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Case Report

Classical homocystinuria presenting with bilateral ectopia lentis and multisystem involvement in a pediatric patient: a case report

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ABSTRACT

Homocystinuria (HCU) is an uncommon inherited metabolic condition caused by a deficiency of the enzyme cystathionine beta-synthase (CBS), which disrupts the normal breakdown of methionine. It leads to elevated homocysteine levels and a wide spectrum of multisystem clinical manifestations. Early recognition and intervention are crucial to prevent irreversible complications. We report the case of a 10-year-old male, firstborn of non-consanguineous parents, presenting with progressive visual impairment, generalized weakness, bilateral knee swelling and increased urinary frequency. Family history revealed early vision loss in a younger sibling. Ocular examination showed bilateral ectopia lentis and optic atrophy. Skeletal features were suggestive of a Marfanoid habitus. Cognitive evaluation indicated borderline intellectual functioning. Laboratory investigations revealed macrocytic anemia, mild liver enzyme elevation and a significantly elevated serum homocysteine level (50 µmol/l), confirming the diagnosis of classical homocystinuria. High-dose pyridoxine and folate supplementation were initiated.

This case highlights the classical phenotype of homocystinuria, including ocular, skeletal, hematologic, hepatic and cognitive involvement. Despite the treatable nature of HCU, diagnostic delays remain common, especially in resource-limited settings. Early diagnosis through clinical suspicion and biochemical testing, along with multidisciplinary management, is essential to reduce morbidity. Homocystinuria should be considered in pediatric patients presenting with ectopia lentis, skeletal disproportions and developmental delay. Timely diagnosis and appropriate treatment can significantly improve outcomes and prevent life-threatening complications.

Keywords: Cystathionine beta-synthase deficiency, Ectopia lentis, Fatty liver, Inborn errors, Intellectual disability, Marfan syndrome-like features, Optic atrophy, Pyridoxine

INTRODUCTION

Homocystinuria (HCU) is a rare autosomal recessive metabolic disorder characterized by impaired methionine metabolism due to a deficiency of the enzyme cystathionine beta-synthase (CBS).[1]

First described by Carson and Neill in 1962, HCU leads to the accumulation of homocysteine and its metabolites, homocysteine and homocysteine-cysteine complexes, in the blood and urine.[2] The defect in the transsulfuration pathway results in a broad spectrum of clinical manifestations, including developmental delay, intellectual disability, ocular abnormalities, skeletal deformities and thromboembolic events.[2] HCU is estimated to affect between 1 in 100,000 and 1 in 200,000 live births worldwide, though rates may vary by region.[3] Timely diagnosis and early treatment, such as vitamin therapy and dietary adjustments, are essential to avoid serious long-term health consequences.[4] However, diagnosis is often delayed due to the nonspecific nature of initial symptoms.[5] Authors present a case of classical homocystinuria in a pediatric patient, highlighting the

diagnostic challenges and the importance of early recognition and intervention to prevent irreversible complications.

CASE REPORT

Chief complaints

A 10-year-old male child presented to our pediatrics outpatient department (OPD) at Hind Institute of Medical Sciences, Sitapur with complaints of progressive loss of vision, generalized body weakness, bilateral knee swelling and increased frequency of urination.

Detailed history

A comprehensive history was obtained from the parents. This case was the first child of a non-consanguineous union. At the time of conception, the mother was 22 years old and the father was 24. Pregnancy was initially confirmed at home using a urine pregnancy test at around three months of gestation. The mother did not attend any antenatal care appointments during the pregnancy. There was no reported history of fever with rash or exposure to radiation during the gestation period. The baby was born at term through an uncomplicated vaginal delivery at home. The postnatal course was smooth and the child received the initial set of vaccinations. According to parental reports, developmental milestones were achieved appropriately for age. A significant family history was noted, with the patient's younger sister also having early-onset vision loss.

Examination

General examination

Showed pallor and dental crowding involving both upper and lower jaws. A dental consultation was sought. No dermatologic signs such as malar flush or livedo reticularis were observed. The patient had brittle hair and thin, dry skin.

Anthropometric assessment

It revealed that the child's height (129 cm) was between the 5th and 10th percentile, weight (24 kg) was below the 5th percentile and body mass index (BMI: 14.4 kg/m²) was between the 5th and 10th percentiles based on CDC standard growth charts.[6,7] The mid-upper arm circumference measured 17 cm on the right and 16.5 cm on the left. Head circumference was recorded at 51.5 cm. Notably, the child's arm span (130 cm) slightly exceeded his height and the upper to lower segment ratio was calculated as 0.95 (63 cm/66 cm), indicating possible skeletal disproportion (Figure 1).

