Clinical Case Report

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Cerebral venous sinus thrombosis due to hyperhomocysteinemia with cystathionine-β-synthase (CBS) gene mutation

A case report

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Abstract

Rationale: Risk factors of cerebral venous sinus thrombosis (CVST) are usually divided into acquired risks (e.g., trauma and pregnancy) and genetic risks (inherited thrombophilia). It is essential but not easy to identify the exact one for each patient.

Patient concerns: A 14-year-old male patient was admitted in our hospital because of progressively exacerbated severe headache and vomiting for 3 days, accompanied by transient weakness once in his right leg.

Diagnosis: CVST due to hyperhomocysteinemia with cystathionine-β-synthase (CBS) gene mutation.

Interventions: Persistent oral anticoagulant therapy.

Outcomes: Follow-ups at 4 months and 1 year showed that the patient's symptoms alleviated and did not recur, accompanied with improved MRV image; however, the cranial MRV image did not display as a completely normal one.

Lessons: We recommend that in case of thrombophilic state, serum homocysteine (Hcy), folic acid, and vitamin B12 levels should be routinely screened; when serum Hcy level is extremely high, congenital diseases caused by gene mutations should be considered. We firstly discovered a new mutation of CBS c.949A>G which had not been reported before.

Abbreviations: ANA = antinuclear antibody, ANCA = antineutrophil cytoplasmic antibody, CBS = cystathionine-β-synthase, CSF = cerebrospinal fluid, CVST = cerebral venous sinus thrombosis, DVT = deep vein thrombosis, ESR = erythrocyte sedimentation rate, Hcy = homocysteine, HHcy = hyperhomocysteinemia, HIV = human immunodeficiency virus, LA = lupus anticoagulant, LMWH = low-molecular-weight heparin, MTHFR = methylenetetrahydrofolate reductase, RF = rheumatoid factor, TPPA = treponema pallidum particle agglutination.

Keywords: case report, cerebral venous sinus thrombosis (CVST), cystathionine-β-synthase (CBS), hyperhomocysteinemia, lens ectopia

1. Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke, usually affecting young individuals. The diagnosis of this case was not difficult; however, its underlying etiology was worth pondering. Predisposing causes of CVST are multiple. The risk factors for venous thrombosis in general are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood. Risk factors are usually divided into acquired risks (e.g., surgery, trauma, pregnancy, puerperium, antiphospholipid syndrome, cancer, exogenous hormones) and genetic risks (inherited thrombophilia).[1] The guideline for diagnosis and management of CVST published in 2011 summarized well about predisposing conditions for CVST and principles in favor of a cause-and-effect relationship. Hyperhomocysteinemia (HHcy) is a risk factor for deep vein thrombosis (DVT) and stroke but has not been clearly associated with an increased risk of CVST,[1] despite that a meta-analysis also revealed that homocysteine (Hcy) is an independent risk factor for CVST.[2]

Timeline (See Supplemental Figure, http://links.lww.com/MD/C813).

2. Presentation of case

2.1. Patient information

A 14-year-old male patient was admitted in our hospital because of progressively exacerbated severe headache and vomiting for 3 days, accompanied by transient weakness once in his right leg. No other new symptoms emerged, such as diplopia, hearing loss,

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A 14-year-old boy with sudden headache and a history of lens ectopia.

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dysarthria, dysphagia, hemiplegia, or walking lability. The cranial computed tomography in emergency room showed high density stripes in left transverse sinus and straight sinus which indicated CVST. He had kept healthy except for a history of recurrent lens dislocation which had not been cured by lens implantation yet. His intake of vegetables and fruits was insufficient. His parents had no consanguineous relationship.

2.2. Physical examinations

During physical examinations, we found that his right pupil was irregularly shaped because of a history of recurrent lens dislocation. He had a relatively taller and slimmer figure than his peers, with longer fingers and higher arched foot, showing a mildly Marfan-like phenotype. Mental state examination revealed that his intelligence and athletic ability had just reached the average level.

2.3. Laboratory data

Lumbar puncture was performed the next day after admission. Cerebrospinal fluid (CSF) pressure was 1.56 kPa. Microbiological and virological tests showed no abnormality. CSF nucleated cell count was 3×10^6/L (normal level, 0–8×10^6/L). Red cell count was 23×10^6/L (normal level, <0/L). Total protein level was 1146 mg/L (normal level, 150–450 mg/L), while albumin level was 750 mg/L (normal level, 0–350 mg/L). Glucose, electrolytes, and LDH were in normal range.

