Methylmalonic aciduria (MMA) is an autosomal recessive disorder of cobalamin (cbl) metabolism. Cobalamin C (cblC) disease is the most common type of MMA and is characteristically concurrent with homocystinemia (HCY) due to impaired synthesis of two active forms of cbl, namely adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). The estimated worldwide incidence of MMA ranges between 1:48,000 and 1:250,000. Mutations of the MMA and HCY type C protein (MMACHC) gene are responsible for cblC disease and were first identified by Lerner-Ellis et al. in 2006. By the year 2016, more than 82 different MMACHC gene mutations have been reported (http://www.hgmd.cf.ac.uk/ac/index.php). Among these mutations, c.609G>A (p.W203X) was reported to be the most frequent cblC mutation in Chinese patients.

Cobalamin C disease could be divided into early- and late-onset types. Less than 20% of cblC cases that have been reported in literature were late onset, and none presented with manic-depressive psychosis at onset. Moreover, sibling cases of cblC disease through autosomal recessive inheritance were rare. Herein, we reported two sibling cases of late-onset cblC disease that presented with manic-depressive psychosis as the first symptom.

On May 25, 2015, two young adult men siblings were seen in our neurological unit simultaneously due to bipolar disorder. The elder brother was 33 years old and had experienced insomnia, exaggerated expression, euphoria, increased irritability, and blurred vision for 18 months. He was treated for manic psychosis at his local hospital with risperidone (2.5 mg/d) and valproate (0.6 g/d). His symptoms had gradually improved. Two months previously, he began to have thoughts of worthlessness and decreased appetite and exhibited reduced vocal expression and withdrawal from social situations and activities. Meanwhile, he walked slowly and could no longer correctly button his coat or wear his shirt. He was further treated for manic-depressive psychosis in his local hospital with escitalopram oxalate tablets (10 mg once per day), sodium valproate (0.2 g three times/d), and clonazepram (2 mg per night). His symptoms did not improve, and he gradually developed weakness in both lower limbs and difficulty in walking. He did not show obvious cognitive impairment as his mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA) scores were 28 and 24, respectively. Physical examination showed that the muscular strength in both lower extremities was Level IV with hyperreflexia of bilateral patellar tendons and a suspicious positive Babinski sign on the left side.
The younger brother was 29 years old. Nine months previously, he became highly irritable and talkative with exaggerated expression and presented with euphoria with less sleep and visual hallucination. He was also treated for manic psychosis in his local hospital with risperidone (2.5 mg/d) and valproate (1.0 g/d). His symptoms gradually improved. Six months previously, he presented with bilateral visual decline, cognitive impairment, and depressive symptoms, similar to his brother. He was treated for manic-depressive psychosis again but showed no obvious improvement. Approximately, 2 weeks previously, he felt weakness in both legs, could not walk without a crutch, and presented with mild euphoria and insomnia. He had obvious cognitive impairment (MMSE and MoCA scores of 23 and 19, respectively) and decreased muscular strength (proximal muscle strength: Level III, distal muscle strength: Level IV) with hyperreflexia and bilateral Babinski sign.

Both patients’ academic performance and athletic ability had been below average since primary school. They had no family history of mental disorders. Their parents were not consanguineous.

Both patients had undergone magnetic resonance imaging (MRI) examination of the spinal cord in their local hospital, and the results were normal, whereas brain MRI showed mild diffuse atrophy of the cerebral cortex in both patients. Ocular fundus examination demonstrated bilateral optic atrophy in both patients and pigmentary retinal degeneration in the left eye of the elder brother. All routine biochemical, microscopic, and immunologic examinations of cerebrospinal fluid (CSF) showed normal results. Gas chromatography-mass spectrometry (GS/MS) and tandem mass spectrometry (MS/MS) analyses revealed significantly elevated methylmalonic acid in urine and homocysteine (Hcy) levels in the plasma, and a reduced methionine level in the plasma [Table 1].

