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Case Report

Internal Medicine Section

Homocystinuria in Adult Siblings

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ABSTRACT

Homocystinuria, an inborn error of amino acid metabolism, is a rare disorder. Here, we are reporting homocystinuria in two adult siblings. The elder brother had seizures, mental retardation, marfanoid habitus and osteoporosis with multiple pathological fractures of the bones and he was operated for a dislocated lens; the younger sister had mental retardation, osteoporosis and untreated dislocated lens in both the eyes. Homocystinuria was diagnosed in both the siblings and they were started on treatment with vitamin B_6, vitamin B_{12} and folic acid. A decrease in the urine and plasma homocysteine levels with a good response was noted after treatment.

Key Words: Homocystinuria, Dislocation of the lens, Mental retardation, Marfanoid features, Osteoporosis, Homocysteine, Vascular thrombosis

INTRODUCTION

Homocystinuria, an autosomal recessive metabolic disorder of aminoacids, which is characterized by elevated levels of plasma and urine homocysteine, was first described in mentally retarded children by Carson et al [1]. The elevated levels of homocysteine are associated with increased risk of dementia, fractures, chronic heart failure, and eclampsia. An increased level of homocysteine is an emerging, independent risk factor for atherosclerosis, because it is both thrombogenic and atherogenic [2]. We are presenting the two cases to interpret the delayed diagnosis of the homocystinuria in adult siblings. Due permissions were obtained from the institutional ethical committee of our hospital before the start of the study. Informed consent was obtained from the study subjects after explaining the objectives of the study to them. Also, due permissions were obtained from the study subjects for the reproduction of the photographs for the publication of this case report.

CASE 1

A young 22-year-old male presented with generalized tonic clonic seizures (GTCS) without headache, vomiting or fever. Born to non-consanguineous parents by an uneventful birth and with a developmental history, he was operated at the age of five years for bilateral dislocation of the lens. He sustained trivial trauma which induced multiple fractures at the upper and lower limbs at different ages, starting at the age of 5 years. He weighed 49kg with a height of 162 cm, an upper segment: lower segment ratio of 0.8:1 (74cm: 88cm) and arm span which was 7 cm more than the height. He had aphakic eyes, a high arched palate, long thin extremities, arachnodactyly, a positive thumb sign and a wrist sign [Table/Fig-1]. His cardiovascular system examination and his peripheral pulses were unremarkable.

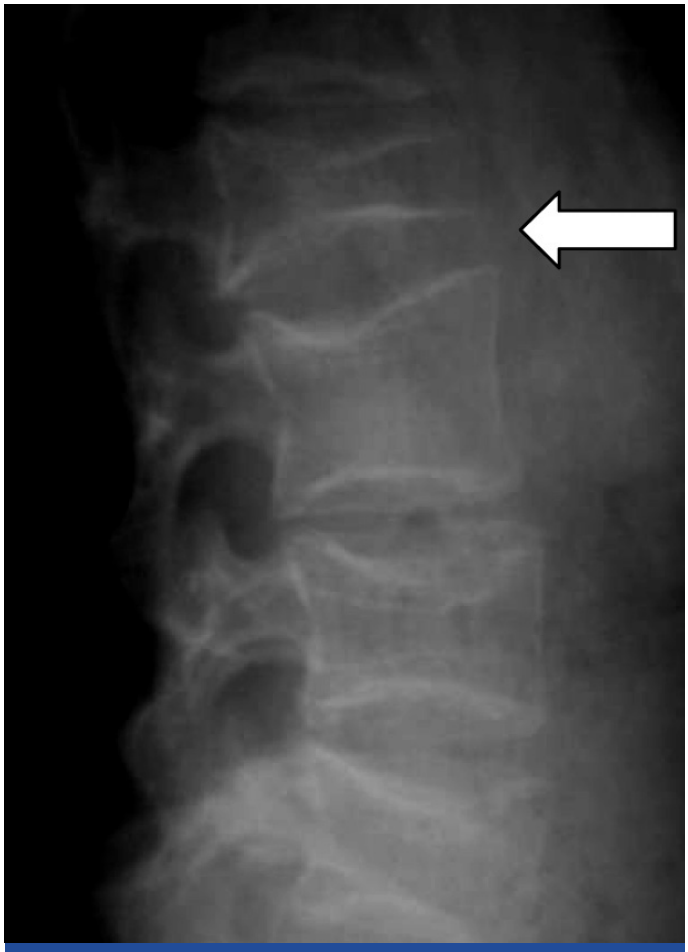
His urine examination, complete haemogram, peripheral smear study, blood sugar levels, thyroid, liver and kidney function tests, vitamin B_{12} and folate levels were normal. His abdominal ultrasound and his echocardiogram were normal. The Doppler study of the vessels showed no abnormality or evidence of occlusion or thrombosis. Computed Tomography (CT) scan of his brain showed evidence of mild cerebral atrophy, while an electroencephalogram (EEG) revealed right fronto temporal epileptiform discharges. X rays of the lumbosacral spine revealed fish mouth vertebrae, marked osteoporosis and fracture of the L2 vertebra [Table/Fig-2]. The T score in bone mass densitometry studies was -2.6, which was suggestive of severe osteoporosis.

