Distinct clinical, neuroimaging and genetic profiles of late-onset cobalamin C defects (cb1C): a report of 16 Chinese cases

Xianling Wang¹, Yanhui Yang², Xuying Li³, Cunjiang Li¹* and Chaodong Wang¹*

Abstract

Objective: The importance of late-onset cobalamin C (cb1C) disorder is underestimated in adults. Improved awareness on its clinical and neuroimaging features helps timely diagnosis and appropriate treatment.

Methods: Totally 16 late-onset cb1C cases were diagnosed based on clinical, biochemical findings and MMAHC gene mutation analysis. Clinical presentations, neuroimaging features and mutational spectrum were reviewed.

Results: The case series included 10 males and 6 females, with average age of 22 (range 13–40) years. All the 16 patients displayed bilateral pyramidal tract signs, and most of the cases (13) had cognitive impairment. Other symptoms included psychiatric symptoms (6), epilepsy (6), peripheral nerve damage (5), ocular symptoms (4) and lower-limb thrombosis (1). The neuroimaging findings were dominated by cerebral atrophy (11/16), followed by white matter lesions (4), cerebellar lesions/atrophy (2) and spinal cord lesions (1). There were also 2 patients with normal imaging. All the MMACHC mutations were compound heterozygous, of which the most and second frequent was c.482G > A (p.R161Q; 15/16 case; allele frequency: 46.88%) and c.609G > A (p.W203X; 6/16 case; allele frequency: 18.75%). In addition, patients carrying frameshift mutations (deletion/duplication) presented more frequently with psychiatric symptoms (57.1%) and optic nerve damages (42.9%) than those carrying point mutations (22.2 and 11.1%, respectively). In contrast, peripheral nerve (44.4%) and white matter lesions (33.3%) were more frequently identified in point mutation-carriers. However, the differences did not achieve statistical significance (all \( p > 0.05 \)).

Conclusion: Compared to the early-onset form, late-onset cb1C displayed some clinical, neuroimaging and mutational profiles, which warrants particular attention in adult neurologic practice. These findings not only broaden our insights into the genotypes and phenotypes of the disease, but highlight the importance of early diagnosis and initiation of appropriate treatments.

Keywords: CblC disease, MMAHC gene, Neuroimaging, Phenotypic heterogeneity

Introduction

Methylmalonic academia (MMA) with homocysteinemia, cobalamin-C (cb1C) type, is the most common subtype of defective intracellular cobalamin (vitamin B12) metabolism [1, 2]. cb1C disease results from mutations in the MMACHC gene, which result in impaired conversion of dietary vitamin B12 or cobalamin (Cbl) to its two metabolically active forms, methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl). MeCbl and AdoCbl are essential coenzymes to methionine synthase and methylmalonyl-CoA mutase, whose functional deficiency leads to methylmalonic academia combined with homocysteinemia. Based on the age of onset, there are two distinct clinical subtypes of cb1C disease, early-onset and late-onset [3]. The early-onset type presents in the neonatal and early infantile period with failure to thrive, acute neurological deterioration, macrocytic anemia, multisystem organ dysfunction, metabolic acidosis and visual impairment (retinopathy, optic atrophy), and has a poor prognosis even with early treatment [4, 5]. Late-onset cb1C patients have been defined as the patients have overt symptoms after 4 years of age. Compared to the...
early-onset form, the late-onset cblC is less common and has less severe presentations and more favorable outcomes if treated promptly [1, 2]. However, the diagnosis of late-onset cblC disease was often delayed and missed in the adult neurology practice, due to the rarity of the disease and lack of awareness by adult neurologists [6].

In recent years, more and more late-onset cases have been diagnosed and the incidence of late-onset appears to be higher than the previous estimate. However, the sample sizes reported late-onset cblC cases in previous studies [6–8] were relatively small, and the total number of reported late-onset cblC cases is < 80 [6](calculated according to the latest literatures). In this study, 16 Chinese cases with late-onset cobalamin C disorder were diagnosed and confirmed by mutation analysis of the MMACHC gene (NM_015506.2). We aim to characterize the clinical and neuroimaging profiles, as well as the mutational spectrum and genotype-phenotype correlation of the late-onset cblC cases.

