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Familial homocystinuria

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CASE REPORT

FAMILIAL HOMOCYSTINURIA

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ABSTRACT

Two cases of siblings diagnosed as cases of familial homocystinuria are reported. Both the cases have classical presentation of familial homocystinuria including history of dislocation of lens of the right eye. Brother had history of psychomotor retardation while sister had a significant history of deep vein thrombosis. Levels of plasma homocysteine were elevated and urinary homocysteine was positive in both the cases.

KEY WORDS: *Homocysteine. Familial homocystinuria. Cystathione-ß synthase. N-methyl tetrahydrofolate reductase.*

INTRODUCTION

In the last two decades, a growing amount of interest has been focussed on hyperhomocystinemia as a risk factor of thromboembolic disease. We present cases of two siblings diagnosed as cases of familial homocystinuria with characteristic clinical presentation and biochemical results.[1] This report highlights the classical presentation of this rare cause of thrombophilia.

CASE REPORT

CASE 1: An 18-year-old female presented in hematology-oncology clinic with complains of pain and swelling in left calf of two weeks duration. Her birth and developmental history was unremarkable. She was born by caesarean section without any complications. There was no history of delayed milestones. Her diet and appetite were normal.

Her past medical history was significant with two catastrophic events. One occurred in August 1994 with swelling and pain in the right calf for 24 hours. Apart from routine laboratory investigations done at that time, a doppler ultrasonographic study revealed thrombosis in deep veins of the leg. This was followed by amputation of the right leg. She also had history of subluxation of the right eye lens in August 1995 followed by surgical correction.

She was a product of consanguineous marriage. Both parents and younger sister were healthy with no history of any significant medical illness. Moreover, her elder brother had significant medical history (described as case 2).

At the time of presentation her general examination showed pallor while examination of limbs revealed swelling and tenderness of left calf. Rest of the systemic examination was unremarkable.

Her complete blood counts at the time of presentation revealed anemia with hemoglobin of 8.3 gm/dl, while TLC, differential count and platelet counts were normal. Peripheral blood film revealed anisocytosis, macrocytes, polychromasia, target cells, poikilocytes and occasional right shift neutrophils. The serum vitamin B_{12} levels and red cell folate levels were normal. Hemoglobin electrophoresis was normal.

She was investigated for various causes of inherited thrombophilia. She was found to have positive urinary homocysteine assay.[1], while the plasma homocysteine levels were elevated i.e. 117.5 µmol/L. Other laboratory investigations were normal.

Based on the clinical presentation and laboratory data, including normal vitamin B_{12} and red cell folate levels along with a high level of plasma homocysteine she was diagnosed to be a case of familial homocystinuria. She was then started on a trial of folic acid, vitamin-B_6 (pyridoxine) and vitamin B_{12} (methylcobolamin) supplementation.

CASE 2: The brother was 21-year-old who presented to the neurology clinic with history of mental retardation since birth. He also complained of pain and swelling of superficial calf veins since 4 months. He was born through a caesarean section. His diet and appetite were also normal. His younger sister was diagnosed to be a case of familial homocystinuria (described as case 1).His past medical history included an event of dislocation of lens of the right eye in 1987 followed by surgical correction.

At the time of presentation, examination of limbs revealed dilated but non-tender superficial veins of right leg. CNS examination revealed psychomotor retardation. Rest of the examination was unremarkable.

In view of his medical and family history, urinary homocysteine was performed and found to be positive. The plasma homocysteine levels were elevated i.e. 364.6 µmol/L. Doppler ultrasonography of the right leg showed no evidence of deep vein thrombosis. His serum B_{12} and red cell folate levels were also found to be normal.

A diagnosis of familial homocystinuria was made and since then he was kept on folic acid, vitamin B_6 (pyridoxine) and vitamin B_{12} (methylcobolamin) supplementation.

In both these cases activity of cystathione- ß synthase and N-methyltetrahydrofolate reductase (MTHFR) could not be done for further characterization of familial homocystinuria.

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because of the unavailability of these tests. However, clinical history and high levels of plasma homocysteine were significant enough to make a diagnosis of familial homocystinuria.

Discussion

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine. Homocysteine is metabolized by one of the two pathways.[2] remethylation and transulfuration. Remethylation is catalyzed by methionine synthase, for which vitamin B_{12} is an essential cofactor. N-methyltetra-hydrofolate is the donor in this reaction and N-methyltetrahydrofolate reductase (MTHFR) act as a catalyst. Under conditions in which excess methionine is present, homocysteine enters transulfuration pathway, a reaction catalyzed by vitamin B_6 dependent enzyme cystathione-ß synthase.

