Case Report

Homocystinuria in Thai Patient - Phramongkutklao Hospital Experience

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Homocystinuria is a rare autosomal recessive disorder of amino acid metabolism. Classic (type I) homocystinuria is the most common type and occurs as a consequence of a deficiency of cystathionine-b-synthase, producing increased blood and urine homocysteine.

The authors report a 15-year-old Thai male who presented with generalized tonic-clonic seizures from superior sagittal sinus thrombosis, bilateral downward subluxation of ocular lenses (ectopia lentis), Marfanoid habitus, osteoporosis, attention deficit and hyperactivity disorder. Urine metabolic screening was positive for cyanide nitroprusside test. Levels of plasma homocysteine and methionine were elevated. The clinical and laboratory findings in this case are consistent with the diagnosis of "type I" or "classical homocystinuria". The treatment was started with a low methionine diet, vitamin B6 or pyridoxine, folic acid, anticonvulsants, antithrombotic treatment and calcium supplementation. Genetic counseling was provided to the family with the recurrent risk of 25%. Definite diagnosis by enzyme assay or mutation analysis and also prenatal diagnosis are not established in Thailand.

Keywords: *Homocystinuria, Homocystinemia, Homocysteine, Cystathionine β-synthase*

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Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Homocystinuria is a rare autosomal recessive disorder, which has been classified into three major categories[1]. Classic (type I) homocystinuria is the most common inborn error of methionine metabolism, which occurs as a consequence of a deficiency of cystathionine-b-synthase. Homocystinuria was first described in 1962[2,3], characterized by a severe elevation in the serum and urine homocysteine. Clinical presentations of homocystinuria include mental retardation, tall stature, lens subluxation, hypercoagulable stage (arterial occlusion and/or venous thrombosis), early osteoporosis and Marfanoid habitus. The severity of the disease depends on the serum homocysteine levels, until now there are no definite treatment. The authors report the first case of the typical homocystinuria with characteristic clinical and laboratory findings in Phramongkutklao Hospital.

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Case Report

A 15 years old Thai male presented with four episodes of generalized tonic-clonic seizures six hours before admission. He was the first son and had two younger sisters. There was consanguinity, both parents were related (Fig. 1). Both parental age were in their 40 s. His father and mother were 160 cm and 153 cm tall, respectively. Both parents and siblings were healthy. The patient s growth and physical development were normal until he was 10 years old, when he had blurred vision in both eyes and needed spectacles. At the same time, his mother had noticed a rapid growth rate and his learning problem. The diagnosis from a psychologist was attention deficit

