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Case Report

Homocystinuria Presenting as Deep Venous Thrombosis in a 14-Year-Old Boy – A Case Report

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Abstract

Background: Homocystinuria is a rare autosomal recessive metabolic disorder caused by a defect in the metabolism of homocysteine, leading to its elevated levels in the blood. Clinically, it presents with a wide range of symptoms including developmental delays, ocular abnormalities, skeletal deformities, and a predisposition to thromboembolic events. While deep venous thrombosis (DVT) is a well-recognized complication in hypercoagulable conditions, its association with homocystinuria is often overlooked.

Case Presentation: We report the case of a young individual diagnosed with homocystinuria who developed deep venous thrombosis. The patient presented with limb swelling and pain, and diagnostic imaging confirmed DVT. Further biochemical evaluation revealed markedly elevated homocysteine levels, leading to the diagnosis of homocystinuria.

Management & Results: Following diagnosis, the patient was initiated on treatment with vitamin B6, B12, and folate supplementation, which contributed to the reduction of homocysteine levels and improvement in clinical symptoms. Anticoagulation therapy was also administered to manage the acute thrombotic event.

Conclusion: This case highlights the importance of considering homocystinuria in the differential diagnosis of unexplained or recurrent venous thromboembolism, especially in younger patients. Early identification and targeted metabolic therapy can reduce the risk of serious thrombotic complications. Greater awareness of rare metabolic disorders like homocystinuria is essential in the evaluation of hypercoagulable states.

Keywords: Homocystinuria, Hyperhomocysteinemia, Inborn Errors of Metabolism, Venous Thrombosis, Vitamin B6.

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Introduction

Homocystinuria is a rare autosomal recessive disorder caused by a defect in amino acid metabolism [1]. The condition most commonly results from a deficiency of the enzyme cystathionine β-synthase (CBS), which disrupts the transsulfuration pathway, leading to elevated levels of homocysteine and methionine in plasma and urine [2]. Even moderate elevations in plasma homocysteine levels have been associated with a significantly increased risk of both arterial and venous thromboembolic events, independent of other known risk factors [3].

Skeletal manifestations of homocystinuria include excessive linear growth, disproportionately long limbs, scoliosis, and pectus excavatum. Thromboembolic complications, particularly within the vascular system, are among the most serious and may present as cerebrovascular accidents, deep vein thrombosis, or pulmonary embolism. These events can occur even in asymptomatic individuals and are often observed in adolescence or early adulthood [4]. Central nervous system involvement may lead to developmental delays, intellectual disability, seizures, psychiatric disturbances, and extrapyramidal symptoms (EPS), such as dystonia [4].

In addition, patients with classical homocystinuria due to CBS deficiency may exhibit craniofacial features such as high-arched palates and dental crowding [5]. Ocular abnormalities are also common, particularly in individuals diagnosed later in life, with ectopia lentis being the most prevalent finding [6]. Cardiac involvement is typically mild but may include valvular abnormalities [7].

We report a case of a 14-year-old boy diagnosed with homocystinuria who presented with deep venous thrombosis, emphasizing the importance of considering metabolic disorders in the differential diagnosis of thrombotic events in pediatric populations.

Case Presentation

A 14-year-old adolescent male presented to the Medical Outpatient Department (OPD) of Saidu Group of Teaching Hospital, Swat, with a one-week history of progressively worsening swelling in the right lower limb. The swelling was associated with localized pain, discomfort, and mild erythema. The patient denied any history of trauma, prolonged immobilization, recent infections, or changes in physical activity levels.

On physical examination, the patient exhibited multiple phenotypic features suggestive of a connective tissue disorder:

His medical history included epilepsy, intellectual developmental delay, and prior surgical correction for ectopia lentis. There was no history of blood transfusions, radiation exposure, or drug allergies.

Diagnostic Assessment

On general examination, the patient was alert and hemodynamically stable. Vital signs were within normal limits:

- BP: 110/80 mmHg
- Pulse: 100 bpm
- Temp: 98.4°F
- RR: 14 breaths/min
- SpO_2: 97% on room air

Examination of the right lower limb revealed swelling extending from the mid-thigh to the ankle, tenderness along the deep venous system, and a positive Homan's sign, indicating pain on dorsiflexion of the foot. There were no signs of cellulitis or overt infection. The left limb was normal. Initial laboratory investigations were as follows:

Doppler ultrasound of the right lower limb confirmed echogenic thrombi in the common femoral, superficial femoral, and popliteal veins, confirming deep vein thrombosis (DVT). The markedly elevated homocysteine level (206 μmol/L) was consistent with homocystinuria.



Figure 1: Pectus excavatum



Figure 2: Increased arm-to-height ratio



Figure 3: Arachnodactyly



Figure 4: High-arched palate



Figure 3: Pes cavus

Table 1: Diagnostic Laboratory Results Supporting the Diagnosis of Homocystinuria and DVT		
Investigation	**Patient Value**	**Reference Range**
Total Leukocyte Count (TLC)	6.7 × 10^3/dL	4.0 – 11.0 × 10^3/dL
Hemoglobin	11.5 g/dL	13.5 – 17.5 g/dL
Mean Corpuscular Volume (MCV)	98.5 fL	80 – 100 fL
Platelet Count	604 × 10^6/L	150 – 450 × 10^6/L
Homocysteine	206 μmol/L	5 – 15 μmol/L
C-Reactive Protein (CRP)	7.8 mg/L	<10 mg/L
Erythrocyte Sedimentation Rate	60 mm/hr	0 – 15 mm/hr
Liver Function Tests (LFTs)	Normal	—
Renal Function Tests (RFTs)	Normal	—

Therapeutic Intervention

Management was initiated for both DVT and homocystinuria:

1. Anticoagulation Therapy

- Enoxaparin (LMWH): 40 mg subcutaneously twice daily for 5 days
- Rivaroxaban: 15 mg orally twice daily for 21 days, followed by 20 mg once daily for 6 months

2. Metabolic Treatment for Homocystinuria

- Dietary methionine restriction
- Pyridoxine (Vitamin B6): 50 mg orally twice daily for 8 weeks
- Vitamin B12: 1000 mcg orally once daily, lifelong
- Folic Acid: 5 mg orally once daily, lifelong

3. Supportive Measures

Graduated compression stockings were recommended to reduce limb swelling and prevent post-thrombotic syndrome.