Familial homocystinuria is an autosomal recessive disorder and a number of defects have been identified.[3] Familial homocystinuria and homocystinemia has been classified into three major categories.[3] Type 1 or classic homocystinuria is due to the deficiency of cystathione-ß synthase - (CBS). It is also the most frequent cause of hyperhomocystinemia.[4] In this type diagnosis is usually made after 3 years of age when sublaxation of lens occurs. Progressive mental retardation is common along with psychiatric and behavioral disorders. Affected individuals may also manifest skeletal abnormalities. Thromboembolic episodes involving both large and small vessels are common and may occur at any age. An elevation of homocysteine is the diagnostic finding. The homozygous form of this disease can be associated with plasma homocysteine concentration of upto 400 µmol /L.[2] Type 2 homocystinuria is due to defects in methylcobalamin formation, which is a cofactor for the enzyme methionine synthase. These patients usually present with history of lethargy, poor feeding and developmental delay in the first few months of life. Laboratory studies reveal megaloblastic anemia, homocystinuria and hypomethioninemia.[3] Type 3 homocystinuria is due to the deficiency of methylenetetrahydrofolate reductase. Complete absence of the enzyme usually causes mental retardation, microcephaly and spasticity. Laboratory findings reveal moderate homocystinemia and homocystinuria. The methionine concentration is low or normal.

Homocysteine (and its dimer homocysteine) ordinarily is detectable only in trace amounts in plasma and urine. Homocysteine may not be detectable in urine until total plasma homocysteine levels exceed 150 µmol/L. On this basis, by measuring urinary homocysteine occasional patients would be missed.[5] So when a strong suspicion is made of this rare entity plasma homocysteine should be measured despite negative urinary homocysteine.

Obligate heterozygote carriers have 22% to 47% cystathione-ß- synthase activity in cultured fibroblasts or long-term cultured lymphocytes. Prenatal diagnosis is available for cystathione-ß-synthase deficiency using cultured chorionic villus cells or amniotic fluid cells to measure the activity of this enzyme.[6] Screening test for familial homocystinuria involves the determination of levels of methionine. Newer methods include direct methionine assay by tandem mass spectrometry.[7] Elevation in methionine level may be minimal during the first 3 days of life until there is adequate protein intake. It may be preferable to screen for this disorder at 2 or 4 weeks of age.[8]

Various definitions have also been used to derive cut-off levels for hyperhomocystinemia. The classification by Kang.[9] is now generally used, distinguishing moderate (15-30 µmol/L), intermediate (>30 to 100µmol/L) and severe hyperhomocystinemia (>100 µmol /L) on the basis of concentration measured during fasting.

Hyperhomocystinemia is now an established independent risk factor for the vascular thrombosis. Various investigators have reported a positive association between hyperhomocystinemia and venous thrombosis.[10] However, in cases of mild to moderate hyperhomocystinemia, controversy remains regarding the association between homocysteine and vascular occlusive disease.

A number of other factors influence homocysteine metabolism, including several disease states and medications. Elevated plasma homocysteine levels are seen in patients with chronic renal failure, hypothyroidism, several types of carcinomas and drugs including methotrexate, phenytoin and theophylline etc. Elevated levels have also been reported in patients with pernicious anemia.[2]

Uptil now, there is no consensus regarding the best method of treatment. However, vitamin supplementation with folic acid, pyridoxine and vitamin B_{12} is generally effective in reducing homocysteine concentration. This, in turn, may help in reducing the occurrence of thromboembolic event.

References

1. Schumann GB, Schweitzer SC. Examination of urine. In: Henry JB, (edi). Clinical diagnosis and management. 18th ed. Philadelphia: *W.B.Saunders* 1991; 437.
2. Welch GN, Loscalzo J. Homocysteine and thrombosis. *N Engl J Med* 1998; **338**: 1042-9.
3. Rezvani I. Metabolic diseases. In: Behrman RE, Kliegman RM, Jenson HB, (edi). Nelson: textbook of pediatrics. 16th ed. Philadelphia: *W.B.Saunders* 2000; 343-450.
4. De Stefeno. Inherited thrombophilia: pathogenesis, clinical syndrome and management. *Blood* 1996; **87**: 531.
5. Moat SJ, Bonham JR, Tanner MS. Recommended approaches for the laboratory measurement of homocysteine in the diagnosis and monitoring of patients with hyperhomocystinemia. *Ann Clin Biochm* 1999; **36**: 372-9.
6. McGill JJ, Mettler G, Rosenblatt DS, Scriver CR. Detection of heterozygotes for recessive alleles. Homocystinemia: paradigm of pitfalls in phenotypes. *Am J Med Genet* 1990; **36**: 45-52.
7. Millington DS, Norwood DL, Kodo N, Roe CR, Inoue F. Application of fast atom bombardment with tandem mass spectrometry and liquid chromatography/mass spectrometry to the analysis of acylcarnitines in human urine, blood and tissue. *Anal Biochem* 1989; **180**: 331-9.
8. Pass KA, Amador PS. Homocystinuria screening in newborns. In: Terrill BL, (edi). Laboratory methods for neonatal screening. Washington, DC: *Am Public Health Assoc* 1993; 125-31.
9. Pietzikk, Bronstrupa. Causes and consequences of hyperhomocystinemia. *Int J Vitamin Nutr Res* 1997; **67**: 398.
10. Angelo, AD, Selhub J. Homocysteine and thrombotic disease. *Blood* 1997; **90**: 1-11.