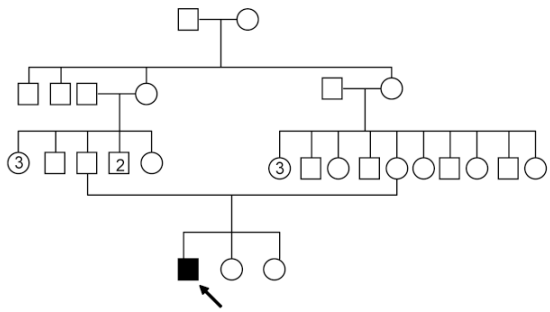

Fig. 1 The pedigree of the patient

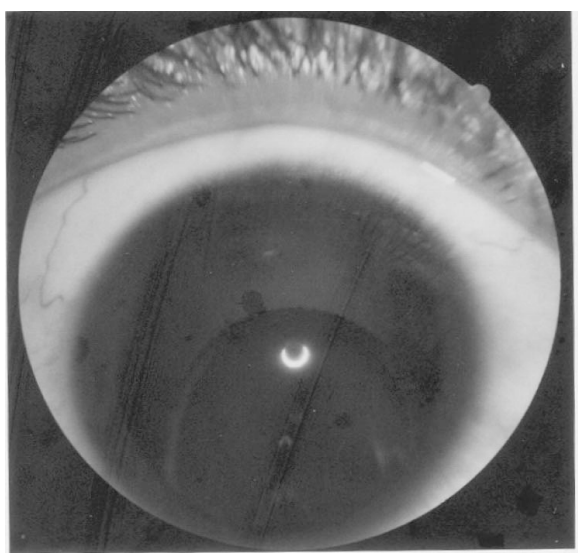

Fig. 2 Shows lens subluxation of the left eye

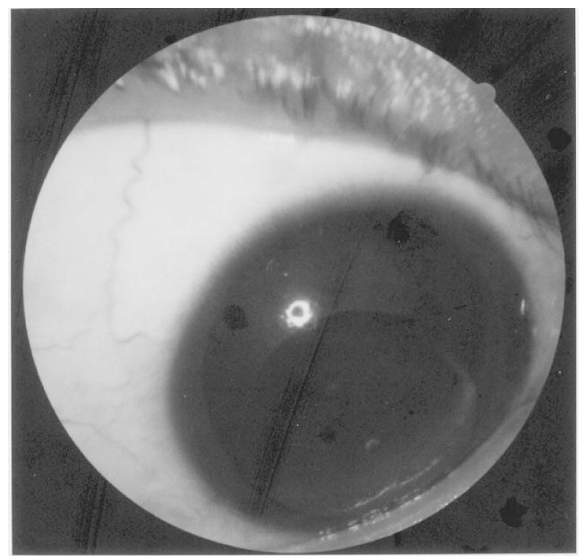

Fig. 3 Shows lens subluxation of the right eye

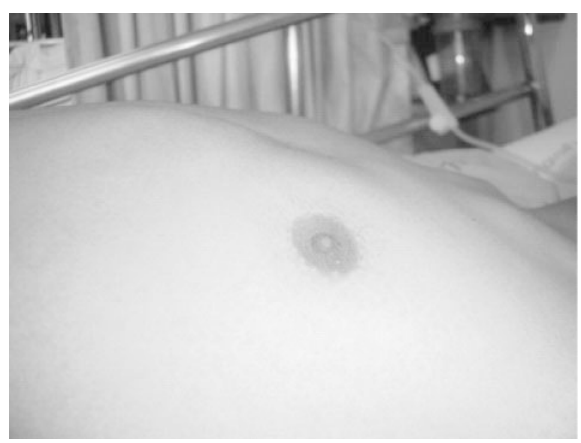

Fig. 4 Shows pectus excavatum

and hyperactivity disorder. He had been placed on methylphenidate 10 mg oral once daily, but there was no improvement after the medication.

Physical examination revealed normal vital signs. He had tall stature (186 cm, more than 97th percentile) with thin and elongated extremities (dolicostenomelia). Arm span was 186 cm long and upper/lower segment ratio was 0.86 (86/100 cm). His neurological examination revealed left hemiparesis and confusion. He had bilateral downward subluxation of the ocular lenses (Fig. 2 and 3), pectus excavatum (Fig. 4), arachnodactyly (Fig. 5), high arch of foot or pes cavus (Fig. 6). Other systems were unremarkable.

Complete blood cell counts, serum electrolytes, serum calcium, serum magnesium, plasma glucose, blood urea nitrogen and creatinine were normal. Liver function test, coagulogram (APTT, PT and TT) and cerebrospinal fluid were also normal. Urine analysis was normal but urine metabolic screening was positive for cyanide nitroprusside test.

Computerized tomography (CT scan) of the brain showed hypodensity of both frontal lobe areas (Fig. 7). Electroencephalogram (EEG) showed diffuse cortical dysfunction. Angiogram of the brain was compatible with superior sagittal sinus thrombosis (Fig. 8). Electrocardiography (EKG) and echocardiography showed no significant abnormality. Duplex ultrasonography of the carotid artery showed no carotid artery stenosis. Bone mineral density showed osteoporosis of the spine and osteopenia of the left hip.

He was investigated for various causes of thrombosis including: protein C 126% (normal 70-140%), protein S 81% (normal 60-140 %), antithrombin III 59% (normal 75-125%), factor V 63.9% (normal 50-200%). His urinary homocysteine assay by urine gas chromatography/mass spectrometry (urine GC/MS) was negative while the serum homocysteine level was 50 mol/L (normal 5-12 mol/L). Serum homocysteine was repeated again at 4 weeks thereafter and the result was 204.7 mol/L, serum methionine level was 330.22 nmol/L (normal 9.77-43.93 nmol/L).