Follow-up and Outcomes

The patient was enrolled in regular follow-up with both medical and hematology teams. Monitoring included:

- Serial homocysteine levels
- Evaluation of anticoagulant efficacy and safety
- Adjustment of metabolic therapy based on clinical response

At subsequent visits, the patient showed gradual reduction in limb swelling and improved mobility. No new thrombotic events were reported during the early follow-up period. Compliance with dietary restrictions and supplementation was emphasized for long-term metabolic control.

Discussion

Homocystinuria is a rare but treatable autosomal recessive disorder caused by a deficiency in the enzyme cystathionine β-synthase (CBS), which disrupts the transsulfuration pathway of methionine metabolism. This enzymatic defect leads to the accumulation of homocysteine, methionine, and their S-adenosyl derivatives in plasma and tissues. The condition primarily affects the ocular, skeletal, central nervous, and vascular systems, with thromboembolic events being the most serious complications, contributing significantly to morbidity and mortality. These events may involve both the arterial and venous systems [8].

Clinically, homocystinuria presents with a wide phenotypic spectrum. Some individuals may exhibit only subtle signs such as lens dislocation and minor skeletal anomalies while maintaining normal cognitive function, whereas others may have profound intellectual disability and severe skeletal deformities. The skeletal abnormalities often arise from disproportionate growth, notably with an increased pubis-to-heel length relative to crown-to-pubis length. Common findings include

abnormal vertebral structures, pectus deformities, genu valgum with widened metaphyses, and epiphyseal changes in long bones. Due to phenotypic overlap, the condition is frequently misdiagnosed as Marfan syndrome [9].

Skeletal involvement typically begins in early childhood, presenting with signs such as genu valgum and pes cavus. During puberty, the disproportionate elongation of the limbs becomes more apparent compared to the trunk. Chest wall deformities, including pectus excavatum or pectus carinatum, may develop alongside spinal abnormalities such as kyphosis or scoliosis. Distinctive craniofacial features—such as a high-arched palate and dental overcrowding—are also characteristic [1]. Although mild valvular abnormalities have been observed in individuals with classical homocystinuria, further studies involving echocardiographic and electrocardiographic evaluations are warranted to better understand the extent of cardiac involvement [7].

A key biochemical feature of homocystinuria is hyperhomocysteinemia (HHcy), defined by elevated plasma homocysteine levels, which serve as a significant risk factor for various vascular and systemic complications. In classic homocystinuria due to CBS deficiency, patients are predisposed to early-onset thrombotic and atherosclerotic events, along with a range of neurological, psychiatric, and skeletal issues. Inborn errors of homocysteine metabolism (IEM) result in varying degrees of HHcy, clinically classified into mild (16–30 μmol/L), moderate (31–100 μmol/L), and severe (>100 μmol/L) levels. This classification is critical for clinical assessment, therapeutic decision-making, and prognostication [9].

Conclusion

Although rare, homocystinuria should be considered a potential underlying cause of deep venous thrombosis (DVT), particularly in individuals with a history of metabolic disorders, cognitive impairment, and characteristic skeletal abnormalities. This case highlights the critical importance of recognizing thromboembolic complications in patients with homocystinuria, as early diagnosis and timely intervention can significantly reduce the risk of life-threatening outcomes such as pulmonary embolism and long-term venous insufficiency. Effective management hinges on the immediate initiation of anticoagulation therapy, combined with strict metabolic control through dietary methionine restriction and vitamin supplementation (pyridoxine, B12, folic acid) to lower homocysteine levels and prevent recurrence. A multidisciplinary approach involving both metabolic and hematology specialists is essential to ensure comprehensive care and ongoing monitoring. This case underscores the need for heightened clinical vigilance when evaluating unexplained thromboembolic events in pediatric patients. Increasing physician awareness of homocystinuria as a possible etiology for unprovoked DVT will enable prompt and targeted interventions, thereby improving patient outcomes and preventing future complications.

Learning Points

- Deep venous thrombosis in children and adolescents, particularly when unprovoked, should prompt evaluation for underlying metabolic or genetic conditions such as homocystinuria.
- Thromboembolic events are a major cause of morbidity and mortality in patients with homocystinuria, and may occur even in the absence of overt systemic illness.
- Skeletal features such as tall stature, pectus deformity, arachnodactyly, scoliosis, and ectopia lentis should raise suspicion for connective tissue or metabolic disorders.
- Optimal outcomes require collaboration between metabolic specialists, hematologists, nutritionists, and primary care providers to manage both the thrombotic event and the underlying disorder.
- Prompt initiation of anticoagulation and metabolic therapy including dietary methionine restriction and vitamin supplementation can prevent recurrent thrombotic episodes and improve long-term prognosis.

Authors' Contributions

All authors meet the ICMJE criteria for authorship. They have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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