Methods
All the 16 cases with late-onset Cobalamin-C (cblC) disease were identified in Department of Neurology of Xuanwu Hospital from April 2009 to June 2018. All these patients presented with acute or insidious onset and extensive neurological signs. Neuroimaging studies and routine lab tests (including blood and CSF) excluded the possibilities of common diseases such as vascular, neoplastic, inflammatory, degenerative or demyelinating diseases. On the other hand, these features, together with the relatively young onset (compared to most of the adult-onset diseases), support the possibility of hereditary and/or metabolic diseases. In this view, a routine metabolic screening, including the measurement of C3 (propionylcarnitine), C3/C0 (free carnitine) and C3/C2 (acetylcarnitine) in the plasma by tandem mass spectrometry, the detection of methylmalonic acid in the urine by gas-chromatography mass spectrometry, and the determination of total levels of homocysteine, vitamin B12 and folate in the serum. All the identified cases showed a significant increase of methylmalonic acid in the urine and serum homocysteine but without decrease of vitamin B12, which are indicative of cblC. Thus, a subsequent genetic test were performed to screen mutations of MMACHC, the causative gene for cblC by polymerase chain reaction (PCR) and direct DNA sequencing, as described previously [9]. Brain MRI, electromyography (EMG), electroencephalogram (EEG), and funduscopia examination were performed in all cases, and spinal cord MRI was performed in 7 cases. After re-evaluation and diagnostic confirmation by two senior neurologists and a geneticist, all cases were treated with parenteral hydroxocobalamin combined with oral betaine, folate and carnitine for 3–4 weeks. The responses to the treatments were reported by the patients. Except case no.1, neuroimaging follow-up were not conducted for these cases after treatment.

Mutational spectrum of MMACHC gene, and clinical and imaging features were compared between patients carrying frameshift (deletion/duplication) and point mutations using chi-square or Fisher Exact Test.

Results
Clinical features and biochemical findings
The cases series included 10 males and 6 females. The average age was the 22 years (range from 13 to 40), and the average onset age was 19 years (range from 11 to 40). Time between the first symptom and diagnosis ranged from 1 month to more than 10 years. Case 9 and 10 were siblings. The other cases were not related. The onset was acute or insidious and the diet changes, pregnancy, fever were most common triggers for the acute onset. The clinical presentations involve multiple neurological systems (Table 1). Cognitive impairment and psychiatric symptoms were the most common symptoms, which were observed in 13 and 6 cases, respectively. Four cases had epilepsy and two had epileptic discharges in EEG without clinical episode. Physical examination revealed bilateral pyramidal tract signs in all cases. Four cases (No.5, 7, 11, 12) presented with progressive paraplegia and bilateral pyramidal tract signs without sensory dysfunction, which were initially misdiagnosed with hereditary spastic paraplegia. Peripheral nerve damaging was detected in 5 cases by neurological examinations and/or EMG examinations. Ocular symptoms were found in 4 cases, among which 2 cases complained blurred vision and 2 cases did not have optic symptoms but were identified to have mild optic nerve atrophy and pigmentary retinal dystrophy by funduscopia. The renal function and hematological condition of all patients were normal. Deep vein thrombosis in the lower extremities was found in one case. The urine metabolic screening detected remarkably elevated urine MMA level in all cases. Elevated plasma homocysteine level was found in all the cases (Table 2), but the level of vitamin B12 and folate in the serum were normal or mildly elevated. By treating with parenteral hydroxocobalamin combined with oral betaine, folate and carnitine for 3–4 weeks, the majority of patients showed marked decrease of the urine MMA and plasma homocysteine levels, as well as different extent of symptomatic improvement. The symptomatic improvement upon treatment has been detailed in Table 1. Among these, the improvement of cognitive decline and psychiatric symptoms were most evident.