Discussion

To our knowledge this patient is the third case of homocystinuria in Thailand[4,5]. Homocystinuria (severe hyperhomocysteinemia) is a rare inherited metabolic disease. Clinical manifestations of the disease depend on the serum homocysteine level. Although the elevation of serum homocysteine concentration can occur due to nutritional deficiency in vitamin cofactors, folic acid and/or vitamin B6, B12 deficiency, hypothyroidism, renal failure, cigarette smoking and other medical illnesses, but marked

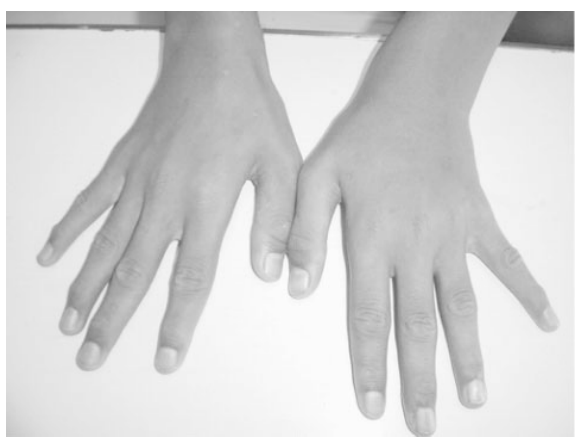

Fig. 5 Shows arachnodactyly

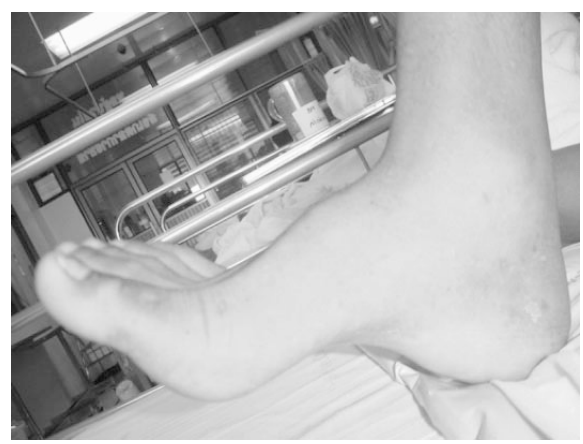

Fig. 6 Shows pes cavus

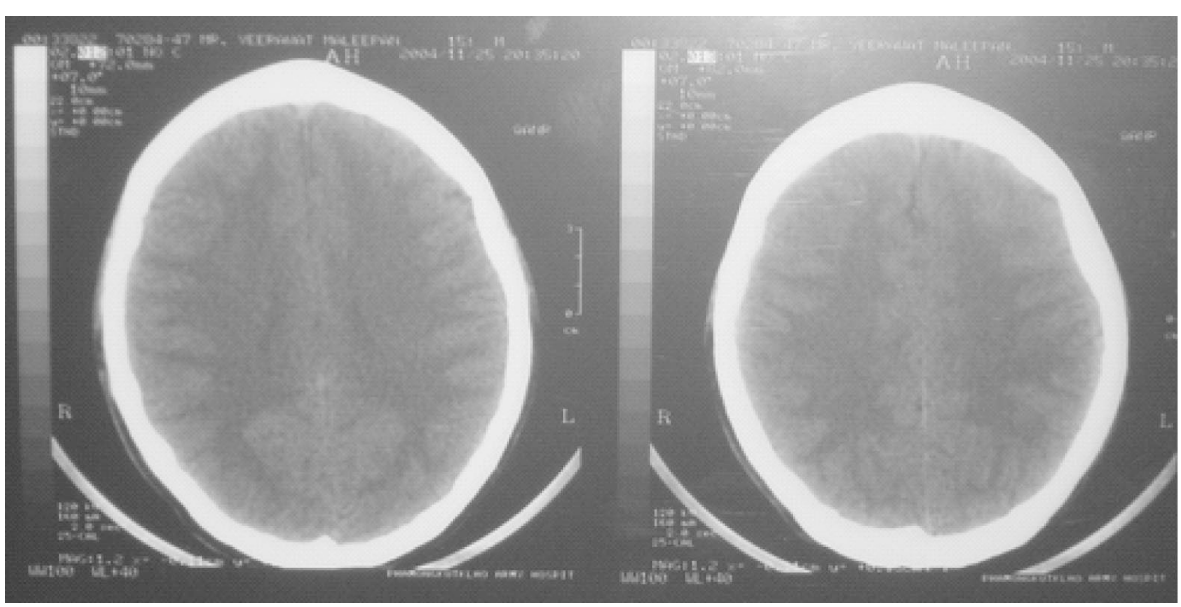

Fig. 7 Shows right frontal lobe edema

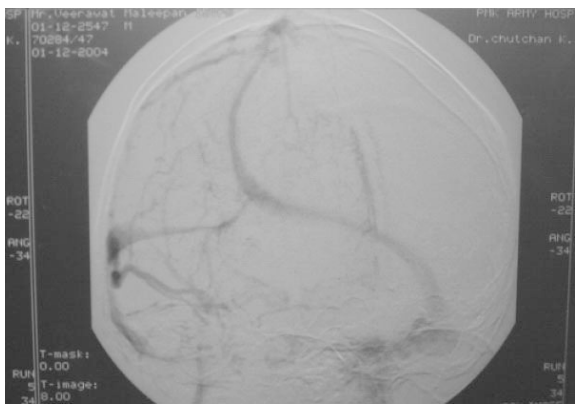

Fig. 8 Shows thrombosis of superior sagittal and left transverse dural sinuses

hyperhomocysteinemia can only be seen in genetic defects in the enzymes involved in homocysteine metabolism[1,6-14].

The patient presented with generalized tonic-clonic seizures with left hemiparesis, tall stature, mental retardation and hyperactivity disorder. On physical examination, the authors found downward subluxation of both ocular lenses (ectopia lentis), high arch palate, pectus excavatum, Marfanoid habitus, and pes cavus. Based on the clinical presentations in the present case, homocystinuria was diagnosed. Serum methionine, serum and urine homocysteine were done to confirm the diagnosis. Normally, homocysteine is detectable only in trace amounts in plasma and urine. Normal plasma homocysteine values are less than 15 mmol/L whereas most untreated classic homocystinuria patients exhibit levels above 200 mmol/L[15]. In the present case, both serum homocysteine and methionine levels were elevated and compatible with type I or classic homocystinuria although urine homocysteine was negative because urine homocysteine may not be detectable if total plasma homocysteine levels do not exceed 150 mmol/L[16]. The cerebral angiogram revealed thrombosis of the superior sagittal sinus and left transverse sinus that