Ocular examination

It revealed bilateral subluxation of the lens in the inferonasal direction, with only perception of light on visual acuity testing (Figure 2). The left pupil was 3 mm in diameter and did not respond to light, while the right pupil measured 5 mm and was similarly unresponsive. Ophthalmologic assessment confirmed optic atrophy in both eyes, with greater severity in the left eye.

Orthopedics assessment

The orthopaedic abnormalities observed in our case include marfanoid habitus [characterized by tall stature, long limbs (dolichostenomelia) and arachnodactyly], lordosis, scoliosis, knee joint swelling, knock knees and flat feet.

Hearing assessment

Brainstem evoked response audiometry (BERA) was performed for hearing assessment and revealed normal auditory function.

Psychological assessment

The child's cognitive abilities were evaluated using the Vineland Social Maturity Scale (VSMS), which assesses social and adaptive behavior.[8] During evaluation, the child's chronological age was 10.3 years (123 months), whereas his mental age was assessed to be approximately 8 years (96 months). This resulted in a Social Quotient (SQ) score of 78, suggesting borderline impairment in socio-adaptive functioning. Based on the findings, recommendations included psychoeducation, parental counselling and skill development training.

Investigations

Blood investigations showed macrocytic anemia, indicated by a raised mean corpuscular volume (MCV) of 108.7 fl, along with normochromic indices such as haemoglobin at 9.9 g/dl, mean corpuscular haemoglobin (MCH) of 37.5 pg and mean corpuscular haemoglobin concentration (MCHC) of 34.5 g/dl. The total leukocyte count was 8,600 cells per cubic millimetre, with a differential count showing 56% neutrophils, 29% lymphocytes, 4% monocytes and 11% eosinophils. Mild eosinophilia was present, with an absolute eosinophil count of 946/µl.

Additional parameters included a red blood cell (RBC) count of 2.63 million/cmm, packed cell volume (PCV) of 28.6%, platelet count of 2.81 lakhs/cmm and a red cell distribution width–coefficient of variation (RDW-CV) of 15%. Coagulation parameters were found to be within the normal reference range. Kidney function parameters were within normal limits, with blood urea at 28 mg/dl, serum creatinine at 0.70 mg/dl and blood urea nitrogen (BUN) measuring 14 mg/dl. Serum calcium was recorded at 8.4 mg/dl.

Evaluation of liver function revealed normal levels of total bilirubin (0.55 mg/dl), direct bilirubin (0.20 mg/dl) and alkaline phosphatase (219 IU/l). However, there was a mild elevation in transaminase levels, with SGOT at 68

IU/l and SGPT at 103 IU/l. Random blood sugar (RBS) was measured at 108 mg/dl, which falls within the normal range. Routine urine analysis revealed no abnormalities. Thyroid function tests were also within normal range: triiodothyronine (T3) was 1.45 ng/ml, thyroxine (T4) was 5.65 µg/dl and thyroid-stimulating hormone (TSH) was 0.47 µIU/ml. Abdominal ultrasound revealed grade I fatty liver. The electrocardiogram (ECG) was unremarkable. Serum homocysteine levels, measured by chemiluminescent microparticle immunoassay (CMIA), were elevated at 50 µmol/l (reference normal range: <15 µmol/l), confirming the diagnosis of classical homocystinuria. Estimation of cystathionine beta-synthase (CBS) enzyme levels was advised, along with whole-exome sequencing (WES) for genetic confirmation and MRI of the brain to rule out structural abnormalities; however, these investigations could not be performed due to financial constraints.

Management

The patient was started on high-dose pyridoxine (Vitamin B6, 500 mg/day), along with folic acid (folvite) and multivitamin supplementation (Vitamin A, vitamin B-complex, vitamin C, vitamin E, vitamin K). Psychoeducation, parental counselling and skill development training were started. In our case, where the patient had bilateral ectopia lentis accompanied by optic atrophy and complete vision loss, the focus of management was on supportive and rehabilitative care, as vision restoration is typically not feasible once optic atrophy has reached an advanced stage. Management of dental crowding affecting both upper and lower jaws included referral for orthodontic assessment and initiation of corrective treatment using braces or aligners to address malocclusion and achieve proper dental alignment. Management of fatty liver in this child focused on nutritional counselling, lifestyle modification and regular monitoring of liver function.

