

Classical Homocystinuria in Two Filipino Patients

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ABSTRACT

Classical homocystinuria is an inborn error of metabolism caused by a deficiency of cystathionine β -synthase that converts homocysteine to cystathionine. This then leads to elevation of homocysteine which results in abnormalities of the eyes, skeleton, central nervous system and vascular system. We present two children with classical homocystinuria. Patient 1 presented with lens dislocation and mental retardation while Patient 2 presented with thromboembolism, mental retardation and lens dislocation. The elevated plasma homocysteine and methionine levels led to the diagnosis of homocystinuria.

Key Words: homocystinuria, cystathionine β -synthase deficiency, mental retardation, lens dislocation, thromboembolism

Introduction

Homocystinuria is an inborn error of sulfur-containing amino acid caused by a deficiency of the enzyme, cystathionine β -synthase.¹ It was first described by Carson and Neill in 1962 in two siblings from Northern Ireland who presented with mental retardation and increased homocysteine in the urine.² Homocysteine is a sulfur amino acid which is metabolized through both remethylation to methionine and transsulfuration to cystathionine. In the former, homocysteine acquires a methyl group from N⁵-methyltetrahydrofolate catalyzed by vitamin B12 dependent methionine synthase or from betaine. On the other hand, if there is excess methionine or decreased levels of cysteine, homocysteine undergoes transsulfuration to form cystathionine catalyzed by the enzyme cystathionine β -synthase.³ (Figure 1)⁴ Homocysteine levels may also be elevated as a result of deficiency of the co-factors or the enzymes involved in these two pathways. As a

consequence, homocysteine accumulates in the tissues, blood and urine leading to homocystinuria.

There are several causes of homocystinuria. Classical homocystinuria is a disorder of transsulfuration, with reduced plasma cysteine and increased homocysteine and methionine levels due to the deficiency of cystathionine β -synthase.⁵ It is associated with severe abnormalities of four organ systems: the eye (dislocation of the lens), the skeleton (dolichostenomelia and arachnodactyly), the vascular system (thromboembolism) and the central nervous system (mental retardation, cerebro-vascular accidents).⁶ Several other disorders are due to remethylation defects, with increased plasma homocysteine and decreased methionine, and in some also methylmalonic aciduria, secondary to disorders affecting cobalamin or folate metabolism. These are much rarer disorders, presenting with megaloblastic anemia, developmental delay and other symptoms.⁵

Classical homocystinuria is an autosomal recessive disorder. The reported incidence of the disease is one per 160,000 births⁵ while the cumulative detection rate of cystathionine β -synthase deficiency is 1 in 344,000.² Herein, we present two Filipino children whose features are compatible with classical homocystinuria.

Clinical Reports

Patient 1

Patient 1 is an 11-year-old male, the second child of non-consanguineous parents of Filipino descent. He had blurred vision at 8 years of age, but was only seen initially after trauma to the right eye at 11 years of age. On ophthalmologic examination, he was found to have ectopia lentis. Physical examination showed a child proportionately small for age with brachycephaly, congested conjunctival vessels, flat nasal tip and mild prognathism. On further evaluation, he was assessed to have moderate mental retardation. A skeletal survey showed reduced bone mineral density and coxa valga. Urine amino acid screening by high voltage electrophoresis showed homocysteine. Plasma amino acid levels were notable for increased homocysteine, 303. $\mu\text{mol/L}$ (Reference value: 5-15 $\mu\text{mol/L}$) and methionine, 991.47 $\mu\text{mol/L}$ (Reference value: 12-43 $\mu\text{mol/L}$). Plasma vitamin B12 and plasma folate levels were within normal range. Based on these findings, he was diagnosed with classic homocystinuria. He was treated with a protein

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restricted diet (1.2g/kg/day natural protein), supplementation with oral Vitamin B12 (200mg/day), folic acid (5mg/day) and betaine (3000g/day). Unfortunately, he was poorly compliant with the treatment regimen and was lost to follow up at age 13 years. At that time, he had bilateral lens replacement, had tolerated the diet well and was advised on special school placement.

