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CASE REPORTS

SUSPECTING CLASSICAL HOMOCYSTINURIA IN AN ADOLESCENT BORN BEFORE THE NEWBORN SCREENING PROGRAM

SUSPEITA DE HOMOCISTINÚRIA CLÁSSICA NUMA ADOLESCENTE NASCIDA ANTES DO RASTREIO NEONATAL PRECOCE

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ABSTRACT

Introduction: Classical homocystinuria (HCU) is an autosomal recessive disorder caused by a deficiency in the cystathionine beta-synthase enzyme and associated with a high probability of vascular complications. Herein is presented the case of an adolescent diagnosed with HCU during cerebral venous sinus thrombosis (CVST) study.

Case Report: A 14-year-old girl presented with thrombophilia screening tests suggestive of HCU during CVST study. After referral to an Inherited Metabolic Diseases Unit, she started supplementation with pyridoxine, folic acid, vitamin B12, betaine anhydrous, and cysteine and was advised to restrict natural proteins and methionine from diet. Genetic analysis revealed a homozygous *CBS* mutation (c.572C>T (p.T191M) with c.699C>T (p.Y233Y) polymorphism.

Discussion: In adolescents born before 2004 (year of implementation of the Portuguese newborn screening program), HCU should be considered when studying hypercoagulability syndromes, as it is a treatable condition and treatment can prevent major morbidity and mortality causes.

Keywords: homocystinuria; neonatal screening; sinus thrombosis

RESUMO

Introdução: A homocistinúria clássica (HCU) é uma doença autossómica recessiva caracterizada por um défice na enzima cistationina beta-sintase, com probabilidade de ocorrência de complicações vasculares associadas. É apresentado o caso de uma adolescente diagnosticada com HCU no decorrer do estudo etiológico de trombose dos seios venosos (TSV).

Descrição do caso: Uma adolescente de 14 anos apresentou um resultado de teste de trombofilia sugestivo de HCU durante o estudo de TSV. A doente foi orientada para uma Unidade de Doenças Hereditárias do Metabolismo, onde iniciou suplementação com piridoxina, ácido fólico, vitamina B12, betaína e cisteína e foi aconselhada a restringir proteínas naturais e metionina na dieta. O estudo genético revelou uma mutação homozigótica do gene CBS (c.572C> T (p.T191M) e o polimorfismo c.699C> T (p.Y233Y).

Discussão: Os autores salientam a importância de considerar a HCU no estudo etiológico da trombofilia, principalmente em adolescentes

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nascidos antes de 2004 (ano de inclusão da HCU no rastreio neonatal), uma vez que se trata de uma doença tratável e o tratamento é capaz de prevenir as principais causas de morbimortalidade associadas.

Palavras-chave: homocistinúria; rastreio neonatal precoce; trombose dos seios venosos

INTRODUCTION

Classical homocystinuria (HCU-OMIM 236200) is a rare autosomal recessive disorder caused by a deficiency in the cystathionine beta-synthase (CBS) enzyme.[1,2] Its real worldwide prevalence is unknown but estimated to range from 1:1,800 to 1:900,000 since the condition was included in newborn screening (NBS) programs.[1]

The wide severity spectrum explains why some patients remain asymptomatic until adolescence and adulthood. Main clinical features include eye, skeleton, nervous system, and vascular system abnormalities.[1,3,4] The latter represents the major cause of morbidity and early death in untreated or poorly controlled HCU patients, with the probability of suffering from a vascular event being as high as 30% before the age of 20 and 50% before the age of 30 years.[2,3,5] Vascular complications more commonly affect the venous territory and include deep venous thrombosis, pulmonary embolism, stroke, and cerebral venous sinus thrombosis (CVST).[1] Since it may present with non-specific clinical manifestations, CVST requires a high suspicion index.

CASE REPORT

A 14-year-old girl with irrelevant past medical and familial history, normal school development, 48.8 kg of weight (P25-50), and 166.5 cm of height (P75) presented to the Emergency Department with severe frontal pulsatile headache with six days of evolution associated with occasional vomiting, neck pain, sleepiness, loss of appetite, and earache. On day one of illness, the girl was observed at the hospital and discharged 24h later after complaint resolution. On day three, she was readmitted and diagnosed with acute otitis media and discharged with antibiotics. The patient returned to the Emergency Department at day six of illness due to complaint aggravation with neck pain over the last 12h and episodes of paresthesia and loss of muscular strength in the left arm and hypovision at left.

Clinical course and investigation

On admission, physical examination (including neurologic) revealed no alterations except for left-eye blurred vision, papillary edema on both eyes, and mild neck rigidity.

Brain computed tomography angiography was performed, revealing increased density of the left transverse, superior sagittal, and straight sinus and some cortical veins with filling defect suggesting venous sinus thrombosis, associated with white matter attenuation on both sides and discrete edema of the frontal lobe.

Coagulation profile revealed normal prothrombin time and activated partial prothrombin time and markedly elevated D-dimer test (1883 ng/mL).

Anticoagulation therapy with intravenous heparin was started and the patient continued to be monitored at the High Dependency Care Unit (HDCU).

