CASE REPORT

VALVULAR HEART DISEASE IN CLASSIC HOMOCYSTINURIA - A RARE PRESENTATION

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Abstract

Homocystinuria is a rare metabolic disease affecting at least 1 per 200,000-335,000 people worldwide. Here we present a child with moderate mental retardation (Intelligence quotient 35-40), severe myopia due to lenticular dislocation and symptomatic valvular heart disease in absence of marfanoid habitus. Metabolic workup such as positive urinary cyanide nitroprusside test and serum level of elevated homocystine and methionine was diagnostic of classic homocystinuria due to cystathionine beta synthase deficiency. CT scan brain showed diffuse cerebral atrophy and echocardiography established an unreported finding of valvular aortic regurgitation. Dramatic clinical improvement was noticed after 6 months with pyridoxine therapy. The unique presence of valvular heart disease in classic homocystinuria emphasizes a detail cardiovascular screening in these children and also it unleashes a new aspect of this metabolic disease.

Key words: Homocystinuria, aortic regurgitation, pyridoxine

Abbreviations: CBS- cystathionine beta synthase, MTHR- methyl tetrahydrofolate reductase, IQ- intelligence quotient, CDC- Centre for Disease Control

Introduction

Homocystinuria is a rare inborn error of methionine metabolism, discovered in 1962 by Carson, Neill, and colleagues when individuals with mental retardation were screened for abnormal urinary amino acids (1). Classic homocystinuria is due to cystathionine beta synthase (CBS) deficiency, associated with recessive mutation of gene on chromosome 21q22.3 and represents a multi-system disorder involving mostly four major organ systems: eye, skeletal, central nervous system, vascular system. Other two causes of homocystinuria are due to defect of methylcobalamine formation and deficiency of methyltetrahydrofolate reductase (MTHR) (2). Cardiovascular morbidities are mostly due to thromboembolic episodes in homocystinuria but valvular heart disease has not yet been mentioned in literature.

Case Report

An eight years old girl born out of non consanguineous marriage presented with poor vision, poor language and communication skill, progressive lateral bending of spine, stereotype behaviour and occasional palpitations. Her elder brother who had same type of illness died 2 yrs back due to cerebrovascular accident. The child had dull expressionless face with height and weight between 25- 50th centile of CDC chart (Upper: Lower segment = 0.98 and arm-span: height =1.01). Ophthalmologic examination showed bilateral inferonasal dislocation of lens with myopia (>10d) and early optic atrophy. There was gross delay of acquisition developmental milestones specially language and socio-personal. High volume collapsing pulse, positive Hill's and Traube's sign, blood pressure of 96/48(arm) and 124/54(leg), down-out cardiac apex and a grade III early diastolic high pitched murmur in neoaortic area was noted. Dorso-lumbar scoliosis with generalised osteoporosis of spine in X-ray was seen. Psychological assessment (Bender gestalt, Vineland social maturity scale and Behavioural assessment scale for Indian children with mental retardation) revealed moderate mental retardation, Intelligence Quotient (I.Q) being 35- 40 with severe receptive and expressive language difficulty. Complete hemogram, liver function, lipid profile, coagulation profile, renal and thyroid functions were within normal limits. CT brain revealed mild diffuse cortical atrophy. Valvular aortic regurgitation was detected on 2D- echocardiography with colour Doppler (ejection fraction >50%, left ventricular systolic dimension <55mm, regurgitant fraction of 0.4) without vegetation and aortic root dilatation. Rheumatic fever, systemic lupus, ankylosing spondylosis and bicuspid valve as a cause of aortic regurgitation were ruled out. Cyanide nitroprusside test was strongly positive in freshly voided urine. Both serum homocystine level- 110.4 mol/L (normal: 5.9-16 mol/L) and methionine level - 86 mol/L (normal: 10-40 mol/L) were elevated. Therapy started with oral pyridoxine 200mg/day along with folic acid 5mg/day. Significant clinical and behavioural improvement was noticed after six months of therapy (IQ: 55- 60) with decline in serum homocystine (24 mol/L) and methionine levels (16 mol/L) and improvement of osteoporotic changes.

Discussion

Classic homocystinuria is a rare metabolic disease affecting about 1 in 344,000 children. It presents with a combination of ectopia lentis (65 - 95%), mental retardation (52- 86%), developmental delay (21- 33%), early thromboembolic disorder (15%), marfanoid characteristics (36%), bony abnormality (23- 40%) and seizures (3%) (3,4).

Cardiovascular manifestations include premature atherosclerosis and thromboembolic episodes which results in significant morbidity and mortality in these children. It is hypothesised that homocystine results in altered expression of thrombomodulin in endothelial cells result in platelet aggregation and thromboembolism involving major arteries and veins. However little is known regarding the presence of valvular heart defects in homocystinuria. It has been seen that offspring's of women with MTHR gene mutation may have congenital heart defects involving abnormalities of the great vessels (e.g. aorta; aortic valve; pulmonary artery; pulmonic valve). MTHFR requires folic acid to convert homocysteine to methionine and when this does not occur, homocysteine can accumulate and may have toxicity for the developing embryo (5). However congenital heart defect involving the aortic valve due to CBS enzyme deficiency as seen in our case has not been mentioned in literature before.

Homocystinuria is usually associated with marfanoid

like habitus, lenticular dislocation in absence of aortic enlargement or dissection. While dislocation of lens occurs secondary to degeneration of zonular fibres, marfanoid habitus is secondary to fibrillin degeneration (6). These changes occur due to increased level of homocystine that interferes with the formation of intra- and inter-chain bonds in the early post-translational modification of collagen. Metabolites of homocystine cause neurotoxicity due to repeated excitation of N-methyl D-aspartate receptors (7). These neurotoxic amino acids along with repeated stoke due to thromboembolism result in mental retardation. Developmental delay, cognitive delay (IQ range from 10-138, median being approximately 64), seizures, dystonia and psychiatric abnormalities are also seen (8).

Elevation of serum homocystine and methionine clinches the diagnosis of classical homocystinuria due to CBS enzyme deficiency. Prenatal diagnosis by enzyme assay in amniocytes and neonatal screening by high performance liquid chromatography are also available (9). Therapy with pyridoxine, folic acid and vitamin B12 in pyridoxine responsive cases and Betaine in pyridoxine unresponsive cases has promising outcomes.

Homocystinuria, being an important cause of reversible mental retardation, needs early and accurate diagnosis to ascertain appropriate therapy. Identification and assessment of cardiovascular risk factors such as thromboembolism, valvular heart disease enables to take early preventive measures to reduce future morbidity and mortality of these children. The present of aortic regurgitation in classic homocystinuria as in our case emphasizes that besides routine coagulation profile, a detailed cardiovascular screening is warranted in all these cases even in the absence of marfanoid habitus.

Source of funding: none
Conflict of interest: none.

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E-published: 1st October 2010. **Art**#59