He was started on tablets of vitamins B_6, B_{12}, folic acid, Calcitriol, calcium carbonate and Carbamazepine, while he was still under regular follow up. Before the treatment, his plasma and urine homocysteine levels were 250 micromoles/L (normal 4- 12 micromoles/L) and 7163 micromoles/L respectively. After one year of treatment with improvement in his bone density (T score -1.5), the plasma and urine homocysteine levels decreased to 50 micromoles/L (normal 4- 12 micromoles/L), and 500 micromoles/L respectively.

CASE 2

This 20-year-old patient who was the younger sister of case one, presented with blurring of vision. Though she was mentally retarded since childhood, she was not investigated earlier. She had bilateral inferolateral dislocation of the lens without any marfanoid features or signs of hyperelasticity, a height of 150 cm and a weight

[Table/Fig-1]: It shows Archnodactlyly, long slender fingers and positive wrist sign in patient 1

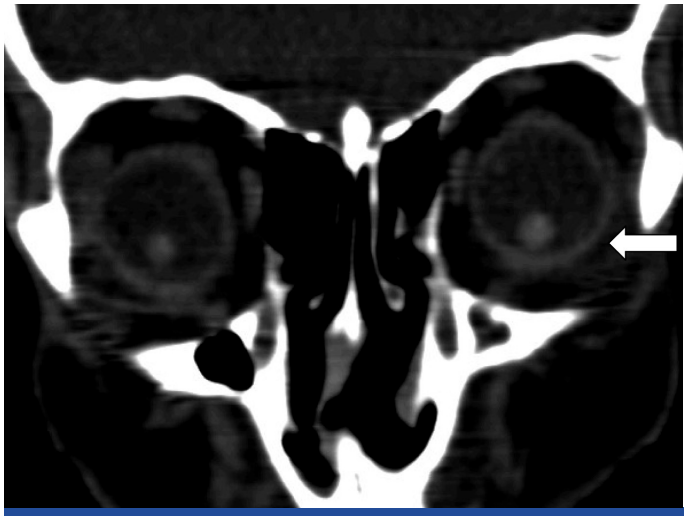


[Table/Fig-2]: It shows the lateral view of lumbar spine showing evidence of osteoporosis and fish mouth appearance of vertebra in Patient - 1

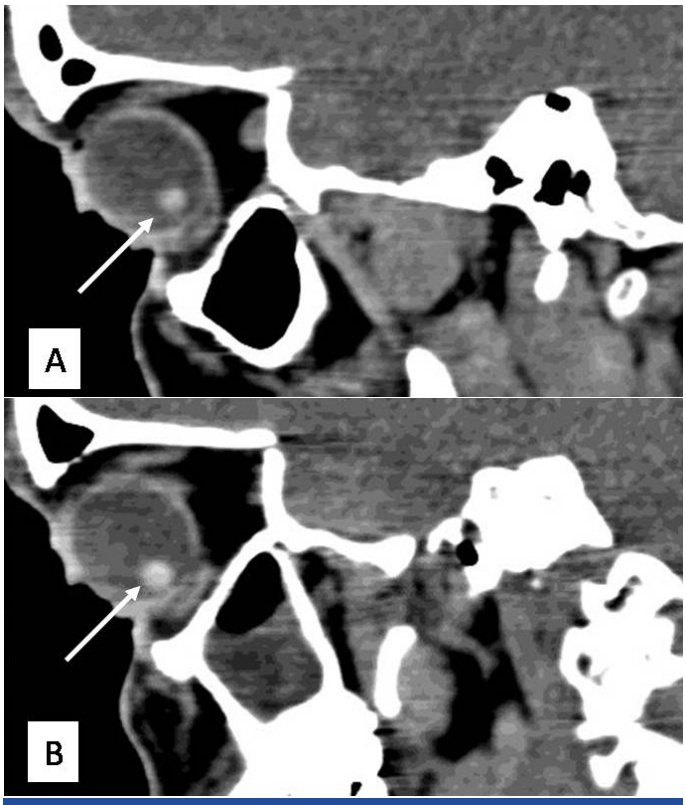
of 45 kg. Her urine examination, complete haemogram, peripheral smear study, blood sugar levels, thyroid, liver and kidney function tests, vitamin B_{12} and folate levels, were normal. The Doppler study of her peripheral and neck vessels , echocardiography, ultrasound of the abdomen and CT scan of the brain were normal. CT scan of both the orbits showed bilateral inferior lens dislocation [Table/Fig-3 & 4]. X rays of the lumbosacral spine showed osteoporosis (T-score in BMD of -2.3). She was started on tablets of vitamins B_6, B_{12}, folic acid and calcium. Her plasma and urine homocysteine levels were 340 micromoles/L (normal 4-12 micromoles/L) and 8250 micromoles/L respectively. After one year of treatment, her plasma homocysteine level was 110 micromoles/L and her urine homocysteine was 1100 micromoles/L.