Neuroimaging findings
The neuroimaging findings were dominated by various degree cerebral atrophy (11/16), followed by high-intensity
| Case No. | Gender | Age (year) | Duration | Onset symptom | Psychiatric symptoms | Cognitive impairment | Epilepsy | Pyramidal tract impairment | Peripheral nerve damage (EMG findings) | Visual impairment other symptoms | Response to treatment |
|----------|--------|------------|----------|---------------|---------------------|---------------------|----------|--------------------------|----------------------------------------|----------------------------------|--------------------------|
| 1        | F      | 14         | 1 m      | Cognitive impairment | Irritability psychosis | Moderate memory decline | –        | Paraplegia Bilateral Pyramidal tract signs | Sensorimotor polyneuropathy of lower limbs (involved both axon and myelin) | – | Memory decline and psychiatric symptoms were remarkably recovered |
| 2        | M      | 14         | 8 m      | Cognitive impairment | Apathy lethargy depression | Severe cognitive impairment deterioration in school performance | Epileptic discharges in EEG | Bilateral Pyramidal tract signs | – | – | Cognitive impairment was partly recovered |
| 3        | M      | 40         | 1 m      | Cognitive impairment | – | Moderate memory impairment | – | Quadriplegia Bilateral Pyramidal tract signs | Sensorimotor polyneuropathy of lower limbs (involved both axon and myelin) | – | All symptoms were fully recovered |
| 4        | F      | 22         | 3 m      | Cognitive impairment | – | Moderate impaired memory and calculation ability | – | Paraplegia Bilateral Pyramidal tract signs | Sensorimotor polyneuropathy of lower limbs (involved myelin) | – | Moderate improvement of cognitive impairment |
| 5        | F      | 18         | 7y       | Gait disturbance | – | Mild memory impairment | Epileptic discharges in EEG | Progressive spastic paraplegia Bilateral Pyramidal tract signs | – | – | Mild improvement of gait disturbance |
| 6        | F      | 13         | 5 m      | Cognitive impairment | Irritability, aggressiveness | Moderate cognitive impairment, deterioration in school performance | – | Mild paraplegia Bilateral Pyramidal tract signs | – | – | Remarkable improvement of cognitive impairment |
| 7        | M      | 26         | 4 m      | Weakness of lower limbs | – | – | Generalized tonic-clonic seizures | Progressive spastic paraplegia, Bilateral Pyramidal tract signs | – | Visual acuity: normal, Funduscopy examination: optic nerve atrophy | Weakness of lower limbs was remarkably recovered |
| 8        | M      | 16         | 2 m      | Weakness of lower limbs | – | – | Generalized tonic-clonic seizures | Paraplegia Bilateral Pyramidal tract signs | – | – | Weakness of lower limbs was remarkably recovered |
| 9        | M      | 32         | 1.5y     | Psychiatric symptoms | Euphoria, agitation auditory and vision hallucinations | Mild memory impairment | – | Paraplegia Bilateral Pyramidal tract signs | Visual acuity: normal, Funduscopy examination: mild optic nerve atrophy | – | Psychiatric symptoms were remarkably recovered |
Table 1: Clinical information of 16 cases with late-onset cblC disease (Continued)

