Methylmalonic Aciduria may be an Innegligible Etiology of Cerebral Venous Sinus Thrombosis

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Abstract
This paper analyzed a case of Methylmalonic Aciduria (MMA) in combination with Patent Foramen Ovale (PFO), presenting as cerebral venous sinus thrombosis (CVST) and cerebral venous infarctions coexisted with fresh arterial infarctions located at bilateral cerebella. From the aspects including clinical manifestations, physical examination, final diagnosis confirmation, comprehensive therapy, and clinical outcomes, this paper will be a very useful reference to clinicians.

Keywords
Cerebral venous sinus thrombosis, Methylmalonic aciduria, Patent foramen ovale, Venous infarction, Arterial infarction, Psychiatric disorders

Introduction
Cerebral venous sinus thrombosis (CVST) is easily misdiagnosed, thus resulting in treatment delay and subsequent poor outcomes, regarding its variable and non-specific clinical manifestations [1]. Recently, some special or complex causes of CVST are emerging, which may display more intricate clinical presentations and require customized management [2,3], although the mainstay treatment still focuses on anticoagulation [4].

Case Report
A 22-year-old female was admitted to our institution with the complaints of left arm and bilateral legs weakness for 14 days, dizziness and progressing headache for 7 days, and epileptic seizures for 3 days. She was once diagnosed as schizophrenia and had taken haloperidol tablet (4 mg, twice a day) for 4 years. No dehydration status occurred prior to this onset. Physical examination revealed hemiplegia and bilateral Babinski sign, NIHSS=7, mRS=3. Intracranial pressure (ICP) was 250 mmH₂O. Peripheral blood tests showed anemia (hemoglobin 89 g/L, [normal reference range: 110-160 g/L]), and abnormally elevated homocysteine (122 µmol/L, [normal reference range: 0-20 µmol/L]) and D-dimer (1.25 mg/L, [normal reference range: 0.01-0.5 mg/L]), while with normal levels of folic acid, vitamin B₁₂, Protein C (70%), antithrombin-III (61%), Protein S (101%) as well as negative antiphospholipid antibodies.

Magnetic resonance imaging (MRI) and contrast MR-venography (MRV) confirmed: the presence of thrombi in multiple cerebral venous sinuses; and distribution of newly infarctions at left frontal, right parietal lobes and bilateral cerebella. Computed tomography angiography (CTA) revealed the involvement of posterior inferior cerebellar arteries (PICA); right internal jugular vein was absent on computed tomography.
Case Report  Ran Meng

Elevated urinary methylmalonic acid (MMA, 58.33 mmol, [normal reference range: 0.2-3.6 mmol]) and blood propionyl carnitine (7.95 µmol/L, [normal reference range: 0.43-4.12 µmol/L]), the ratio of propionyl carnitine/acetyl carnitine being 0.31, blood ammonia (73 µmol/L, [normal reference range: 0-100 µmol/L]) and other details were displayed in our supplementary file. Furthermore, the outcomes of MMACHC gene sequencing showed mutations at sites of c. 482G>A and c. 609 G>A, which are two of the most frequent mutations reported amongst Chinese patients and accounted for approximately 48% and 7% of disease alleles, respectively [5].

This patient then received etiological treatments (Betaine, L-carnitine, and methylcobalamin) imaging of neck (Figure 1). Vascular ultrasound identified that the deep venous thrombi (DVT) were distributed in the right jugular vein and the deep veins of bilateral legs. Tran’s esophageal ultrasound and contrast-echocardiogram sonography confirmed the existence of patent foramen ovale (PFO, diameter, 1.2 mm). No abnormalities were found in electromyography (EMG) examination.

