mental status and IQ increased to 60. There were no fresh thrombotic episodes or seizures and hemiparesis improved. The silver nitroprusside test and paper chromatography for homocysteine and methionine were negative.

Discussion

Homocystinuria is a metabolic disorder resulting from a defect in the metabolism of sulphur containing aminoacids and results in accumulation of homocysteine in cells and body fluids. This interferes with the normal cross-linking of collagen thus playing a major role in ocular, skeletal and vascular complications.

The most frequent skeletal abnormalities found in patients with homocysteinuria are thickening and lengthening of long bones leading to the development of a Marfanoid habitus by late childhood.

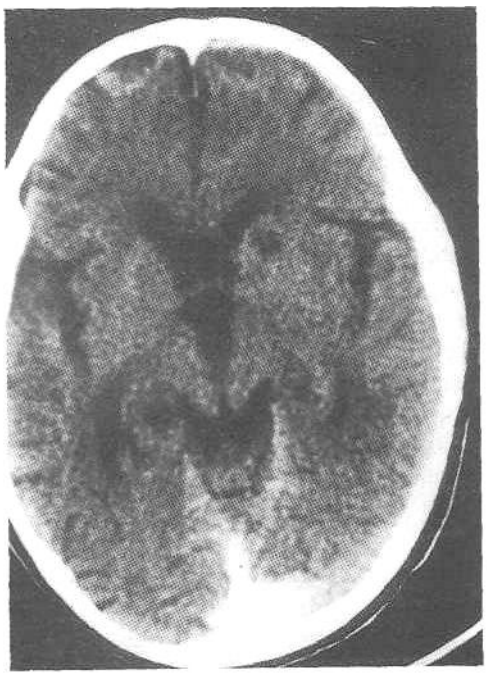

Fig. 1. CT scan of head shows right caudate head infarct and left hippocampal infarct with cortical atrophy and ventriculomegaly.

Osteoporosis of bone is another characteristic finding in 50% of cases by the end of second decade of life(6). Both these findings were absent in the index case probably due to his young age.

Ophthalmological changes are characteristic of homocystinuria. Altered collagen in the suspensory ligament of the lens leads to downward displacement of lens which is the most frequent abnormality. The other eye changes which may be detected are glaucoma, optic atrophy, retinal detachment and degeneration, cataracts and corneal abnormalities. Of these only optic atrophy was seen in our patient(7,8).

The striking features in the index case which suggested homocystinuria were the presence of bilateral infarcts, mental retardation and abnormal behavior. Hemiparesis or focal neurologic signs suggest the presence of cerebrovascular disease. Homocystinuria should be considered in all patients with acute infantile hemiplegia. A major cause of morbidity and the most frequent cause of death in this disorder is thromboembolism. Myocardial, cerebral, renal and pulmonary infarction characteristically occur and are often fatal before third decade of life(6,9,10). Thus in all young patients presenting with vascular lesions without other risk factors, homocystinuria should always be excluded. The most frequent abnormality of central nervous system in this condition is mental retardation(11). Often this is the first recognized sign of cystathione synthetase deficiency, presenting as developmental delay during the first and second year of life. The IQ scores covered in 1982-83 international survey ranged from 10 to 138 with the median of cumulative frequency curve at approximately 64(6).

About 21% of patients with homocystinuria not treated from early infancy have seizures usually of grandmal type. These patients with or without seizures

may show EEG abnormalities(6). The index case also had hepatomegaly which may be due to fatty change of the liver(12).

In an earlier study(13), high dose pyridoxine was given in 3 patients suffering from homocystinuria; 1 responded dramatically while another showed partial response and no information was available on the 3rd patient. Depending on the presence or absence of the missense mutation 1278T in the CBS gene, the patient may respond dramatically, partially or not at all to pyridoxine therapy.

The patient was started on high doses of Vitamin B_6 (500 mg) and folic acid. High dose of pyridoxine is reported to be associated with sensory neuropathy. However, studies in children with doses upto 800 mg/day given over long periods of 7-24 years (mean=16 years) have not shown any evidence of neuropathy in extensive clinical and neurophysiological studies(14). The index case showed dramatic response within 6 months of therapy and there is no evidence of neuropathy on follow up to date.

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