| Case No. | Gender | Age (year) | Duration | Onset symptom | Psychiatric symptoms | Cognitive impairment | Epilepsy | Pyramidal tract impairment | Peripheral nerve damage (EMG findings) | Visual impairment other symptoms | Response to treatment |
|----------|--------|------------|----------|---------------|----------------------|-----------------------|----------|-----------------------------|--------------------------------------|-------------------------------|----------------------|
| 10       | M      | 29         | 9 m      | Weakness of lower limbs | Euphoria, agitation irritability aggressiveness | Mild memory impairment | –        | Paraplegia Bilateral Pyramidal tract signs | –                                   | –                            | Psychiatric symptoms were remarkably recovered |
| 11       | F      | 15         | 1y       | Weakness of lower limbs | – | Mild memory impairment | – | Progressive spastic paraplegia Bilateral Pyramidal tract signs | – | – | Weakness of lower limbs was partly recovered |
| 12       | M      | 23         | 2 m      | Weakness of lower limbs | – | Mild memory impairment | – | Progressive spastic paraplegia Bilateral Pyramidal tract signs | – | – | Weakness of lower limbs was remarkably recovered |
| 13       | M      | 15         | 4 m      | Cognitive impairment | Impaired memory and calculation ability | Mild paraplegia Bilateral Pyramidal tract signs | – | Sensory polyneuropathy of lower limbs (involved axon) | Decreased vision (right eye 0.15, left eye 0.5, optic nerve damage) | Moderate improvement of vision and weakness |
| 14       | M      | 29         | 11y      | Cognitive impairment | Moderate impaired memory speech difficulties | Paraplegia Bilateral Pyramidal tract signs | – | Sensorimotor polyneuropathy of four limbs (involved both axon and myelin) | – | Mild improvement of cognitive impairment |
| 15       | M      | 20         | 6y       | Epilepsy | – | Generalized tonic-clonic seizures | Bilateral Pyramidal tract signs | – | Thrombosis of peroneal vein and intramuscular vein of left lower limb | Epilepsy and thrombosis were improved with antiepileptic and anticoagulant drugs |
| 16       | F      | 24         | 10y      | Decreased vision depression | Moderate depression | Mild memory impairment | Generalized tonic-clonic seizures | Paraplegia Bilateral Pyramidal tract signs | Decreased vision (left eye 0.2, right eye 0.6, bilateral optic nerve atrophy) | Mild improvement of vision and depression |

Bilateral Pyramidal tract signs presented positive Babinski sign in all cases on neurological examination.
lesions in white matter (4/16), cerebellar lesions (1/16), cerebellar atrophy (1/16) and spinal cord lesions (1/16). There were also 2 patients with normal imaging (Table 2). Different from the diffuse white matter swelling in early-onset cblC cases, the white matter lesions in these late-onset cases presented with bilateral symmetric patchy lesions mainly in centrum ovale, corona radiate and periventricular area (Fig. 1a-d). Case 8 only presented small lesions in unilateral posterior ventricular area (Fig. 1e, f). Cerebellum lesions were rarely reported in cblC cases. In this study, bilateral cerebellar cortex lesions were found in one case (firstly reported in our previous report [8]) and cerebellum atrophy in case 13 (Fig. 2a, b). The spinal cord MRI examinations showed spinal cord lesions in case 1 (Fig. 2c, d) and the lesions disappeared after treatment. None of the cases showed the basal ganglion lesions, hydrocephalus or diffused white matter swelling, which were the common features in early-onset cobalamin C disorder. Only case No. 4 had MR spectroscopy data from areas of bilateral centrum ovale and corona radiata lesions, which showed decreased N-acetylaspartate (NAA) and increased choline (Cho) and lactate (Lac) peak in lesions of both sides.

**Mutation and genotype-phenotype correlation analyses**

*MMAHC* mutations were detected in all the 16 cases, including 11 Known mutations. All the mutations in *MMAHC* gene were compound heterozygous mutations and c.482G > A (p.R161Q) was the most frequent cblC mutation detected in 15/16 patients, affecting 15 of 32 *MMAHC* alleles (46.88%). The second common mutation was c.609G > A (p.W203X) in 6/16 patients and affecting 6 of 32 *MMAHC* alleles (18.75%). c.567dupT, c.565C > A was respectively found in 2/16 cases (Table 2). The spectrum of MMACHC gene mutations in these late-onset cases was shown in Fig. 3. The c.394C > T mutation, which was most commonly related to early-onset disease in previous studies [1, 2], was not found in these late-onset cases.

