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High prevalence of cerebral venous sinus thrombosis in seven Chinese patients with cystathionine β-synthase deficiency

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Homocystinuria due to cystathionin-β-synthase (CBS) deficiency is a rare genetic disease that most often diagnosed in childhood and can cause damage to the multiple systems.[1,2] The inherited mode of *CBS* gene deficiency is usually autosomal recessive inheritance. More than 160 mutations have been identified in *CBS* genes so far (http://cbs.lf1.cuni.cz/index.php), one of the most common mutations is c.833T>C point mutation, and then followed by c.572C>T, c.919G>A, and c.1006C>T point mutations. In 2018, Li *et al*[2] found eight brand new mutation sites in patients with CBS deficiency in China, pointing out that the *CBS* mutant site spectrum of Chinese people is significantly different from that of other races. In this paper, we further conducted a retrospective analysis of seven homocystinuric patients of *CBS* deficiency admitted to our institute.

Data of seven patients with *CBS* deficiency from five Chinese families were collected from July 2016 to July 2019. Patients 1 and 2 are siblings, and patients 3 and 4 are siblings, while the other three patients (patients 5–7) are unrelated. Five patients (1, 3, 5–7) visited our hospital because of vascular events. Patients 2 and 4 were detected by family screening. The DNA samples of the proband were sequenced by the second-generation sequencing using the targeted capture strategy. The pathogenicity of the suspected mutation sites were preliminarily analyzed and identified. Then Sanger sequencing was used to verify these loci. Finally, family screening was carried out with Sanger sequencing in all their patients and affected siblings.

All patients were treated with three B vitamins (including mecobalamine: 0.5–1.5 mg/day, Folic acid tablets: 5–15 mg/day, Vitamin B6: 30–60 mg/day) once severe hyperhomocysteinemia (HHCY) is diagnosed. If homocystinuria with *CBS* deficiency was determined and plasma homocysteine (Hcy) did not get back to normal, pyridoxine responsiveness would be further determined by measuring plasma Hcy after oral administration of B6 (300–600 mg/day) for at least 2 weeks. Pyridoxine responders were regarded as those with a decrease of plasma Hcy level to below 50 μmol/L; patients with no or little decrease were regarded as non-responsive. For pyridoxine non-responsive patients, betaine supplementation (3–6 g/day) and low-methionine diet was advised. All patients were followed up regularly after discharge, and the median time of follow-up was 16 months (6–36 months). Follow-up neuroimaging (including either gadolinium enhanced-magnetic resonance venography or computed tomography venography) was performed in five patients with cerebral venous sinus thrombosis (CVST).

As shown in Table 1, five patients (1, 3, 5–7) were revealed with multiple thrombus in the intracranial venous sinus, with secondary epilepsy in three patients (1, 3, and 6). Two patients (5 and 7) had no symptoms typical for *CBS* deficiency other than vascular disorders at the time of diagnosis, while other five patients (1–4, 6) had multi-system damage, with eye disorders to be the common presentation. All seven patients had significantly increased plasma total Hcy (48–242 μmol/L) and decreased plasma levels of Vitamin B12 (below 50 pg/mL) and folic acid (below 1 ng/mL). The plasma methionine was significantly increased in seven patients (127–438 μmol/L) except one unavailable data in patient 5. Urine organic acid screening of all patients showed no abnormality. The second-generation sequencing results revealed a considerable genetic heterogeneity and identified eight mutations in *CBS* gene in seven Chinese patients with *CBS* deficiency [Table 1]. As in other populations, the most common *CBS*

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Table 1: Clinical characteristics and genetic mutations of seven homocystinuric patients with cystathionin-β-synthase deficiency.

Patient No.	Sex	Age (years)	Vascular system	Other clinical characteristics	Hcy (μmol/L)	Met (μmol/L)	Vitamin B12 (pg/mL)	Folic acid (ng/mL)	MTHFR (C677T)	Nucleotide change	Hcy after 1 month (μmol/L)	Hcy after 6 months (μmol/L)	Responsiveness
1	Female	26	CVST	Myopia	221	323	<50	<1	CC	c.[526G>A]+ [919A>G]	143	134	–
2	Male	32	Not found	Biocular ectopia lentis	189	357	<50	<1	CC	c.[526G>A+[919A>G]	125	107	–
3	Female	14	CVST	Intellectual disability, psychological and behavioral abnormalities, congenital binocular ectopia lentis, exotropia, myopia, Long fingers, osteoporosis, hyperpigmentation, hyperkeratosis	149	438	<50	<1	CC	c.[551T>C]+ [949A>G]	86	32	+
4	Female	16	Not found	Ataxia, irascibility, intellectual disability, Psychological and behavioral abnormalities, congenital binocular ectopia lentis, myopia, long fingers, osteoporosis, kyphoscoliosis	156	415	<50	<1	CC	c.[551T>C]+ [949A>G]	98	41	+
5	Male	22	CVST	Not found	48	NA	<50	<1	CC	c.[833T>C]+[833T>C]	23	21	+
6	Female	16	CVST, AT	Not found	170	350	<50	<1	CT	c.[1006 C>T]+[407 T>C]	159	156	–
7	Male	20	CVST	Not found	77	175	<50	<1	CC	c.[833 T>C]+[572 C>T]	13	11	+