The scenario of CVST was not well controlled with standard anticoagulation (low molecular heparin bridged to warfarin, INR is 2.5), and the abnormally elevated homocysteine could not be explained as CVST with PFO. Thereafter, the organic acids and blood ammonia were detected, and the findings were listed as follows: abnormally elevated urinary methylmalonic acid (MMA, 58.33 mmol, [normal reference range: 0.2-3.6 mmol]) and blood propionyl carnitine (7.95 µmol/L, [normal reference range: 0.43-4.12 µmol/L]), the ratio of propionyl carnitine/acetyl carnitine being 0.31, blood ammonia (73 µmol/L, [normal reference range: 0-100 µmol/L]) and other details were displayed in our supplementary file. Furthermore, the outcomes of MMACHC gene sequencing showed mutations at sites of c. 482G>A and c. 609 G>A, which are two of the most frequent mutations reported amongst Chinese patients and accounted for approximately 48% and 7% of disease alleles, respectively [5].

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and homocysteine inhibitors accompanied with standard anticoagulation. Within 2 weeks of inpatient follow-up after the intervention: the levels of homocysteine, MMA and ICP were decreased to 34.8 µmol/L, 12.6 mmol and 150 mmH2O, respectively; NIHSS=0, mRS=0. During 9 months of outpatient follow-up: no dizziness, headache, mental disorders and epilepsy recurrence were complained; no newly formed brain lesions of either venous or arterial infarctions were identified on MRI/diffusion weighted imaging (DWI) images. Recanalizations of CVST and DVT were confirmed by MRV and vascular ultrasound.

Discussion

Cerebral venous infarction subsidiary to CVST caused by MMA in adults is uncommon. MMA, a type of organic acid metabolic disorder, often results in multi-system dysfunctions. Based on the age at initial onset, MMA can be divided into early-onset (in neonatal) and late-onset (in childhood or adult) subtypes, the latter of which displays a significantly higher incidence of neurological and psychological symptoms [6,7]. MMA can also be classified as idiopathic and acquired ones; the former is caused by abnormal metabolism of organic acid and/or vitamin B12, while the latter is likely attributed to malabsorption and/or disorders of transport [6]. In terms of the efficacy of vitamin B12 treatment, MMA consists of vitamin B12 positive and negative subtypes [8]. Obviously, taken the data above together, our case belongs to the idiopathic late-onset with hyperhomocysteinemia and vitamin B12 positive MMA subtype.

In this case, similar to the infarcted brain lesions distributed at left frontal and right parietal lobes, bilateral cerebellar infarctions were likely to be associated with MMA-related CVST. The pathogenesis of cerebral infarctions in MMA is currently understood to be induced by the disruption of mitochondrial aerobic glucose oxidation as a result of excessive accumulation of organic acids, leading to a decrease in cellular energy generation and subsequent excitotoxicity [9]. Nevertheless, it cannot rule out another possibility, that is, cerebellar infarctions may be derived from PFO related arterial emboli [10], considering the fact that blood flow of PICA was interrupted in the right and absent in the left on CTA, even though the infarctions did not seem to be located within the typical PICA territory.

It was postulated that both CVST and DVT were associated with hyperhomocysteinemia of MMA [6]. Symptomatic epilepsy was likely caused by cortical venous infarctions secondary to CVST, while psychiatric symptoms might be a feature of MMA. It should be noted that the late-onset subtype of MMA more frequently presents with psychiatric symptoms when compared with the early-onset one. Before the organic acid screening, the psychiatric disorders and CVST of this case were once regarded as two independent issues. After confirmation of the diagnosis of MMA, the psychiatric disorders were well explained. It has been well known that hyperammonemia is observed in a large percentage of patients with MMA. The ammonia-induced cellular redox changes on mitochondrial function and alterations of the glycine/glutamate cycle might contribute to MMA-induced excitability [11]. However, the blood ammonia level of this patient was within normal range.

Conclusion

This case demonstrates that screening for MMA is necessary, particularly when a young patient with CVST presenting severe hyperhomocysteinemia and psychiatric disorders. Furthermore, standard anticoagulation therapy is not adequate for MMA-related CVST, and strategies aiming at etiological levels are required on this condition.

Conflict of Interest

All authors report no disclosures or conflicts of interest.

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Case Report

Ran Meng

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522 Neuropsychiatry (London) (2018) 8(2)