

## Homocystinuria due to cystathionine beta synthase deficiency

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### ABSTRACT

A two year-old male child presented with cutis marmorata congenita universalis, brittle hair, mild mental retardation, and finger spasms. Biochemical findings include increased levels of homocysteine in the blood-106.62  $\mu\text{mol/L}$  (normal levels: 5.90-16 $\mu\text{mol/L}$ ). Biochemical tests such as the silver nitroprusside and nitroprusside tests were positive suggesting homocystinuria. The patient was treated with oral pyridoxine therapy for three months. The child responded well to this therapy and the muscle spasms as well as skin manifestations such as cutis marmorata subsided. The treatment is being continued; the case is reported here because of its rarity. Homocystinuria arising due to cystathionine beta-synthase (CBS) deficiency is an autosomal recessive disorder of methionine metabolism that produces increased levels of urinary homocysteine and methionine. It manifests itself in vascular, central nervous system, cutaneous, and connective tissue disturbances and phenotypically resembles Marfan's syndrome. Skin manifestations include malar flush, thin hair, and cutis reticulata / marmorata.

**Key Words:** B6 responsiveness, Cystathionine beta-synthase, Cutis marmorata.

### INTRODUCTION

Homocystinuria due to cystathionine beta-synthase (CBS) deficiency is an autosomal recessive disorder of methionine metabolism that produces increased levels of urinary homocysteine and methionine.<sup>[1]</sup> It manifests itself in vascular, central nervous system (CNS), and connective tissue disturbances and phenotypically resembles Marfan's syndrome. Skin manifestations include malar flush easily seen after vigorous exercise or after exposure to the cold, livedo reticularis on the extremities, and thinning and diffuse hypopigmentation of the hair. CNS manifestations include mental retardation, grand mal seizures, depression, chronic behavioral disorders, obsessive compulsive disorders, and personality disorders. Cardiovascular system manifestations include thrombosis of both veins and arteries; ocular manifestations include progressive ectopia lentis, detachment of the retina and sclera, and significant myopia. Skeletal manifestations include limitation of joint mobility and osteoporosis. Other manifestations include

pancreatitis, pseudocysts, and colicky abdominal pain. Untreated homocystinuria leads to systemic and ocular complications that can be prevented with early treatment. Therapeutic response depends on B6 responsiveness. Complications of homocystinuria including ectopia lentis, thrombosis, and spinal osteoporosis are less severe with B6-responsive patients.

### CASE REPORT

A two year-old male child [Figure 1], the product of a consanguineous marriage, presented with delayed developmental milestones, cutis marmorata congenita universalis [Figure 2], brittle hair, mild mental retardation, and finger spasms. There were no hair shaft abnormalities and no facial dysmorphism.

Biochemical tests such as the silver nitroprusside and nitroprusside tests were positive, suggesting homocystinuria. Biochemical findings include increased

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**Figure 1: Features of mild mental retardation with cutis marmorata**



**Figure 3: Cutis marmorata subsided completely after treatment**



**Figure 2: Both limbs showing cutis marmorata**

levels of homocysteine in the blood-106.62  $\mu\text{mol/L}$  (normal levels: 5.90-16  $\mu\text{mol/L}$ ). The thyroid profile and blood counts were within normal limits.

The child was treated with daily oral Vitamin B6 (Pyridoxine) 50mg and folic acid 10mg for three months and a one time dose of Vitamin B12-1000  $\mu\text{g}$ . The child responded well [Figure 3] to this therapy over a period of three months with subsidence of the muscle spasms and skin manifestations such as cutis marmorata; the treatment is being continued.

## DISCUSSION

Differential diagnosis of homocystinuria includes Marfan syndrome and sulfite oxidase deficiency. Individuals with sulfite oxidase deficiency and Marfan syndrome have normal concentrations of plasma homocysteine, total homocysteine and methionine.

Increased concentrations of homocysteine or methionine also occur in several other biochemical genetic disorders.<sup>[2-5]</sup>

Homocystinuria is a biochemical abnormality, not a specific disease entity. By far, the most common cause of this disease is a defect in the enzyme, cystathione beta-synthase (CBS) because of recessive mutations in its gene. Less common causes of homocystinuria are defects in 5,10-Methylene tetrahydrofolate reductase activity-a heritable vitamin B12 deficiency as a result of absorption abnormalities (Imerslund syndrome) and transcobalamine deficiency, leading to defective cellular uptake of vitamin B12 [Figure 4].<sup>[6]</sup>

The major clinical manifestations of CBS deficiency include dolichostenomelia, ectopia lentis, chest and spinal deformities, skin manifestations like malar flush, thin hair, and cutis reticulata / marmorata. As homocystinuria is a treatable disease, it should be included in the differential diagnosis of Marfan's syndrome, thromboembolism, and severe psychomotor retardation.

The mechanism underlying the cutaneous manifestations of homocystinuria is not clearly known. When a neonate is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and blue cutaneous vascular pattern known as cutis marmorata appears over most of the body surface. It is a vascular change representing an accentuated physiological vasomotor response and it disappears over time. Persistent and pronounced cutis marmorata occurs in Menkes disease, familial dysautonomia, Cornelia de Lange, Down's syndrome, Trisomy 18 syndromes and in homocystinuria.