The normal ranges of plasma Hcy, Met, vitamin B12, and folic acid were 0 to 15 μmol/L, 8 to 50 μmol/L, 180 to 900 pg/mL, >2.35 ng/mL, respectively. Pyridoxine responsiveness was determined by measuring plasma Hcy after oral administration of B6 (300–600 mg/day) for at least 2 weeks. Hcy: Homocysteine; Met: Methionine; MTHFR: Methylenetetrahydrofolate reductase; CVST: Cerebral venous sinus thrombosis; AT: Atrial thrombosis; +: Responsive, plasma Hcy level decreased below 50 μmol/L; –: Non-responsive, Hcy levels almost unchanged, remain above 50 μmol/L.

mutation c.833T>C (p.I278T) was present in two patients (5 and 7) and homozygous mutations of c.833T>C was present in patient 5. The *CBS* gene mutations were compound heterozygous mutations in six patients, with three mutations (c.949A>G, c.407T>C, and c.551T>C) of them only reported in Chinese populations. The family analysis showed that their parents were all carriers of single mutation.

After nearly 1 month of treatment with oral mecobalamin, vitamin B6 and folic acid tablets, the plasma Hcy of two patients (patients 5 and 7) decreased close to normal, while the plasma Hcy of other five patients remained higher than 50 μmol/L. After increasing the dose of vitamin B6 to 300 to 600 mg/day, the plasma Hcy of two patients (3 and 4) decreased significantly to below 50 μmol/L in about 2 weeks, suggesting responsive to vitamin B6 treatment. However, the plasma Hcy levels of three patients (1, 2, and 6) were still above 100 μmol/L, which did not go down obviously after about 6 months of betaine supplementation and low-methionine diet. For five patients with CVST, follow-up neuroimaging showed venous sinus thrombosis improved greatly, though did not return to completely normal after several months of anticoagulant treatment. A median time of follow-up for 16 months showed that none of these venous sinus thrombosis relapsed. However, patient 4 died of hemorrhagic stroke 2 years later, which may be related to her poor adherence to medication and abnormality in psychological state.

Previous reports have shown that the prevalence of thrombotic complications in patients with *CBS* deficiency varies from 23% to 42%, and it increases with age.[3] Our data revealed that CVST was the most prominent clinical feature for five homocystinuric patients, which reminded us to pay more attention to *CBS* deficiency in routine thrombophilia screening in Chinese population. *CBS* deficiency can present as multi-system damage, including mental retardation, lens dislocation, osteoporosis, marfanoid syndrome, and thrombotic vascular disease.[2] Generally, the first symptom of most patients with *CBS* deficiency is congenital lens dislocation, but it is easily overlooked due to its variety of clinical manifestations and lack of specificity. In this group, eye disorders was the initial presentation for five patients in their childhood. Unfortunately, none of them were timely diagnosed. Our data revealed that both patients (5 and 7) with CVST to be the sole clinical feature had the mutation c.833T>C and were pyridoxine responsive, consistent with previous reports that *CBS* deficient patients with vascular events to be sole clinical complication tend to manifests at greater ages, have a high ratio of pyridoxine responsiveness/non-responsiveness, and the mutation c.833T>C is often present,[3] in contrast with patients with multi-system damage typical for *CBS* deficiency. Once *CBS* deficiency is diagnosed, B vitamins should be used for treatment as soon as possible, so as to reduce significantly the cardiovascular risk.[3] Studies have shown that about half of *CBS* deficient patients were responsive to treatment with pyridoxal phosphate,[3] and the treatment effect of pyridoxal phosphate is closely related to the mutation site of *CBS*. For example, mutation sites such as c.833T>C and c.1006 C>T are usually responsive for pyridoxal phosphate treatment. However, mutation sites such as c.919G>A usually do not respond to the treatment of pyridoxal phosphate, so it is necessary to use betaine and/or follow low-methionine diet. In this study, the plasma Hcy levels of three patients (1, 2, and 6) were still above 50 μmol/L in spite of the supplement of vitamins B and the commencement of low-methionine diet, suggesting resistance to

pyridoxal phosphate treatment. In addition, we identified three mutations (c.949A>G, c.407 T>C, and c.551T>C) that were only reported in Chinese populations,[2] revealing that two mutations sites (c.949A>G and c.551T>C) seems to be pyridoxal responsive, while c.407 T>C mutation were pyridoxal non-responsive. On the other hand, timely and effective Hcy-lowering therapy for severe HHCY can significantly could reduce the vascular risk in patients with *CBS* deficiency in those of pyridoxal non-responsiveness, despite the fact that the post-treatment Hcy levels were still significantly higher than the normal range.[3]

In general, this study highlights that plasma Hcy should be screened for unexplained thromboembolic disease, especially in patients with mental retardation, scoliosis, lens dislocation, and skin pigmentation. For *CBS* deficiency, lifelong medication of B vitamins is needed, for pyridoxine non-responsiveness, betaine together with dietary restriction is recommended.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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