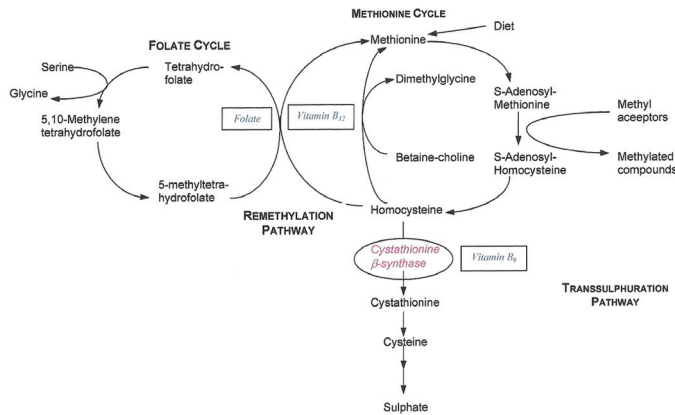


Figure 1. Transsulfuration and remethylation pathway of methionine metabolism.⁴

Patient 2

Patient 2 is a 16-year-old female, the 5th child of a non-consanguineous couple of Filipino descent. She was seen at our institution due to poor wound healing of the right foot after injury. On review of the history, she had blurred vision since two years of age. At eight years old, bilateral corneal opacities were noted. She was initially worked-up for diabetes but laboratory results showed normal fasting blood sugar and HbA1c levels.

She was seen by the Genetics Service at 16 years of age. On physical examination, she had bilateral corneal opacities and necrotic, gangrenous wounds of the right foot. Doppler studies showed the presence of peripheral arterial occlusive disease of the right extremity. Ophthalmologic exam showed cataract and bilateral anteriorly displaced lenses. She had profound mental retardation when assessed with developmental quotients. Homocystinuria was considered and this diagnosis was confirmed when a urine metabolic screening showed homocysteine. The plasma homocysteine levels was elevated at 258.2umol/L (Reference value:4.45-12.42 umol/L). Skeletal survey was normal.

She was prescribed oral vitamin B12, folic acid and betaine. This patient was lost to follow-up after the initial management of her condition.

Discussion

In 1932, the American biochemist Vincent DuVigneaud discovered a new amino acid homocysteine. The first case of homocystinuria was reported in 1962 by a group of researchers in Belfast who discovered elevated urine homocysteine levels in children with mental retardation.⁷

We report the first two confirmed cases of homocystinuria in the Philippines. The diagnosis of homocystinuria was suspected based on the ophthalmologic findings and presence of mental retardation.

Ectopia lentis is the hallmark ophthalmologic finding and the most consistent clinical finding in classical homocystinuria.⁵ Cruysberg et al.⁸ reported its prevalence at 76% of patients, citing it as a risk factor for strabismus, dense cataract, glaucoma, retinal detachment and unilateral blindness. Both patients presented initially with blurred vision and later with dislocated lenses on ophthalmologic examination. Patient 2 already had late signs having developed cataracts. Homocysteine inhibits linking of collagen and elastic tissue which predisposes zonule generation of the eye and can lead to myopia and lens dislocation.⁹

Osteoporosis is the most common skeletal abnormality reported in classic homocystinuria.⁴ The skeletal survey of Patient 1 showed reduced bone mineral density while patient 2 was normal. Other skeletal findings in these patients include tall stature with thinning and elongation of long bones, enlarged metaphyses and epiphyses especially at the knees and arachnodactyly.⁶ These abnormalities result from damage to fibrillin and reduction in collagen cross-linking.¹⁰