was assumed to cause left hemiparesis and epilepsy. The mechanisms of the thromboembolic complications in homocystinuria were promotion of leukocyte recruitment by up regulating monocyte chemoattractant protein-1 and IL-8 expression and secretion[17], prothrombotic effects of homocysteine[18], increase smooth muscle cell proliferation and enhance collagen production[19], increase free radical formation result by oxidation of reduced homocysteine[20,21], increase platelet aggregation due to prothrombotic effect of homocysteine[22,23] and decrease in nitric oxide synthesis by inhibition of nitric oxide synthase[22,24].

The aim of treatment is to reduce plasma homocysteine to near normal while maintaining normal growth rate. Treatment in classic homocystinuria with high doses of vitamin B6 or pyridoxine (200-1,000 mg/day) causes dramatic improvement in patients who are responsive to this therapy. Folic acid (5-10 mg/day) should be added to the treatment regimen[25]. Restriction of methionine intake with cysteine supplementation is recommended especially in pyridoxine non-responsive homocystinuria. Betaine (trimethylglycine 6-9 g/day or maximum dose of 150 mg/kg/day), which also serves as a methyl group donor, lowers homocysteine levels in body fluids by remethylating homocysteine to methionine[1]. This treatment has produced clinical improvement in patients who are non-responsive to pyridoxine therapy[26,27]. In the present case, the treatment was started with a low methionine diet, vitamin B6 500 mg/day, folic acid 10 mg/day, anticonvulsants, antithrombotic treatment and calcium supplementation. After 3 months of treatment, there was clinical improvement but serum homocysteine was still elevated (207 mol/L). Vitamin B6 was increased to 1,000 mg/day for 3 months but the serum homocysteine was still elevated. Other treatments such as betaine should be considered because this patient may have pyridoxine non-responsive homocystinuria. Genetic counseling should be provided to the family with the recurrent risk of 25% due to its autosomal recessive inheritance.