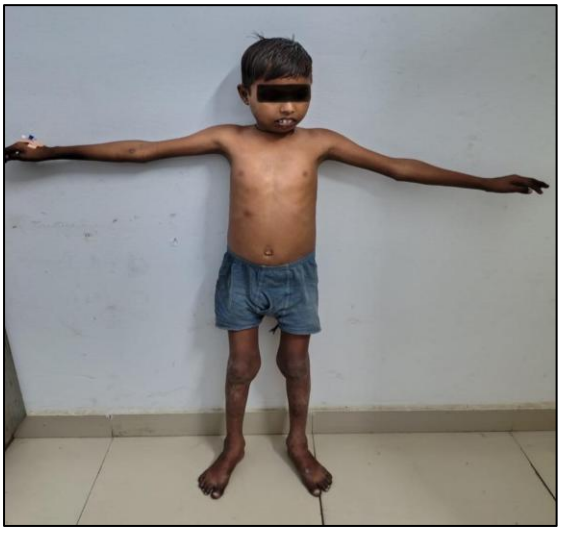

Figure 1: Comparison of child's arm span and height showing greater arm span than height.

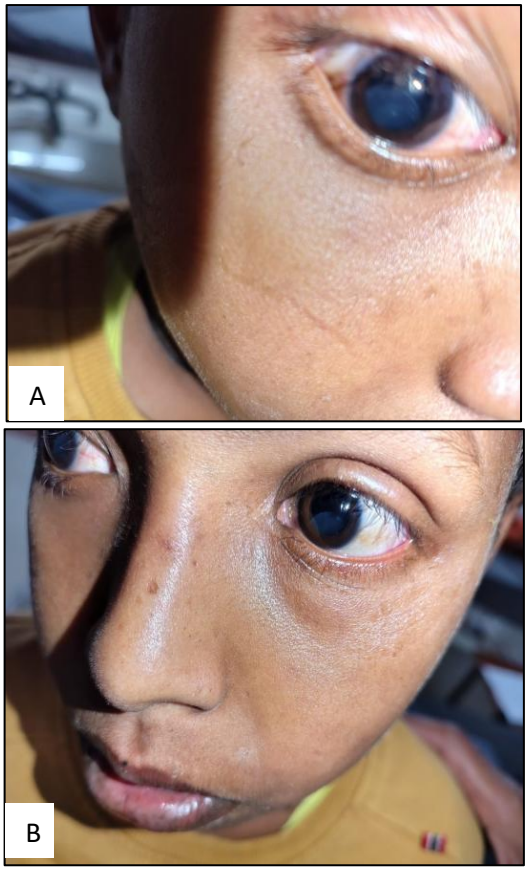

Figure 2: Bilateral inferonasal lens subluxation. (A) Right Eye. (B) Left Eye.

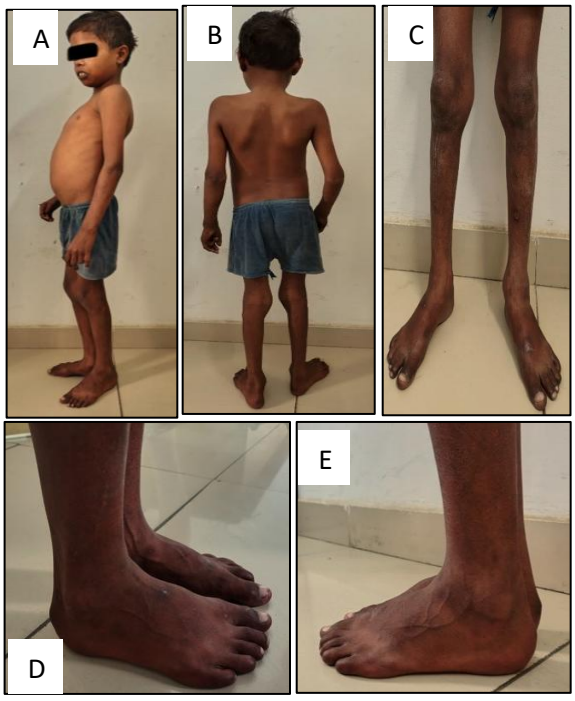

Figure 3: Orthopedics abnormalities observed. (A) Lordosis (B) Scoliosis, (C) Knee joint swelling, (D, E) Flat foot.

DISCUSSION

HCU is an uncommon inherited metabolic disorder characterized by the accumulation of homocysteine and its derivatives due to a disruption in the methionine metabolism pathway.[1] Homocysteine, a sulfur-containing amino acid, is generally broken down through two primary metabolic pathways.[2] In the transsulfuration pathway, the enzyme cystathionine β-synthase (CBS), which requires vitamin B6 (pyridoxine) as a cofactor, facilitates its conversion into cystathionine.[2] The remethylating pathway, on the other hand, converts homocysteine back to methionine using methionine synthase and methyl-cobalamin (vitamin B12), with folate acting as a methyl donor.[2] A defect in either pathway leads to elevated homocysteine levels in the plasma and urine, manifesting as classical or variant forms of homocystinuria.[2]

This case exemplifies the classical presentation of homocystinuria, with hallmark findings including bilateral ectopia lentis, which is among the earliest and most consistent ocular features.[3,4] Subluxation of the lens, along with optic atrophy, is well-documented in the literature and has been associated with progressive vision loss when left untreated.[3,4,9] The ophthalmologic complications observed in our patient underscore the importance of early ophthalmic evaluation in all suspected cases of HCU. Notably, despite the clinical recommendations, the patient declined specific ocular interventions due to financial constraints, highlighting the socioeconomic barriers to care in resource-limited settings.