### Table 2 Neuroimaging presentations, gene mutations, plasma homocysteinemia and urine MMA level of 16 cases with late-onset cblC disease

| Case No. | Brain MRI | Spinal cord MRI | Plasma homocysteinemia level (μmol/L, normal range: 5.0–15.0) | MMA level (μg/mg creatinine, normal range: 0.2–3.6) | MMAHC mutation |
|----------|-----------|----------------|--------------------------------------------------|---------------------------------|----------------|
| 1        | Bilateral white matter lesions in the centrum ovale and corona radiata | Thoracic lesions | 101.60 | 232.18 | c.482G > A, c.609G > A |
| 2        | Bilateral white matter lesions in the bilateral periventricular white matter | – | 135.7 | 191.22 | c.482G > A, c.567dupT |
| 3        | Cerebral atrophy and bilateral cerebellar cortex lesions | – | 57.2 | 70.53 | c.482G > A, c.1A > G |
| 4        | Bilateral white matter lesions | – | 79.8 | 166.64 | c.482G > A, c.609G > A |
| 5        | Cerebral atrophy | Normal | 99 | 321.12 | c.482G > A, c.609G > A |
| 6        | Mild cerebral atrophy | – | 88 | 340.8 | c.482G > A, c.626dupT |
| 7        | Cerebral atrophy | Normal | 97.7 | 172.4 | c.567dupT, c.565C > A |
| 8        | Cerebral atrophy and white matter lesions in unilateral posterior ventricular area | – | 99.1 | 189.16 | c.467G > A, c.482G > A |
| 9        | Normal | – | 115.3 | 253.68 | c.482G > A, c.656_658del |
| 10       | Mild cerebral atrophy | – | 75.7 | 262.03 | c.482G > A, c.656_658del |
| 11       | Cerebral atrophy | Normal | 121 | 168.05 | c.482G > A, c.427C > T |
| 12       | Normal | Normal | 93.6 | 81.62 | c.482G > A, c.609G > A |
| 13       | Cerebral atrophy and bilateral cerebellar atrophy | – | 102.6 | 58.42 | c.482G > A, c.658_660del |
| 14       | Cerebral atrophy | – | 86 | 288.85 | c.482G > A, c.609G > A |
| 15       | Hippocampus atrophy | Normal | 114.1 | 116.04 | c.326_329del, c.482G > A |
| 16       | Mild cerebral atrophy | Normal | 124.5 | 184.71 | c.482G > A, c.609G > A |
frequencies for each detected mutation between our patient series and previously published studies and in the public database (ExAC, gnome AD), the c.482G > A variant in our cases were much more prevalent than other reported cases, and c.609G > A seemed to be ethnically related to Chinese patients (Additional file 1: Table S1). Among all MMACHC mutations, frameshift and point mutation accounted for 56.3% (9/16) and 43.8% (7/16), respectively. And patients with symptoms involving damage from peripheral nerve and white matter accounted for 31.3% (5/16) and 25% (4/16), respectively. Comparing clinical and imaging features (Table 3), patients carrying frameshift mutations (deletion/duplication) presented more frequently with psychiatric symptoms (57.1%) and optic nerve damages (42.9%) than those carrying point mutations (22.2 and 11.1%, respectively). In contrast, peripheral nerve (44.4%) and white matter lesions (33.3%) were more frequently identified in point mutation-carriers. However, the differences did not achieve statistical significance (all \( p > 0.05 \)).

Discussion
Using the largest series of Chinese cases, we comprehensively analyzed the clinical and imaging and genetic features of late-onset cblC. Compared with the early-onset type, the late-onset cblC presents more extensive but milder symptoms of the nervous system, and has a much better prognosis. Except one with thromboembolic complications, none of the cases had multisystem organ dysfunction and metabolic acidosis. In general, neuroimaging findings showed less severe damages in the central nervous system (CNS) among the late-onset patients. The cases displayed more cerebral atrophy and focal/patchy deep white matter lesions than early-onset ones without extensive and severe swelling and hydrocephalus. Moreover, the mutational spectrum of the MMACHC gene in late-onset cblC is significantly different from that in the early-onset type, as well as that previously reported in the late-onset cases.

