

A Tall and Thin Boy with a Bad Headache: A Case Report of Homocystinuria

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Case report

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Abstract

Background: Homocystinuria is a rare inborn error of metabolism, resulting in the accumulation of homocysteine and methionine in tissues, which manifests as disorders of the connective tissues and increased risk of thromboembolism. The latter is the primary cause of morbidity and mortality, and can be prevented by the prompt start of the specific therapy aimed at lowering homocysteine plasma levels.

Case presentation: A nine-year-old boy was admitted to the Emergency Department for a severe headache associated with torticollis, dysarthria, difficulty in walking and extreme irritability. His past medical history was relevant for bilateral lens ectopia and epilepsy, associated with a “marfanoid habitus”. A brain CT scan was consistent with cerebral venous thrombosis. The association between the marfanoid habitus and the thromboembolic event raised the suspicion of homocystinuria, which was eventually confirmed by the high levels of serum homocysteine, and the genetic testing. Anticoagulation therapy was started, together with pyridoxine and folate, and eventually betaine and dietary protein restriction, with a consequent satisfactory fall in homocysteine levels, along with clinical recovery.

Conclusions: This case enhances the importance of dosing serum homocysteine in every child investigated for a marfanoid habitus, given the impact of the early diagnosis and treatment in the prevention of thromboembolic events.

Introduction

The so-called “marfanoid habitus” consists of a constellation of signs common to different syndromes (Table 1). Most of these conditions depend on mutations of genes codifying for structural/connective proteins. The association between a marfanoid habitus and issues like ocular disorders (ectopia lentis, myopia), neurological symptoms (mild to moderate intellectual disability, epilepsy) and thromboembolic events should always raise the suspicion of homocystinuria and suggest the execution of a plasmatic dosage of homocysteine.

Table 1
Main syndromes associated with a marfanoid habitus and genes involved

Loeys-Dietz syndrome	TGFBR1/2
Shprintzen-Goldberg syndrome	FBN1 and other
MASS phenotype	FBN1 and other
Mitral valve prolapse syndrome	MVP1, MVP2, MVP3 and other
Congenital contractural arachnodactyly	FBN2
Weill-Marchesani syndrome	FBN1, ADAMTS10
Ectopia Lentis Syndrome	FBN1, LTBP2, ADAMTSL4
Familial thoracic aortic aneurysm and dissection syndrome	TGFBR1/2, ACTA2
FTAAD with bicuspid aortic valve	ACTA2
FTAAD with patent ductus arteriosus	MYH11
Ehlers-Danlos syndrome	COL3A1, COL1A2, PLOD1
Homocystinuria	CBS
Arterial Tortuosity Syndrome	SLC2A10
Stickler syndrome	COL2A1, COL11A1
Klinefelter's syndrome	47 XXY
Congenital bicuspid aortic valve disease with associated aortopathy	NOTCH1, KCNJ2 and other
Aortic coarctation with associated ascending aortic enlargement	NOTCH1, ERBB4, unknown
Lujan-Fryns	MED12, UPF3B (Xq25-q26)

Case Presentation

A nine-year-old boy was admitted to the Emergency Department for a severe headache associated with torticollis, dysarthria, difficulty in walking and extreme irritability. Consciousness was preserved, although the patient experienced some degree of confusion. For the last few days, he had been presenting weakness, anorexia and occasional vomiting.

In his past medical history, the boy had been investigated for Marfan syndrome, suspected for the finding of bilateral lens ectopia associated with the characteristic habitus, but the specific FBN1 gene sequencing excluded any mutation. Some months before, he had also started carbamazepine for epilepsy with occipital paroxysms.

A brain computerized tomography (CT) scan showed two hyper-dense linear images at the left occipital region consistent with venous vessels confluent in the transverse sinus (Fig. 1A) and no opacification of this sinus after administration of the contrast medium (Fig. 1B). These findings were suggestive of cerebral venous thrombosis of the transverse sinus. Laboratory tests, including blood count, acute phase reactants and coagulation, were unremarkable.

Because of the worsening level of consciousness associated with signs of cardiovascular instability, the child was admitted to the Pediatric Intensive Care Unit for advanced support and prompt initiation of anticoagulation therapy.

