Journal of Neurology (2019) 266:2434–2439
https://doi.org/10.1007/s00415-019-09432-8

ORIGINAL COMMUNICATION

Treatable cause of hereditary spastic paraplegia: eight cases of combined homocysteinaemia with methylmalonic aciduria

Yanping Wei[1] · Yan Zhou[1] · Jing Yuan[1] · Jun Ni[1] · Min Qian[1] · Liying Cui[1] · Bin Peng[1]

Received: 27 April 2019 / Revised: 8 June 2019 / Accepted: 11 June 2019 / Published online: 15 June 2019

Abstract

Combined homocysteinemia with methylmalonic aciduria (MMA/HCY) are genetic disorders of intracellular cobalamin (cbl) transport and processing that cause downstream deficiencies in methylcobalamin and adenosylcobalamin. Untreated disease is characterized biochemically by methylmalonic aciduria and hyperhomocysteinemia, while the clinical features are variable. When spastic paraplegia (SP) dominates, it is difficult to differentiate from hereditary spastic paraplegia (HSP). Clinical, biochemical and imaging features were reviewed in eight patients with MMA/HCY that mimicked HSP. Seven males and one female were enrolled. The median onset age was 13 years old (range 7–26 years old). The median time delay of diagnosis was 20.5 months (range 2–60 months). Spastic gait was the first symptom in four patients, while the other four patients presented with chronic emotional abnormalities or cognitive impairment. The main clinical manifestation was SP, and other neurological symptoms included cognitive impairment (5/8), spastic dysuria (3/8), personality change and depression (3/8), ataxia (2/8), seizures (2/8), limb numbness (2/8), and developmental delay (2/8). When patients were diagnosed, the mean serum homocysteine level, the methylmalonic acid level in urine, the serum propionylcarnitine (C_3) level and the ratios of C_3-to-acetylcarnitine (C_2) and free carnitine (C_0) were all dramatically elevated. Cranial MRIs showed nothing remarkable except mild brain atrophy. All spinal MRIs were normal except for case 8. Definite compound heterozygous mutations in MMACHC were detected in five cases. Follow-up indicated partial improvement in all the patients after intramuscular cbl, oral betaine and folate, supporting the diagnosis of MMA/HCY. Our data highlight the need for extensive investigation of intracellular cbl transport and processing, when spastic paraparesis is a prominent component of the clinical picture. Testing for urine methylmalonic acid and serum homocysteine levels is a simple but critical approach in suspected cases. Genetic testing, especially for MMACHC gene mutations, is needed. Raising awareness of this disorder could result in the timely initiation of targeted treatment, which may significantly improve patient outcomes.

Keywords Hereditary spastic paraplegia · Methylmalonic aciduria · Homocysteinemia · Cobalamin · CblC · Mutation · Diagnosis

Introduction

Hereditary spastic paraplegia (HSP) refers to a clinically and genetically heterogeneous group of disorders characterized by bilateral lower limb spasticity and weakness that may be chronic and slowly progressive [1]. Neurological examinations show spasticity, hyperreflexia, and extensor plantar responses indicating corticospinal tract involvement; these are occasionally accompanied by involvement of the spinal posterior column and peripheral nerves. HSP can be classified into pure and complicated forms [1]. Complicated HSP is associated with additional neurological and extra-neurological signs, including cerebellar ataxia, intellectual deficiency, epilepsy, neuropathy, retinal degeneration, extrapyramidal features, deafness, white matter lesion and a thin corpus callosum [1].

The definitive diagnosis of HSP is challenging and can only be achieved by genetic testing [1]. Although great progress has been made in our understanding of the molecular genetics of HSP in recent years, a negative genetic test does not exclude a diagnosis of HSP because many disease-causing genes remain unknown. Furthermore, because it is a

✉ Yanping Wei
yp924@sina.com

[1] Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Shuaifuyuan 1, Dongcheng district, Beijing 100730, China

type of inherited neurodegenerative or neurodevelopmental disorder, there are currently no specific disease-modifying therapies for HSP. Therefore, it is extremely important to be familiar with the many different reasons of SP that could mimic HSP, especially those that are treatable, and a thorough investigation should be performed.