Complete blood count, biochemical test, TPPA, HIV, thyroid function, HbA1C, and ESR were normal. ANA, RF, ANCA, LA, antithrombin, and protein S were in normal range. His D-D dimer was 3.49 ug/mL FEU (normal level, <0.5 ug/mL FEU). Protein C level was 65% (normal level, 70%–142%) and serum Hcy level was 102.2 umol/L (normal level, 6–14 umol/L). His folic acid level was less than 1.00 ng/mL (normal level, >2.33 ng/mL), and his vitaminB12 level was less than 50 pg/mL (normal level, 180–914 pg/mL). The main abnormal serum markers are summarized in Table 1.

2.4. Imaging data

Chest X-ray and ECG were normal. Ultrasound examinations showed no disorders in his heart, liver, gallbladder, spleen, pancreas, kidneys, ureters, and bladder. And peripheral vascular ultrasound displayed a smooth intima without atherosclerosis. MRV (Fig. 1) strongly suggested CVST. Besides, scattered long T2 signals were distributed in left caudate nucleus, putamen, thalamus, radiate corona, and semiovale center.

Cranial digital subtraction angiography was performed further confirming the diagnosis of CVST. And there existed no enough signs for plaques and stenosis in arteries.

2.5. Gene detection data

Gene detection of methylenetetrahydrofolate reductase (MTHFR) and cystathionine-β-synthase (CBS) confirmed a compound heterozygous mutation of CBS in this patient. And the 2 different heterozygous mutations in the pair of chromosome21 were confirmed by Sanger Sequencing from his parents accordingly, detailed in Table 2 and Figure 2. Notably, this patient's MTHFR C677 gene revealed a type of CC, which indicated low risk of HHcy in general.

2.6. Diagnosis, treatment, and follow-up

Considering the diagnosis of probable CVST, we initiated anticoagulation treatment with LMWH 6250U subcutaneously twice a day immediately after the patient was hospitalized. His symptoms caused by cranial hypertension improved gradually and no more other new symptom appeared.

We kept wondering the underlying reason of CVST in this patient because there was no obvious triggers before the symptoms occurred, such as intense exercise or diaphoresis. A significantly high Hcy level in serum drew our attention, thus further examinations for risk factors of HHcy were performed. Then we found this patient was severely lack of folic acid and vitaminB12, which was probably caused by his diet short of vegetables and fruits. However, we doubted whether it was the only explanation for HHcy. After oral vitamins supplement for about 2 months, his serum folic acid and vitaminB12 reverted to normal range; but HHcy still existed (Table 1). It indirectly suggested there might be some other underlying reasons.

Therefore, we screened all the suspicious gene mutations for HHcy and found a compound heterozygous mutation in his CBS gene, which caused insufficiency of CBS. Finally, this patient's HHcy was proved to be caused by congenital CBS. High serum Hcy level induced thrombophilic state. In this patient, thrombophilic state affected both arterial and venous systems, indicated by both CVST and ischemic lesions in the brain. Because of the persistent CBS deficiency, anticoagulation, vitamins supplement, and dietary restriction might be lifelong.

At 4 months' and near 1 year's follow-up, cranial MRV image showed that his CVST improved but still did not display as a completely normal one. Thus anticoagulation is still going on.

3. Discussion

102.2 umol/L of serum Hcy level was significantly high in such a young patient. Thus, we kept trying to figure out the underlying reasons of the extremely high serum Hcy level in this case. Theoretically, poor function of MTHFR or CBS, or deficiency of folic acid, vitaminB6 or vitaminB12, will lead to HHcy. We reviewed catabolism of Hcy. Hcy has been proved to be an independent risk factor for cerebrovascular events.[3]

Table 1

Several important serum markers alterations.

Serum	Results (onset)	Results (2 mo later)	Normal range
D-D dimer	3.49 ug/mL FEU		<0.5 ug/mL FEU
Protein C	65%		70%–142%
Homocysteine	102.2 umol/L	61.0 umol/L	6–14 umol/L
Folic acid	< 1.00 ng/mL	>24.80 ng/mL	>2.33 ng/mL
VitaminB12	< 50 pg/mL	785 pg/mL	180–914 pg/mL