The association between a marfanoid habitus and a thromboembolic event raised the suspicion of homocystinuria. The extremely high levels of total serum homocysteine (250 $\mu\text{mol/L}$ with normal range 5–12 $\mu\text{mol/L}$) confirmed the diagnosis.

Pyridoxine and folate were started in order to reduce homocysteine values, without a significant benefit after two weeks, allowing to classify the patient as pyridoxine-resistant. Thus, betaine was started along with a restriction of the methionine intake, with a consequent satisfactory fall in homocysteine levels.

At the six-month follow-up, the clinical and neurological recovery was complete. Considering the evidence supporting an increase in platelet activation in patients with homocystinuria¹, after heparin withdrawal, long-term therapy with low-dose aspirin was started, in view of the greater manageability compared to oral anticoagulants.

The genetic test confirmed the diagnosis showing compound heterozygosity of the cystathionine beta-synthase gene (CBS), namely c.1224-2A > C and c.1145 + 1G > A.

Discussion And Conclusion

Homocystinuria is a rare inborn error of metabolism, whose classical form is due to the autosomal recessive inherited deficiency of the pyridoxine-dependent enzyme CBS, accountable for the conversion of homocysteine into cysteine by trans-sulfuration. Affected patients tend to display an accumulation of homocysteine and methionine in plasma, urine and tissues, which presents in the form of disorders of the connective tissues, and increased risk of thromboembolism.

The clinical spectrum is broad with variable age at onset and severity of symptoms, ranging from dramatically affected children to asymptomatic adults.^{2,3} Thromboembolism, in particular venous thrombosis, is the leading cause of morbidity and early death, although prompt recognition and treatment may considerably improve outcomes.⁴ Its occurrence in homocystinuria is estimated to be as high as a quarter of affected patients⁵, often presenting in the form of recurrent episodes, and it can represent the first manifestation of the disease. Although thrombus pathogenesis remains unclear, a direct toxic effect of homocysteine, leading to patchy endothelial desquamation and subsequent increased platelet

adhesiveness and consumption has been suggested.⁶ Superimposed precipitating factors, such as infections, dehydration and hormonal changes, could eventually interfere.

The high level of plasma homocysteine and methionine is the leading biochemical finding of CBS deficiency. The extreme elevation of plasma homocysteine (higher than 100 $\mu\text{mol/L}$) narrows the differential diagnosis between genetic causes of hyperhomocysteinemia and secondary causes (i.e. folate, B12 and B6 deficiencies, ongoing treatment with methotrexate, isoniazid, carbamazepine).

Anticoagulant therapy (mainly based on low molecular weight heparin) and antiedema medication are the cornerstones of the management of any acute venous cerebral thrombosis.

Specific treatment for homocystinuria aims to lower plasma homocysteine concentration to a safe level and should be started immediately after the diagnosis to prevent the occurrence of complications.

First-line therapy consists of pyridoxine and folate administration. Vitamin B12 should be monitored and supplemented if defective. For those who respond to this therapy, the target level of plasma homocysteine should ideally be $< 50 \mu\text{mol/L}$.

In pyridoxine unresponsive patients, who do not achieve acceptable homocysteine levels, a restriction in the dietary protein intake, along with supplementation of Met-free L-Amino Acids must be started. In these patients, betaine acts as a methyl group donor in the re-methylation of homocysteine to methionine and could, therefore, be associated, with the goal of total homocysteine plasma level below 120 $\mu\text{mol/L}$.⁷

Lifelong treatment is required, and lack of adherence to the low-protein diet is a frequent concern, particularly in adolescents and young adults.

This case enhances the importance of dosing plasma homocysteine levels in every child investigated for marfanoid habitus, given the impact of the early diagnosis and treatment in the prevention of thromboembolic events.

List Of Abbreviations

CT: computerized tomography; CBS: cystathionine beta-synthase gene

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

The patient's guardians gave their consent for the publication of this article.

Availability of data and material:

Not applicable.