Conclusion

Homocystinuria is the form of severe hyperhomocysteinemia, which is an autosomal recessive disorder. In the present case, type I or classic homocystinuria was diagnosed due to typical clinical presentations and laboratory findings. Typical clinical manifestations include ectopia lentis, dolichostenomelia, osteoporosis, superior sagittal sinus thrombosis, attention deficit and hyperactivity disorder. The laboratory findings showed elevated serum homocysteine and methionine levels. Unfortunately, no definite diagnostic laboratories offering either enzyme assay or molecular diagnosis for classic homocystinuria are available in Thailand. However, clinical presentation and laboratory findings especially high levels of serum homocysteine and methionine were significant enough to make a diagnosis of homocystinuria. Until

now there is no definite treatment for homocystinuria, some complications can be improved by the supplementation of vitamin B6, folic acid and/or vitamin B12. The severity of the disease depends on the specific type of enzyme deficiency. Genetic counseling is the useful tool to prevent new cases of homocystinuria.

Acknowledgements

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โรคโฮโมซิสตินูเรียในโรงพยาบาลพระมงกุฎเกล้า: รายงานผู้ป่วย

เจษฎา พันธวาศิษฏ์, บุญชัย บุญวัฒน์, อภัสนี บุญญาวรกุล, มหัทธนา กมลศิลป์, อัมพา สุทธิจำรูญ

โรค homocystinuria เป็นโรคที่มีการถ่ายทอดทางพันธุกรรมแบบจีนด้อยที่พบได้ไม่บ่อยและเกี่ยวข้องกับเมตาบอลิสมของกรดอะมิโน classic homocystinuria หรือ type I homocystinuria เป็นชนิดที่พบบ่อยที่สุด เกิดจากการลดลงหรือขาดการทำงานของเอนไซม์ cystathionine-β-synthase เป็นผลให้มีการคั่งของโฮโมซิสเตอีน ในเลือดและปัสสาวะ

รายงานผู้ป่วยชายไทย 1 ราย อายุ 15 ปี มาด้วยอาการชักกระตุกทั้งตัวจากภาวะลิ่มเลือดใน superior sagittal sinus ตรวจพบเลนส์ตาเคลื่อนลงล่างทั้ง 2 ข้าง ตัวสูงและแขนขายาว กระดูกพรุน และมีภาวะสมาธิสั้น การตรวจกรองทางเมตาบอลิกของปัสสาวะพบผลบวกต่อ cyanide nitroprusside มีการเพิ่มขึ้นของระดับโฮโมซิสเตอีนและเมไทโอนีนในเลือด อาการทางคลินิกและผลการตรวจทางห้องปฏิบัติการของผู้ป่วยเข้าได้กับ "type I" หรือ "classic homocystinuria" ผู้ป่วยได้รับการรักษาด้วย การรับประทานอาหารที่มี methionine ต่ำ วิตามินบี 6 กรดโฟลิก ยากันชัก ยาป้องกันเลือดแข็งตัว การให้แคลเซียมเสริม และครอบครัวของผู้ป่วยได้รับคำปรึกษาทางพันธุศาสตร์ โอกาสเกิดซ้ำในบุตรคนต่อไป ร้อยละ 25 การวินิจฉัยที่แน่นอนโดยการตรวจวิเคราะห์เอนไซม์ หรือการตรวจวิเคราะห์หาการกลายพันธุ์ รวมทั้งการวินิจฉัยก่อนคลอดยังไม่สามารถทำได้ในประเทศไทย