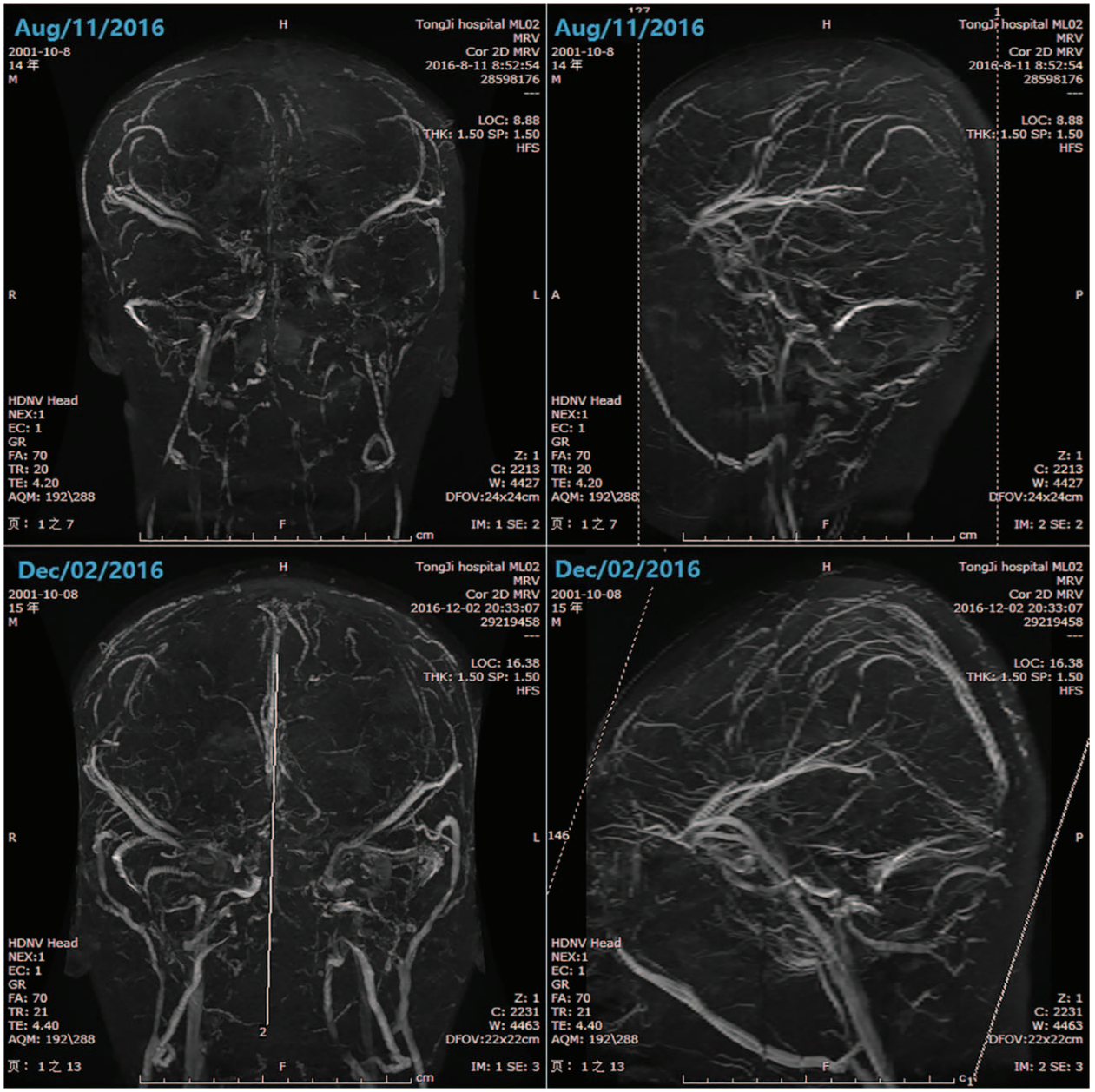

Figure 1. MRV images at the time of onset and about 4 months later. The straight sinus and superior sagittal sinus became recognized, 4 months after anticoagulation, and oral supplement of folic acid and VitaminB12. The images seemed not recovered to common ones. It is not clear that how the transverse sinuses distribute and whether there exist malformations of the transverse ones.

Mechanisms underlying thrombosis caused by HHcy are still under investigation, probably including its toxicity on endothelial cells, promotion in smooth muscle cell proliferation and intimal thickening, decrease in generation of nitric oxide and prostacyclin, increase in platelet adhesion and activation of Factor V.[4] In this case, with a compound heterozygous mutation in the patient's CBS gene, thrombotic predisposition might always exist. Consequently, anticoagulation therapy is essential; and

Table 2

Gene detections of the patient and his parents.

Gene detection (the patient)	Gene	Exon	Genome coordinates	Nucleotide change	AA change	rs-ID	Hom/Hct/Hem	References
	CBS	Exon6	chr21:44485731	c.526G>A	p.E176K	–	Hct	(5, 7)
	CBS	Exon10	chr21:44483068	c.949A>G	p.R317G	–	Hct	–
Gene detection (parents)		Mother of the patient				c.526G>A		
		Father of the patient				c.949A>G		