The common presentations in these late-onset cblC cases include cognitive impairment, psychiatric symptoms, epilepsy, pyramidal tract signs and peripheral neuropathy, which is similar to a previous report [4, 10]. In addition, physical exam revealed frequent (100%) bilateral pyramidal tract signs but rare compromise in deep somatic sensory, which is different from subacute combined degeneration of the spinal cord (SCD), and easily misdiagnosed as hereditary spastic paraplegia (HSP). Spastic paraparesis is one of the multiple presentations of inborn errors of metabolism (IEMs) in children and adults, and even the only symptom for years in some cases. Therefore, it is essential not only to recognize the spastic paraparesis as one of the manifestations of IEMs, but also to include IEMs in the general diagnostic approach to spastic paraparesis [11]. Contrasting to previous reports, damage in optic and peripheral nerves was not rare, but the degree was relatively mild and even subclinical [12]. Moreover, the manifestations and severity vary among cases, suggesting considerable clinical heterogeneity of the diseases.

The neuroimaging features of late-onset cblC have not been clearly established. Diffuse supratentorial white matter swelling, variably severe white matter loss, hydrocephalus, thinning of the corpus callosum, symmetric bilateral lesions in the basal ganglia, the common and characteristic imaging findings in early-onset cblC [5, 13, 14], were not revealed in our late-onset cases. In contrast, cerebral atrophy and patchy lesions in deep white matter were common in late-, but not early-onset cases. In addition, we first identified 2 patients with high-intensity lesions (T2-weighted) or atrophy in the bilateral cerebellar hemisphere.

Over 75 MMACHC mutations have been detected in cblC diseases [1, 2, 14], among which c.271dupA and c.331C > T are the most common for early-onset cblC and c.394C > T was associated mainly with the late-onset.
subtype [13, 15–18]. However, none of them was detected in our late-onset cases. We revealed c.482G > A as the most common (15/16) cause of the late-onset cblC in Chinese, which is also highly prevalent in other ethnicities including those with Hispanic, Caucasian and mixed backgrounds [19, 20]. Homozygous c.609G > A is the second common mutation related to early-onset cblC [21], but all mutations detected in our late-onset cases were heterozygotes. Moreover, patients carrying different mutations presented with distinct clinical and imaging features and showed different genotype-phenotype correlation from previous reports.

The molecular mechanisms underlying the phenotypic differences between the early- and late-onset cblC remain elusive, but may be related to the distinct mutational spectrum and different functional effects of these mutations. In general, late-onset cases rarely carry the homozygous mutations (especially nonsense and frameshift), which are functionally more pathogenic than heterozygous ones. At transcript level, different mutations have different levels of allelic expression and influence the MMACHC mRNA transcript level to different degrees. The early-onset c.271dupA mutation was underexpressed compared with the late-onset mutations and the MMACHC mRNA transcript levels in cell lines homozygous for the late-onset c.394C > T mutation had significantly higher transcript levels than those for the early-onset mutations [16]. At the protein level, pathogenic mutations, such as R161G and R161Q, can specifically impair the catalytic activities of MMACHC [22]. Moreover, other phenotypic modifiers, including the intracellular reactive oxygen species (ROS) and rate of apoptosis, may influence the expressivity and severity of different subtypes of cblC cases [23]. Nevertheless, all these evidences were obtained in cell models, and animal models are lacking for systematically investigating the molecular machineries underlying the phenotypic diversity.
Table 3 Comparison of the clinical symptoms and neuroimaging presentations between the cases with point mutations and frameshift mutations