Two types of homocystinuria have been reported based on its treatment: one is B6-responsive while the other

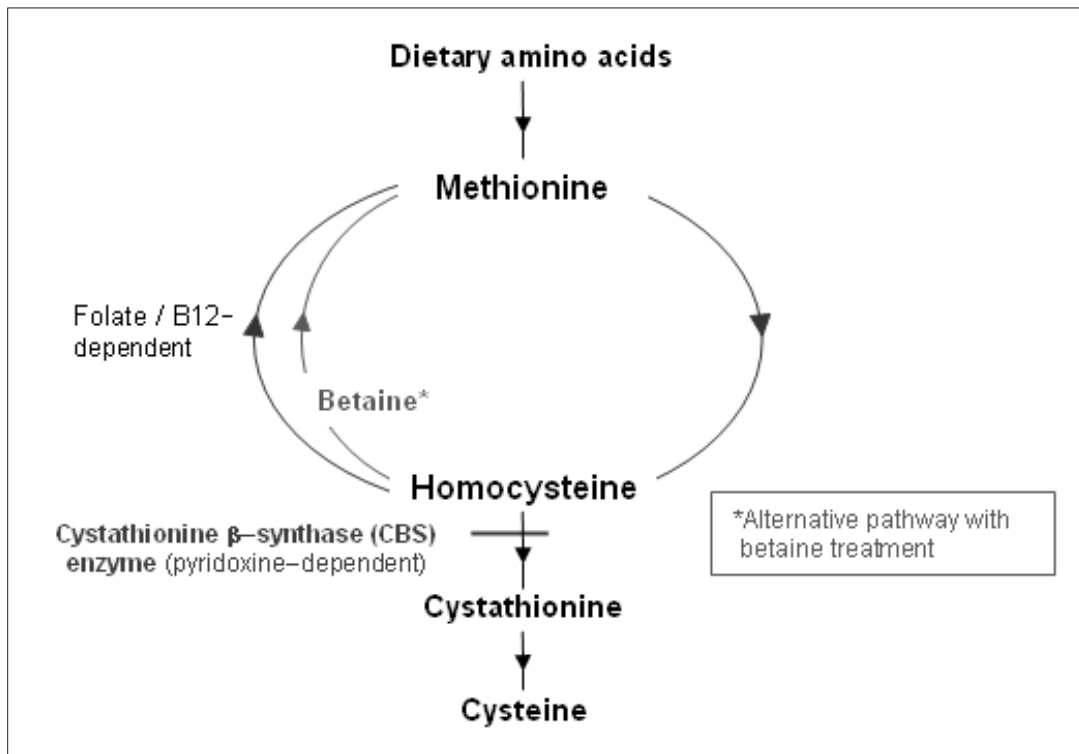


Figure 4: Methionine metabolic pathway

is not. Treatment of B6-responsive patients includes a combination of folic acid, vitamin B12, and pyridoxine, which significantly reduces homocysteine levels.<sup>[7-11]</sup> Treatment of B6-nonresponsive patients includes lowering of urinary levels of homocysteine and its disulphide derivative, as well as adherence to a methionine-restricted diet. Methionine levels increase over baseline with betaine therapy, but usually remain at levels that are not associated with adverse effects. Our case was B6-responsive and responded well to three months of pyridoxine therapy.

The principles of treatment are to correct the biochemical abnormalities, especially to control the elevated plasma homocysteine concentration as much as possible and to prevent or at least reduce, the complications of homocystinuria<sup>[12]</sup> and to prevent further complications such as thrombosis. The best results occur in those individuals identified by the newborn screening program, who are treated shortly after birth to maintain the plasma homocysteine concentration < 11  $\mu\text{mol/L}$

Treatment with pyridoxine at a dose of approximately 200 mg/day should be given to those who have been shown to be B6-responsive. Pyridoxine may also be included in treatment despite evidence of B6-nonresponsiveness, typically in doses of 100-200 mg daily.

The majority of B6-responsive individuals also require

a protein-restricted diet for metabolic control. B6-nonresponsive neonates require a methionine-restricted diet with frequent metabolic monitoring. This diet should be continued indefinitely.

Treatment with betaine provides an alternate remethylation pathway to convert excess homocysteine into methionine and may help to prevent complications, particularly thrombosis.<sup>[13,14]</sup> In converting homocysteine to methionine, betaine lowers the free plasma homocysteine and total homocysteine concentrations but raises the plasma concentration of methionine. Although betaine is typically provided orally at 6-9 g/day in two divided doses, its optimal dose has not been determined.<sup>[15]</sup>

Folate and vitamin B12 optimize the conversion of homocysteine to methionine by methionine synthase, thus helping to decrease the plasma homocysteine concentration. When the red blood cell folate and serum B12 concentrations are reduced, folic acid is given orally at 5 mg/day and vitamin B12 is given as hydroxocobalamin at 1 mg IM per month.

As homocystinuria is a genetic disorder, frequent monitoring of blood homocysteine levels should be done and the duration of treatment should be life long. Affected individuals should be monitored at regular intervals to detect any of the clinical complications that may develop;

appropriate therapy for the complications should be given as soon as possible.

Even though the diagnosis of homocystinuria is made with the help of clinical features, it requires the estimation of homocysteine in the blood as well as other biochemical tests such as the silver nitroprusside and nitroprusside tests. In our case, the homocysteine level was elevated in blood-106.62  $\mu\text{mol/L}$  (normal level: 5.90-16  $\mu\text{mol/L}$ ) and the silver nitroprusside and nitroprusside test results were positive.

It is noteworthy that only a few cases of homocystinuria with cutis marmorata have been reported from India, most of these cases were detected accidentally.

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