Spastic paraplegia (SP) is not uncommonly encountered in inborn errors of metabolism (IEMs), even though it is occasionally the only symptom for years [2]. Combined homocysteinemia with methylmalonic aciduria (MMA/HCY) is a genetic disorder of intracellular cobalamin (cbl) transport and processing that results in the defective synthesis of both methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) [3]. The former is the cofactor for methionine synthase, which catalyses the conversion of homocysteine into methionine in the cytosol, while the latter is the cofactor for methylmalonyl-CoA mutase, which converts methylmalonyl-CoA into succinyl-CoA in mitochondria. Therefore, MMA/HCY patients are characterized biochemically by the coexistence of methylmalonic aciduria (MMAuria) and hyperhomocysteinemia (hyperHCY), which has many types including cblC, cblD, cblF, cblJ type and transcobalamin (TC) deficiency, with CblC the most common type [3, 4]. Here, we review the clinical and biochemical features of a cohort of eight patients with MMA/HCY that mimicked HSP.

Patients and methods

The study was conducted as a retrospective analysis from 2012 to December 2018. To be included, subjects needed to fit the following criteria: (1) mainly presented with a slowly progressive course of spastic paraparesis; (2) showed dominating corticospinal tract involvement on neurological examinations; (3) other possible acquired factors, including nutritional deficiency, myelitis, and cervical myelopathy, were excluded; (4) the serum total HCY levels and urine methylmalonic acid levels were greatly elevated on biochemical investigation; (5) there was at least partial clinical and biochemical response to cb1 supplementation; and/or (6) a definitely pathogenic gene mutation was found to be closely related to MMA/HCY.

A detailed medical history, family history and the extent of multiorgan involvement were reviewed. All patients underwent tandem mass spectrometry (MS/MS) to measure plasma amino acid levels and the blood acylcarnitine profile, while gas chromatography–mass spectrometry (GC/MS) was performed to measure urine concentrations of organic acids. The serum levels of folate, vitamin B12 and total homocysteine (tHCY) were determined. Other laboratory tests included routine blood, liver and kidney function and lactic acid, ceruloplamin, blood glucose and blood ammonia levels. Mutations in the MMACHC and MMADHC genes were detected in five patients using PCR and DNA sequencing. All patients underwent cranial MRI, spinal MRI and electrophysiological examinations, including electromyography and nerve conduction velocities. The MRI studies were performed on a 1.5-T or 3.0-T system and included T1-weighted images, T2-weighted images, and fluid-attenuated inversion recovery (FLAIR).

Results

A total of eight patients (seven males and one female) fit the criteria described above for MMA/HCY and were enrolled.

Clinical features

The demographic and clinical findings in each patient are presented in Table 1.

The main clinical features were listed in Table 1. Of the eight included patients, two presented their first clinical symptoms at younger than 10 years old (25%), while the age of onset was between 10 and 20 years old in four patients (50%) and older than 20 years old in the other two patients (25%). The median onset age was 13 years old (range 7–26 years old). The median time delay of the diagnosis from disease onset was 20.5 months (range 2–60 months). Spastic gait was the first symptom in four patients, while the other four patients presented with chronic behavioural or emotional abnormalities, personality changes or declines in academic performance that were easily neglected. The main clinical manifestation in all these patients was SP, although other neurological symptoms were observed, included the following in order of frequency: cognitive impairment (5/8), spastic dysuria (3/8), personality change and depression (3/8), ataxia (2/8), seizures (2/8), limb numbness (2/8), and developmental delay (2/8). Cases 5 and 7 had only two seizures in 5 years without regular oral antiepileptic medications. On neurological examination, pyramidal signs were disclosed in all patients and included spasticity, hyperreflexia, and bilateral extensor plantar responses. The muscle strength of the lower extremities in these patients was between MRC 4/5–5/5, while the upper extremities were all normal. In addition, five patients scored 24–27 on the mini-mental state examination (MMSE), mainly due to memory impairment and arithmetic retardation. Two patients had decreased hypoesthesia below the knees, and another two patients presented with truncal and limb ataxia. Moreover, extra-central nervous system involvement was only found in three patients, optic atrophy in two patients and renal insufficiency in another patient.