DISCUSSION

Homocystinuria due to the deficiency of cystathionine beta synthetase (CBS) is the commonest of the seven biochemical types which have been reported so far [3]. CBS deficiency results in the excessive accumulation of homocysteine in the plasma and other tissues, leading on to increased excretion of urinary homocysteine. This results in changes in the eyes, the skeletal system, the central nervous system, and the vascular system [3]. Homocystinuria in siblings had been reported worldwide [4-6]. As it is an autosomal recessive disorder, each parent carries one copy of the mutated gene, but do not manifest the disease. But when children are born to two carrier parents, they manifest the signs and symptoms. In this study, our siblings who were born by a non consanguineous marriage, had many similarities. Both had mental retardation, lens dislocation, and osteoporosis, but only the elder one had seizures. The parents were screened and they tested negative for homocystinuria. High levels of methionine



[Table/Fig-3]: It shows the Coronal CT sections of orbit showing bilateral inferiorly dislocated lens in Patient - 2



[Table/Fig-4]: It shows the sagittal CT Sections of right (A) and left (B) orbits showing bilateral inferiorly dislocated lens in Patient - 2

and homocysteine penetrate and damage the brain; the excitotoxic effect of homocysteic acid causes mental retardation and seizures [7].

Though it is slowly progressive, homocystinaemia is second only to phenylketonuria as a cause of mental retardation [4]. Without treatment, the children with homocystinuria may develop permanent mental retardation and behavioural problems. An early diagnosis, before the occurrence of the mental retardation may prevent it in 50% of the cases [4]. Of late, newborns are being screened for homocystinuria by heel prick tests before they leave the hospital.

Interference with collagen cross linking by the sulfhydryl groups of homocysteine causes subluxation of the lens and multiple skeletal deformities like genu valgum, pes cavus and long extremities [7]. The close differential diagnosis for homocystinuria is Marfan's syndrome. The dislocation of the lens is upwards in Marfan's syndrome and downwards in homocystinuria. Both will have lens

dislocation, but osteoporosis, mental retardation and the thrombotic tendency are rare in Marfan's syndrome [4]. Cardiac lesions which are usual in Marfan's syndrome, are rare in homocystinuria. Though both siblings had dislocated lenses, the elder one got operated, while the younger one refused treatment.

Osteoporosis in these patients develops before the age of 30-years and hence they are prone for fractures [8]. Bisphosphonates are a group of drugs which are used in the treatment of osteoporosis, which act by inhibiting the osteoclasts, thereby decreasing bone resorption. In a study which was done by Tomasz Szafranski et al, Zoledronic acid was tried to increase the BMD in a homocystinuric patient [9]. The osteoporosis of both the siblings improved after their diagnosis and treatment, with a better BMD score. The elder sibling who had multiple fractures and severe osteoporosis never had fractures after the treatment. Since the early treatment of osteoporosis can prevent the complications of osteoporosis, the diagnosis of premature osteoporosis should prompt the consideration of homocystinuria in such patients.

The natural history of homocystinuria predicts a high risk of an thromboembolism event at an earlier age. Due to sulfation factor like effects, vascular endothelial rupture occurs, followed by platelet thrombosis, causing vascular occlusion [7] resulting in myocardial occlusion, peripheral vascular disease, cerebral and renal artery occlusion, venous sinus occlusion, etc. Both the patients did not have any evidence of vascular thrombosis.

The diagnosis of homocystinuria is often missed or delayed. In a study which was done by Cruysberg et al [10], there was a mean delay of 11 years between the first major signs of the disease and the final diagnosis of homocystinuria. Lens dislocation is observed in 85% of patients with homocystinuria. Even though the first sibling got operated for dislocated lens at the age of 5-years, followed by treatment for multiple fractures at varying intervals, there was still a 15 years delay in the diagnosis.

Homocysteine metabolism is intimately linked with the metabolism of folate, vitamin B_{12}, and pyridoxine and some patients respond to the above therapy [2]. The symptoms of homocystinuria can be prevented by a diet which is low in methionine and rich in cystine, betaine, choline and arginine. Vitamin supplementation decreases or even normalizes the plasma homocysteine levels in many patients. Even carrier parents who never manifested homocystinuria, were found to have deficiencies of vitamin B_{12} and folate. Both our patients were started on treatment with vitamins B_{12}, and B_6, and folic acid and they responded well to the treatment.

CONCLUSION

A high index of suspicion of homocystinuria is warranted in any patient who presents with a combination of mental retardation and Marfanoid features. Homocystinuria usually presents with multisystem involvement – skeletal, neurological, vascular, and eye involvement. An early diagnosis of homocystinuria will reduce the incidence of vascular thromboembolism and mental retardation.

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