Mental retardation is the most common central nervous system abnormality and is the first recognizable sign of cystathione β-synthase deficiency, affecting 60% of patients.^{4,6} At least one third of patients have normal intelligence with an average IQ of 80.¹¹ Both our patients showed profound mental retardation. It has been hypothesized that cystathione β-synthase plays a role in the development and maintenance of the central nervous system. In a study by Enokido,¹² cystathione β-synthase was noted to be present in the cerebellar molecular layer and hippocampal dentate gyrus. In its absence, cerebellar morphological abnormalities were observed. An alternative possibility is that chemical abnormalities contribute to mental retardation. Patients with homocystinuria are found to have decreased adenosine concentrations that cause depressed cerebral actions. Untreated patients with cystathionine-β-synthase deficiency are expected to have increased S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). AdoMet when applied to rat sensorimotor cortex showed increased spontaneous firing of neurons. L-homocysteic acid and L-homocysteine sulfinic acid which is increased in patients with homocystinuria were found to be agonists at the glutamate-binding site of NMDA receptors exerting cytotoxic effects on neurons. An alternative to the biochemical hypothesis of the central nervous system dysfunction is that repeated cerebral vascular thromboses produce many infarctions of the brain causing neurologic signs and mental retardation.¹⁰

Thromboembolism is the cardinal vascular sign of homocystinuria.⁴ Mild hyperhomocystinemia is associated with increased risk of atherosclerotic vascular disease, although it is not clear whether in fact this is causative, or if the hyperhomocystinemia is secondary to mild atherosclerotic renal dysfunction. Boushey et al,¹³ reported that an increase in plasma homocysteine concentration by 5 μmol per liter signals an increased risk of coronary artery disease equivalent to an increase of 20 mg per deciliter in the cholesterol concentration. The mechanism that contributes to the atherogenic propensity of hyperhomocystinemias is possibly related to endothelial dysfunction and injury which leads to platelet aggregation and thrombus formation. Patient 2 presented with peripheral arterial occlusive disease manifesting as a non-healing wound in her extremity. Vascular occlusion may occur at any age and the natural history of clinically detected thromboembolic events is such that 30% will have an event by age 20 and increase to 50% by the age of 30.¹⁴

Early diagnosis of classic homocystinuria is crucial in order to prevent these complications and ensure normal development.⁵

Plasma amino acid analysis is the investigation of choice to confirm a suspected case of homocystinuria. Plasma amino acid analysis that shows increased methionine, homocysteine and cysteine-homocysteine disulfide, low cystine and no increase of cystathionine is typical of cystathionine β -synthase deficiency.⁶ The diagnosis can be confirmed by quantization of cystathionine β -synthase activity, but in the presence of typical biochemical and clinical indicators, this is usually unnecessary.

The aim of treatment is to reduce the plasma total homocysteine levels to as close to normal as possible while maintaining normal growth rate.⁶ This is achieved by the following approaches: (1) large doses of pyridoxine have been effective in reducing biochemical abnormalities in about 50% of patients with cystathionine- β -synthase deficiency who have milder mutations;⁵ (2) folic acid may be given as an adjunct to betaine to lower homocysteine levels by remethylation^{4,5} and; (3) dietary modification by giving a low-methionine/high-cystine diet.⁵ Vitamin B12 supplementation has also been noted to aid in the regulation of blood homocysteine levels.¹⁵

For other complications such as thromboembolic events and risk for atherosclerosis, there have been reports that Vitamin C supplementation may ameliorate endothelial dysfunction in cystathionine β -synthase deficient patients suggesting possible value in reducing long-term risk of atherothrombotic complications.⁶ It must be emphasized that treatment prevents or delays the onset of complications but cannot reverse the damage already caused by the disease.

A study done by Yap et al,¹⁶ showed that patients with cystathionine β -synthase deficiency treated with various combinations of low-methionine diet, pyridoxine, folic acid,

vitamin B12 and betaine have much improved vascular outcome although biochemical control achieved by treatment did not result in normal levels of homocysteine. It is possible that some of the treatment modalities that lowered homocysteine levels may have had other as-yet-unidentified protective effects related to vascular events, since even modest lowering of the greatly increased homocysteine levels resulted in greatly reduced risk of vascular events.

Newborn screening has facilitated the early diagnosis and treatment of homocystinuria. To date, most screening of newborns for cystathionine β -synthase deficiency has relied on the detection of hypermethioninemia. It is recommended that homocystinuria be included in the panel of newborn screening.

In summary, we present two Filipino children whose clinical features were compatible with classic homocystinuria. Since most of the serious clinical consequences such as life threatening thromboembolic events at a young age, mental retardation and ectopia lentis can be prevented by early detection and prompt treatment, early recognition of the features is indeed necessary.

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