Table 1 The demographic and clinical findings in 8 patients with MMA/HCY

	1	2	3	4	5	6	7	8
Sex	M	M	M	F	M	M	M	M
Age onset	7 yr	16 yr	13 yr	10 yr	24 yr	13 yr	7 yr	26 yr
Duration before diagnosis	3 yr	2 mo	4 yr	5 yr	2 mo	5 mo	5 yr	3 mo
Initial symptom	Decline performance	sp	sp	Depression	sp	sp	Decline performance	Cognitive impairment
Spastic paraplegia	+	+	+	+	+	+	+	+
Cognitive impairment	+	−	+	+	−	−	+	+
Spastic Dysuria	−	+	−	−	+	−	−	+
Depression	+	−	−	+	−	−	−	+
Seizures	−	−	−	+	−	−	+	−
Ataxia	−	+	−	+	−	−	−	−
Numbness	−	−	−	−	+	−	−	+
Development delay	−	−	−	−	+	−	−	+

Laboratory investigations

A summary of the findings of laboratory investigations is listed in Table 2.

The main auxiliary investigations were listed in Table 2. The serum homocysteine level when patients were diagnosed was obviously elevated (range 75.4–250.1 μmol/L; reference range 5–15 μmol/L), while the median value was 157.65 μmol/L. The methylmalonic acid level in urine was 44.1–1731.4 times higher than the values found in the normal control of the same age group. The blood acylcarnitine profile revealed increased propionylcarnitine (C_3) levels and increased ratios of C_3-to-acetylcarnitine (C_2) and C_3-to-free carnitine (C_0) (C_3/C_2 and C_3/C_0). The serum C_3 level was between 7.06 and 12.31 μmol/L (reference range, 0.5–4 μmol/L). The ratio of C_3/C_2 was between 0.49 and 1.266 (reference range 0.01–0.24), and the ratio of C_3/C_0 was between 0.467 and 0.97 (reference range 0.04–0.15). Serum folate and vitamin B12 levels and all other routine blood test results were normal in all patients except that moderately elevated creatinine levels were detected in case 5. The serum level of lactic acid was normal or mildly elevated to between 0.99 and 3.1 mmol/L (reference range 0.5–1.6 mmol/L). Cranial MRIs showed mild brain atrophy in six patients (Fig. 1), while findings were roughly normal in the other two patients. All of the spinal MRIs were normal except for case 8, in which the spinal cord MRI showed abnormally high intensity signal

Table 2 The laboratory investigations in eight patients with MMA/HCY

	1	2	3	4	5	6	7	8	Normal range
HCY-b (μmol/L)	217.4	119.3	96.2	153.3	162	75.4	250.1	221.8	5–15
Therapy	Cyncbl	Hydrocbl	Hydrocbl	Cyncbl	Hydrocbl	Hydrocbl	Hydrocbl	Cyncbl	Null
HCY-a (μmol/L)	104.5	50.8	45.7	97.4	72.1	40.8	89.4	104.9	5–15
MMAuria	1514	233.46	1731.4	344.7	770.5	44.1	70.8	395.91	Increased fold over control
MMAserum (mg/dL)	0.926	0.453	0.947	0.607	0.821	0.115	0.147	0.619	≤0.047
C_3 (μmol/L)	10.93	7.06	9.32	10.27	12.31	8.13	9.05	12.01	0.5–4
C_3/C_0	0.833	0.81	0.73	0.58	0.51	0.97	0.467	0.713	0.04–0.15
C_3/C_2	1.266	0.82	0.91	0.67	0.71	0.84	0.49	0.696	0.01–0.24
Brain MRI	Atrophy	Atrophy	Atrophy	Normal	Normal	Atrophy	Atrophy	Atrophy	Atrophy
Spinal MRI	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	C3-7
Mutation1	c.482G > A	ND	c.394C > T	ND	c.482G > A	c.914 T > C	c.482G > A	ND	
Mutation2	c.609G > A	ND	c.565C > A	ND	c.658_660 del	c.278G > A	c.656_658 del	ND	