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Luisa Cortellazzo Wiel and Giulia Caddeo drafted the first version of the manuscript; Chiara Zanchi and Giulia Gortani managed the patient during the acute period and edited the manuscript; Flavio Faletra performed the genetic analysis; Irene Bruno and Andrea Magnolato addressed the patient's follow-up and chronic management and revised the manuscript; Egidio Barbi edited the final version of the manuscript. All the authors approved the final version of the manuscript and take full responsibility for its contents.

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Figures

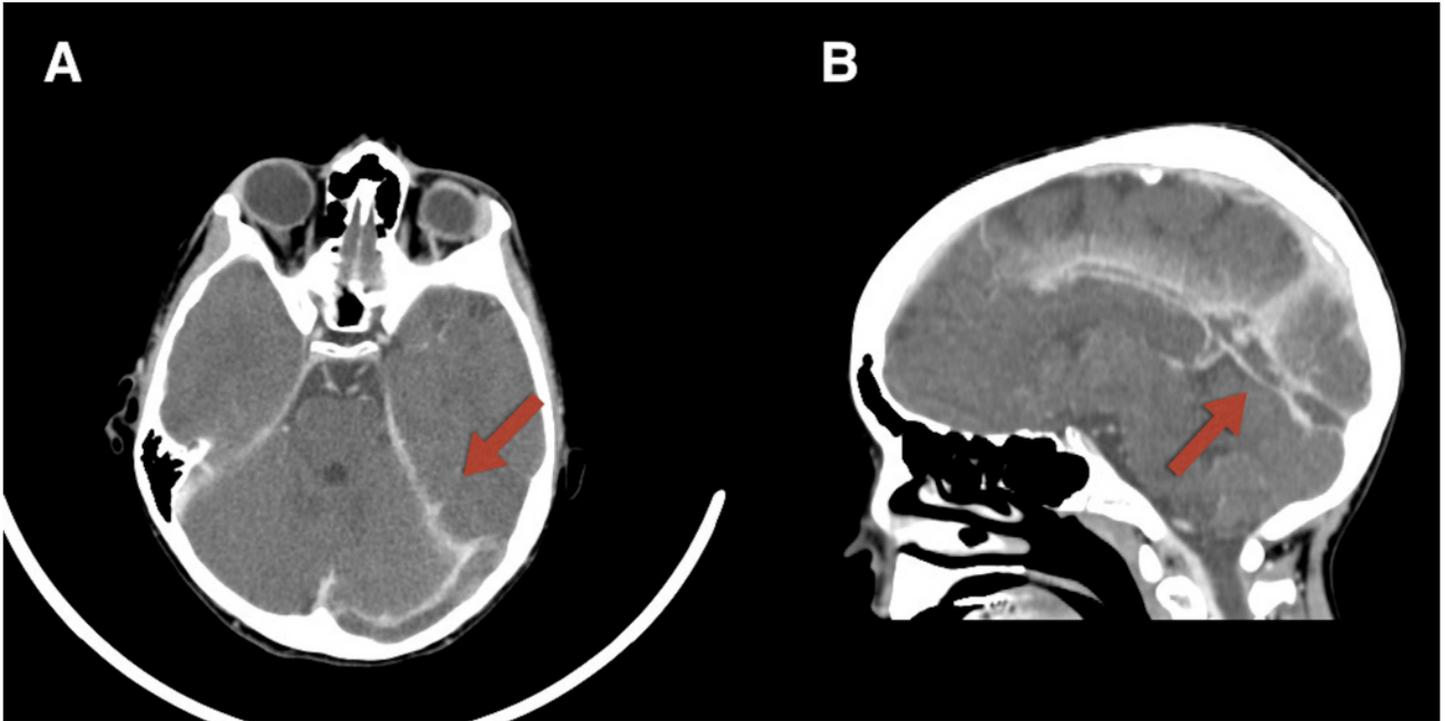


Figure 1

A: Computerized tomography axial scan showing hyperdense vascular linear images at the left occipital region consistent with venous vessels confluent in the transverse sinus. B: Computerized tomography sagittal scan showing no opacification of the transverse sinus after administration of the contrast medium, suggesting venous thrombosis at this level.

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