The skeletal features noted in this case, including increased arm span, low upper-to-lower segment ratio, scoliosis, lordosis and knock knees, suggest a marfanoid habitus, which is well-recognized in HCU. These features, while similar to Marfan syndrome, can be differentiated by the presence of thromboembolic events, cognitive impairment and elevated homocysteine levels, which are more characteristic of HCU.[10] The patient also had bilateral knee swelling, which, although not a typical finding, may be attributable to structural skeletal abnormalities or vascular inflammation.[10] Long-standing osteoporosis can lead to various complications, including spinal curvature (scoliosis), increased susceptibility to pathological fractures and vertebral compression or collapse.[10] Other frequently observed skeletal deformities may include genu valgum (knock knees), chest wall deformities like pectus excavatum or pectus carinatum and pes cavus (high-arched feet).[10] Unlike the joint hypermobility typically observed in Marfan syndrome, affected individuals often exhibit restricted joint mobility, particularly in the limbs.[10]

Cognitive assessment revealed a borderline intellectual disability (SQ=78), aligning with the neurodevelopmental variability observed in HCU. Cognitive deficits are likely multifactorial, involving the neurotoxic effects of homocysteine as well as possible underlying structural brain changes.[11] Brain MRI was recommended to assess for white matter changes, cerebral atrophy or stroke, which are common in untreated HCU, but could not be performed due to financial limitations.[11] This case also expands the spectrum of systemic involvement in HCU. The presence of macrocytic anemia, mild hepatic transaminitis, grade I fatty liver and increased urinary frequency points toward multi-organ involvement, which has been documented in various reports.[1,12] While the cardiovascular system is often emphasized due to the risk of thromboembolic events, this case highlights the broader systemic burden, including gastrointestinal, hepatic and urinary manifestations.[1,13]

A definitive diagnosis was made based on an elevated serum homocysteine level (50 µmol/l) using chemiluminescent microparticle immunoassay (CMIA).[14] Early biochemical diagnosis remains vital, as delayed treatment may result in irreversible complications such as visual impairment, as seen here.[4] Genetic confirmation through CBS gene sequencing and enzyme assay was advised, but could not be performed due to economic constraints, a limitation commonly encountered in low-resource settings.[15]

Management of HCU involves a multidisciplinary approach. Patients responsive to pyridoxine benefit from high-dose Vitamin B6 therapy, which can lower homocysteine levels.[1] In addition, supplementation with folic acid, vitamin B12 and sometimes betaine may enhance remethylation.[1,16] Dietary restriction of methionine and protein-controlled diets are essential components of long-term therapy.[1,16] In our patient, high-dose pyridoxine (500 mg/day) and folic acid supplementation were initiated, with the aim of preventing further complications, particularly thrombotic events, which are the most serious outcomes in untreated cases.

Ophthalmologic intervention was not pursued due to financial limitations and the advanced stage of optic nerve atrophy. In such cases, visual rehabilitation, including special education, mobility training and psychosocial support, becomes essential.[4,17] Similarly, orthodontic referral was made for dental crowding and nutritional counselling was provided for the management of fatty liver. This case reaffirms the clinical diversity of HCU and underscores the importance of early recognition, especially in children with lens dislocation, skeletal disproportion, family history and neurodevelopmental delay. Timely intervention can significantly reduce the risk of irreversible organ damage and improve long-term outcomes.

CONCLUSION

This case underscores the diverse clinical manifestations and systemic involvement of classical homocystinuria, a rare but potentially treatable metabolic disorder. Early identification through clinical suspicion, especially in the presence of ectopia lentis, Marfanoid features, developmental delays and a positive family history, is

essential for timely intervention. Although definitive treatment can mitigate long-term complications, delayed diagnosis, socioeconomic limitations and lack of awareness continue to challenge disease management, especially in resource-limited settings. A multidisciplinary approach involving nutritionists, geneticists, ophthalmologists and paediatricians remains critical for optimal patient outcomes. Continuous monitoring and long-term follow-up are necessary to assess treatment response and prevent life-threatening complications such as thrombosis.

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