M, male; F, female; sp, spastic paraplegia; yr, years; mo, months; +, positive findings; -, negative findings; HCY-b, serum total HCY before therapy; HCY-a, serum total HCY after therapy; cyncbl, cyanocobalamin; hydrocbl, hydroxycobalamin

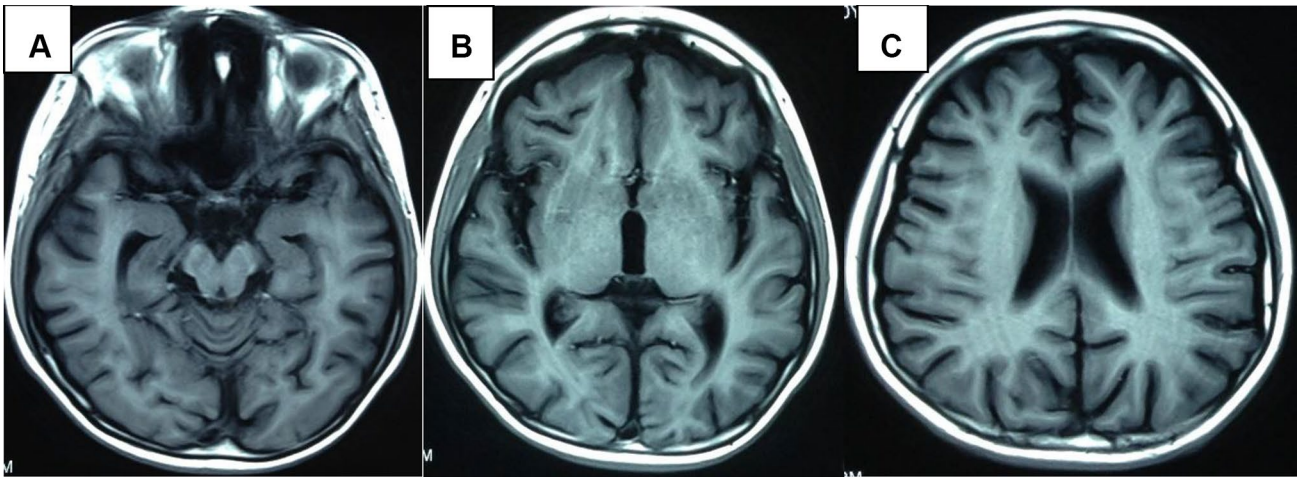

Fig. 1 T1-weighted MR images of brain in case 8: diffuse brain atrophy presented with widened and deepened cerebral sulcus and enlarged ventricles

on T2-weighted sequences that involved the posterior columns and pyramidal tract between the cervical 3 (C_3) and C_7 levels (Fig. 2). Electrophysiological measurements revealed reduced sensory and motor conduction velocity and decreased amplitudes in peripheral nerves in case 5, indicating peripheral neuropathy; the others all had normal findings.

Definite pathogenic mutations were detected in five patients, while the other three patients refused to undergo genetic testing. The compound heterozygous mutations in the MMACHC gene included c.482G>A and c.609G>A in case 1, c.394C>T and c.565C>A in case 3, c.482G>A and c.658_660del in case 5, c.914 T>C and c.278G>A in case 6, and c.656_658del and c.482G>A in case 7.

Follow-up

All patients were administered intramuscular cyanocobalamin or hydroxycobalamin (1 mg, once a day) for 1 week followed by a half-dose for 3 weeks. Moreover, oral l-carnitine,