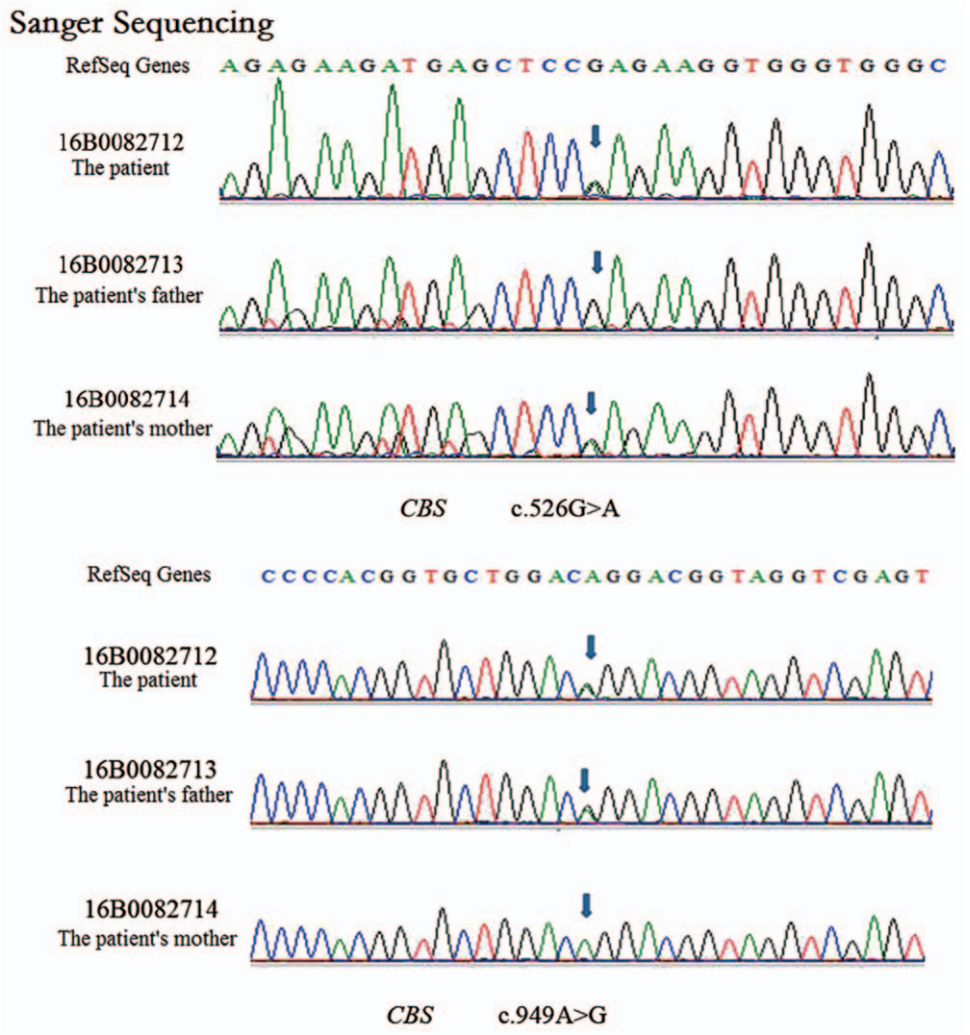

Figure 2. Sanger sequencing of the patient and his parents.

vitamins therapy for increasing Hcy catabolism via MTHFR pathway is subsidiary.

So far, there are few researches about the relationship of degree of HHcy and gene mutations. Recently, Hainsworth et al[5] defined mild-moderate HHcy by Hcy concentrations in the range of 10 to 100 μM, and severe HHcy as >100 μM, by which the latter situation may suggest CBS or MTHFR gene mutations. As lacking enough evidence, application of this definition directly in clinical practice is restricted. This case also provides us a hint that more researches about associations between increasing degree of serum Hcy level and gene mutations are needed to be performed.

After 2 months of sufficient vitamin therapy, the patient's serum Hcy level was still as high as 61.0 umol/L. It might be a characteristic of HHcy caused by gene mutations. As genetic screen costs a lot, the clinical decision-making problem should be considered. Perhaps this could be 1 solution: initiate vitamins therapy once HHcy is detected; retest serum Hcy level after abundant supplement; if obvious HHcy still exists, genetic screen should be considered.

Recurrent lens dislocation and progressive myopia, a Marfan-like phenotype, osteoporosis, mental retardation, and cerebrovascular and cardiovascular thrombosis are all the common manifestations of homocystinuria. In this case, recurrent lens ectopia, the Marfan-like phenotype and CVST were all observed.[6] Actually, recurrent lens ectopia is the most special and recognizable clinical sign. Retinal and lens proteins are liable to be attacked by homocysteinylation and oxidative stress under the influence of HHcy.[7] CVST combined with lens ectopia highly suggests homocystinuria and serum Hcy level test is recommended. Both MTHFR deficiency and CBS deficiency are reported to result in HHcy and lens luxations.[6,8] As to CBS gene mutations, c.526G>A was reported twice.[9,10] In this case we discovered a new mutation of CBS c.949A>G which had not been reported before.

4. Patient Consent Statement

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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