|                     | Point mutation (n = 9) | Frameshift mutation (n = 7) | \( \chi^2 \) | p       |
|---------------------|-----------------------|-----------------------------|--------------|---------|
| Psychiatric symptom (+) | 2 (22.2)          | 4 (57.1)                     | 2.05         | 0.15    |
| Psychiatric symptom (—) | 7 (77.8)          | 3 (42.9)                     |              |         |
| Cognitive impairment (+) | 8 (88.9)          | 5 (71.4)                     | 0.79         | 0.38    |
| Cognitive impairment (—) | 1 (11.1)          | 2 (28.6)                     |              |         |
| Epilepsy (+)       | 3 (33.3)            | 3 (42.9)                     | 0.15         | 0.70    |
| Epilepsy (—)       | 6 (66.7)            | 4 (57.1)                     |              |         |
| Peripheral nerve (+) | 4 (44.4)            | 1 (14.3)                     | 1.67         | 0.20    |
| Peripheral nerve (—) | 5 (55.6)            | 6 (85.7)                     |              |         |
| Optic nerve damage (+) | 1 (11.1)           | 3 (42.9)                     | 2.12         | 0.15    |
| Optic nerve damage (—) | 8 (88.9)           | 4 (57.1)                     |              |         |
| White matter lesion (+) | 3 (33.3)           | 1 (14.3)                     | 0.76         | 0.38    |
| White matter lesion (—) | 6 (66.7)           | 6 (85.7)                     |              |         |
| Cerebral atrophy (+) | 6 (66.7)            | 5 (71.4)                     | 0.04         | 0.84    |
| Cerebral atrophy (—) | 3 (33.3)            | 2 (28.6)                     |              |         |
| Spinal cord lesion (+) | 1 (11.1)           | 0 (0.0)                      | 0.83         | 0.36    |
| Spinal cord lesion (—) | 8 (88.9)            | 7 (100.0)                    |              |         |
| Cerebellar lesion (+) | 1 (11.1)            | 1 (14.3)                     | 0.04         | 0.85    |
| Cerebellar lesion (—) | 8 (88.9)            | 6 (85.7)                     |              |         |

Conclusion
In summary, using one of the largest late-onset cblC case series, we have characterized the distinct clinical, neuroimaging and genetic profiles of the disease in Chinese. These findings not only broaden our insights into the genotypes and phenotypes of the disease, but also increase our awareness of these inborn errors of metabolisms in adult neurology practice to improve the diagnosis and appropriate treatment. Moreover, the unique mutational spectrum and genotype-phenotype correlation implied by these late-onset cases highlights the importance of early diagnosis and initiation of appropriate treatments.

Additional file

Additional file 1: Table S1. Comparison of allele frequencies of identified mutations between our patients and other reports. (DOC 48 kb)

Abbreviations
AdoCbl: Adenosylcobalamin; Cbl: Cobalamin; CblC: Cobalamin C disease; EEG: Electroencephalogram; EMG: Electromyography; FLAIR: Fluid attenuated inversion recovery; HSP: Hereditary spastic paraplegia; MeCbl: Methylcobalamin; MMA: Methylmalonic academia; PCR: Polymerase chain reaction; ROS: Reactive oxygen species; SCD: Subacute combined degeneration of the spinal cord

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Availability of data and materials
All data generated or analysed during this study are available from the corresponding author on reasonable request.

Authors’ contributions
XLW, CJL and CDW designed the study and participated in data acquisition, analysis and interpretation, as well as draft & revision of the manuscript. YHL were involved in neuroimaging data analysis. XYL participated in data acquisition and mutational analyses. All authors read, critically revised, and approved the final manuscript.

Ethics approval and consent to participate
All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (the Institutional Review Board of Xuan Wu Hospital, Capital Medical University, Beijing, China). Written informed consent was obtained from the patient or patient’s parent.

Consent for publication
Each patient or patient’s parent signed consent for publication.

Competing interests
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Author details
1Department of Neurology, Xuanwu Hospital, Capital Medical University, 45 Changchun Street, Xicheng District, Beijing 100053, People’s Republic of China. 2Department of Radiology, Xuanwu Hospital, Capital Medical University, Beijing, China. 3Department of Neurobiology, Xuanwu Hospital, Capital Medical University, Beijing, China.