On the fourth day at HDCU, she experienced another paresthesia episode in the left arm and face, with deviation of the labial commissure to the left, which spontaneously regressed within one minute. Severe headache persisted for seven days. Brain magnetic resonance imaging (MRI) was performed on the fifth day at HDCU, showing extensive CVST affecting the superior longitudinal, straight, and left transverse sinuses and the left internal cerebral vein, with acute leukoencephalopathy signs. It also showed involvement of the right optic nerve, prompting decision to start oral acetazolamide. The heparin dosage was titrated according to coagulation profile and warfarin was initiated on day 14 to maintain an International Normalized Ratio of 2–2.5 times normal. At discharge (day 20), the patient maintained acetazolamide and warfarin. Results of thrombophilia screening tests revealed increased total homocysteine (tHcy >500 µmol/L; normal: 4–12 µmol/L) and methionine (Met; 841 µmol/L; normal: 4–44 µmol/L) and low levels of cystine (Cys; 9 µmol/L; normal: 18–122 µmol/L). Initial serum folate levels were within the normal range and vitamin B12 levels were decreased.

Due to HCU suspicion, the patient was referred to the Inherited Metabolic Diseases (IMD) consultation.

Management and outcome

At the IMD Unit, the patient initiated supplementation with cofactors involved in Met metabolism: pyridoxine (B6) 450 mg once daily, folic acid 2.5 mg daily, and intramuscular administration of vitamin B12 2.5 mg. She also received supplementation with betaine anhydrous and cystine and was advised to start a diet with restriction of natural proteins and 500 mg daily Met intake. One week later, a decrease in tHcy (206.5 µmol/L) and Met (438 µmol/L) and an increase in Cys (13 µmol/L) were observed. Supplementation with synthetic Met-free and Cys-supplemented amino acid mix was prescribed, together with caloric supplements to prevent catabolism and minimize hyperhomocysteinemia, since the patient had lost weight

and referred starvation. Genetic analysis revealed a homozygous *CBS* mutation non-responsive to pyridoxine (c.572C>T (p.T191M), with c.699C>T (p.Y233Y) polymorphism, and pyridoxine supplementation was reduced to avoid neuropathic side effects. Subsequent analytic evaluations showed a consistent tHcy decrease (<50 µmol/L) and adequate Met and Cys control.

Ten months after diagnosis, the patient remains hypocoagulated with warfarin and is gradually reducing acetazolamide, after control MRI showing edema improvement and intact optic nerve. Cardiac evaluation showed no alterations and ophthalmologic assessment revealed improvement and no evidence of *ectopia lentis*. The girl maintains periodic evaluation and compliance to dietary and pharmacologic treatment.

DISCUSSION

To the best of our knowledge, only a few reports in the literature refer to patients diagnosed with HCU during CVST study.

CVST is a rare condition most often affecting young adults, which may be secondary to head injury, infection, pregnancy, and prothrombotic conditions, as HCU. An HCU predisposing event can be identified in about 85% of CVST patients.[6] The most common clinical manifestation is headache, identified in more than 90% of patients, which is also a very common symptom in the pediatric Emergency Department, especially in adolescent girls. Therefore, the pediatrician must be aware of red flags suggesting an underlying secondary pathology that can be treatable if timely diagnosed.[6,7] In the present case, there were other signs suggestive of CVST, such as visual impairment, loss of muscular strength, and paresthesia.[6]

HCU is a multisystemic disorder characterized by eye, skeleton, central nervous system, and vascular system involvement.[1,4,8] The most prevalent associated disorders are dislocation of the optic lenses, osteoporosis and 'marfanoid' habitus, learning difficulties, and thromboembolism predisposition.[5] Although rare, HCU is the second most common treatable aminoacidopathy, with well-described natural history and prolonged asymptomatic phase. Several studies suggest that patients benefit from early treatment, reasoning its eligibility for NBS programs.[9,10] Most NBS programs use only Met concentration measurements in dried blood spot samples through tandem mass spectrometry, which is a low-specific method that identifies several benign MAT I/III deficiency forms usually requiring no specific treatment.[11] Use of a second-tier test (tHcy) enhances the specificity and positive predictive value of HCU screening and has been adopted in several NBS programs.[9,11] In Portugal, HCU was first included in NBS program in 2004 and the second-tier test in 2014 and, until the last annual report in 2018, the condition's birth prevalence was 1:624,588. All newborns were asymptomatic, started treatment, and remained asymptomatic until now. There are no known HCU missing case reports since NBS implementation, although more prospective studies are required to confirm that.[11]

HCU can present two phenotypes, defined according to pyridoxine responsiveness. In Portugal, the most prevalent CBS gene mutation is p.T191M, characterized for being B6-non-responsive.[11,12] The main treatment goal is to prevent vascular events by reducing tHcy to levels below 50 µmol/L, and in B6-nonresponsive homocystinuria compliance to dietary treatment is even more important and should be lifelong.[1]

The present patient was born shortly before the inclusion of HCU in Portuguese NBS program[13] and remained asymptomatic until the referred episode. This case highlights the importance of considering HCU diagnosis in adolescents and adults with hypercoagulability syndrome born before the inclusion of HCU in Portuguese NBS, since it is a treatable condition and early identification prevents morbidity and mortality.

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