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

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Homocystinuria due to cystathionine-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.3 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 was 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 mecobalamin: 0.5–1.5 mg/day, Folic acid tablets: 5–15 mg/day, Vitamin B6: 30–60 mg/day) once severe hyper-homocysteinemia (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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Pyridoxine responsiveness was determined by measuring plasma Hcy after oral administration of B6 (300 mg/day) for at least 2 weeks. Hcy: Non-responsive, Hcy levels almost unchanged, remain above 50 μmol/L. After increasing the dose of vitamin B6 to 300 mg/day, the plasma Hcy of two patients (3 and 4) were still above 100 μmol/L in about 6 months of betaine supplementation. After nearly 1 month of treatment with oral mecobalamin, the plasma Hcy of two patients (5 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. 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. 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, 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. Studies have shown that about half of CBS deficient patients were responsive to treatment with pyridoxal phosphate, 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

| 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 (3877T>C) | Nucleotide change | Hcy after 1 month (μmol/L) | Hcy after 6 months (μmol/L) | Responsiveness |
|------------|-----|-------------|-----------------|-------------------------------|--------------|-------------|---------------------|-------------------|-----------------|----------------|---------------------|----------------------|---------------|
| 1          | Female | 26         | CVST            | Myopia                        | 221          | 323         | <50                 | <50               | C                  | [526G>A] [919A>G] | 143               | 134               | –               |
| 2          | Male  | 32         | Not found       | Biocural ectopia lenti         | 189          | 357         | <50                 | <50               | C                  | [526G>A] [919A>G] | 125               | 107               | –               |
| 3          | Female | 14         | CVST            | Intellectual disability,       | 149          | 438         | <50                 | <50               | C                  | [551T>C] [949A>G] | 86                | 32                | +               |
| 4          | Female | 16         | Not found       | Ataxia, irasibility,          | 156          | 415         | <50                 | <50               | C                  | [551T>C] [949A>G] | 98                | 41                | +               |
| 5          | Male   | 22         | CVST            | Not found                     | 48           | NA          | <50                 | <50               | C                  | [833T>C] [1833T>C] | 23                | 21                | +               |
| 6          | Female | 16         | CVST, AT        | Not found                     | 170          | 350         | <50                 | <1               | C                  | [1006C>T] [407T>C] | 159               | 156               | –               |
| 7          | Male   | 20         | Not found       | Not found                     | 77           | 175         | <50                 | <50               | C                  | [833T>C] [572C>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.
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 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.

References

1. An H, Fan CQ, Duan JG, Ren Y, Dong K, Zhang Q, et al. Severe hyperhomocysteinemia with two novel mutations of c.154T>C and c.457G>A in cystathionine beta-synthase gene. Chin Med J 2018;131:2368–2370. doi: 10.4103/0366-6999.241801.
2. Li DX, Li XY, Dong H, Liu YP, Ding Y, Song JQ, et al. Eight novel mutations of CBS gene in nine Chinese patients with classical homocystinuria. World J Pediatr 2018;14:197–203. doi: 10.1007/s12519-018-0135-9.
3. Yap S, Boers GH, Wilcken B, Wilcken DE, Brenton DP, Lee PJ, et al. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: a multicenter observational study. Arterioscler Thromb Vasc Biol 2001;21:2080–2085. doi: 10.1161/hq1201.100225.

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