The methylenetetrahydrofolate reductase gene (MTHFR) analysis identified a heterozygous C>T mutation in the younger brother and a homozygous C>T mutation in the elder brother. Further MMACHC gene analysis confirmed the consistent heterozygous mutations of c.482G>A [Figure 1c1 and 1d1] and c.658_660del [Figure 1c2 and 1d2]. Further testing identified that c.482G>A and c.658_660del originated from their father [Figure 1a1 compared to the normal control of Figure 1b1] and mother [Figure 1b2 compared to the normal control of Figure 1a2], respectively. After the diagnosis of cblC disease was made, antipsychotic drugs were discontinued and the patients were treated with levocarnitine (intravenous injection, 1 g/d), MeCbl (intramuscular injection, 1 mg/d), folic acid (oral, 5 mg/d), and Vitamin B6 (oral, 30 mg/d). The symptoms of mental abnormality, blurred vision, and weakness in both legs were obviously improved after 1 week of treatment. During the 3-month follow-up, the patients showed no recurrence of psychiatric disorders or weakness of the legs. Although their vision improved considerably, fundus examination showed no improvement in optic atrophy. Repeated GS/MS analysis showed a significant reduction in the plasma MMA level, while the plasma Hcy level remained high [Table 1]. Then, betaine (oral, 3 g/d) was added, and the dose of MeCbl (intramuscular injection, 2 mg/week) was maintained. During the 6-month follow-up, the plasma Hcy level decreased significantly.

Cobalamin C disease is usually considered a neonatal disease. The late-onset form is rare and difficult to diagnose due to its wide spectrum of clinical manifestations. In 1984, Shinnar and Singer[4] reported the first case of cblC with gradual dementia. Since then, only 12 sibling cases of MMA have been cited in PubMed to date. Among them, five pairs were identified as the late-onset cblC type, with ages ranging from 4 to 32 years, and most of them presented with neurological symptoms including cognitive regression, myelopathy, hypertensive encephalopathy, unsteady gait, and behavioral abnormalities. Only one case presented with psychiatric symptoms as dissociative symptoms and delusions of persecution with visual and auditory hallucinations.[5] None presented with manic-depressive psychosis at the first onset as we describe in the present cases.

Both the two siblings described herein had concurrent heterozygous mutations of c.482G>A and c.658_660del. Among these, c.482 G>A has been confirmed to be associated with the late-onset type of cblC disease.[6] One previous study of more than 300 cblC patients, diagnosed mostly in Switzerland and Canada, showed that c.271dupA (42%) and c.394C>T (20%) mutations were the most common pathogenic alleles while only 13 and 2 patients carried the c.482G>A and c.658_660del mutations, respectively.[6] In contrast, a study of cblC cases in China showed that the two most common alleles were c.609G>A and c.482G>A, which accounted for 48.1% and 13.9% of mutant alleles, respectively.[1] A standardized treatment with MeCbl, levocarnitine, folic acid, Vitamin B6, and betaine was given when MMA was diagnosed. Both siblings exhibited a rapid response to MeCbl. Both neuropsychiatric symptoms and biochemical indexes were improved after treatment. This further confirmed our diagnosis.

### Table 1: GS/MS and MS/MS test results for Cases 1 and 2

| Items (normal range) | Admission | 3-month follow-up | Admission | 3-month follow-up |
|----------------------|-----------|--------------------|-----------|-------------------|
| Urine methylmalonic acid (0.2–3.6), mmol/mol/creatinine | 253.68 | 104.59 | 262.03 | 191.83 |
| Plasma methionine (5.72–28.38), μmol/L | 8.86 | 13.58 | 9.70 | 13.12 |
| Plasma homocysteine (0–20), μmol/L | 65.00 | 81.70 | 115.30 | 84.50 |

GS/MS: Gas chromatography mass spectrometry; MS/MS: Tandem mass spectrometry.
In summary, manic-depressive psychosis could be one of the first symptoms of late-onset cblC disease. Early diagnosis and treatment are quite necessary to achieve good outcomes.

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Conflicts of interest
There are no conflicts of interest.

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Figure 1: Heterozygous missense mutation and frameshift mutation of the human MMACHC gene. Results of sanger sequence (a-d). DNA sequencing of exon 4 of MMACHC in their parents (a and b), and the two cases confirm the presence of the R161Q mutation (c.482G>A) and the frameshift mutation c.658_660del. MMACHC: Methylmalonic aciduria and homocystinemia type C protein.