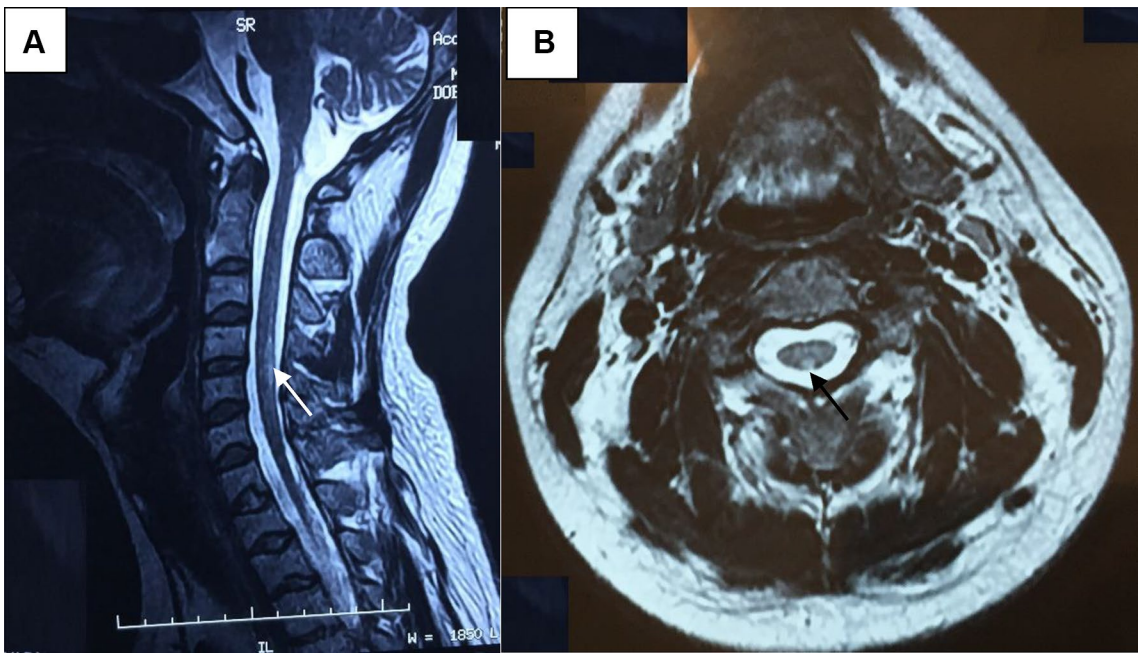

Fig. 2 T2-weighted MR images of cervical spinal cord in case 8: Sagittal image showed hyper-intensity signal located in the posterior column at C_3–C_7 level. (**a**, white arrow). Axial image showed the same lesion of posterior column. (**b**, black arrow)

betaine and folate were orally administered. One month later, the levels of serum HCY and urine MMA were slightly decreased, and the symptoms of all patients had gradually resolved. Cognitive impairment and depressive mood showed significant improvement, while the muscle strength of the lower limbs increased to some extent, resulting in gait improvement.

Discussion

The clinical hallmarks of our patients were progressive spastic paralysis of the bilateral lower extremities, which conformed to SP. Furthermore, the onset ages were very young, with the median onset age 13 years old and most cases between 10 and 20 years old. HSP was an easily identified cause. HSP is characterized by gradual and progressive spastic weakness of the lower extremities and lacks effective therapy [1]. The median time to diagnosis from disease onset was 20.5 months and ranged from 2 months to 5 years. Four patients acquired definite diagnoses in less than 1 year, and these included cases 2, 5, 6, and 8. Among these cases, cases 2 and 6 reported poor athletic performance in a child without attention. Case 6 showed renal sufficiency 3 years before the presentation of SP. Only case 8 was roughly normal before subacute onset of SP. Table 1 shows that subacute onset is more common in patients with late onset. Moreover, there were some other neurological and extra-neurological manifestations in addition to SP, and these are worth mentioning. Four of these patients first presented with declining school performance and personality change, which was mistaken for a rebellious phase in puberty and therefore ignored. The diagnosis of these patients was much delayed because of delayed presentation to the hospital and was therefore found only after the appearance of gait disorder. The parents did not recognize these mental and cognitive abnormalities until a thorough medical history was collected. In addition, other symptoms, including peripheral neuropathy, ataxia, seizure, optic atrophy and renal insufficiency were accompanied spastic gait, which indicated multiple lesions in addition to those in the pyramidal tract. Therefore, thorough investigations should be made before achieving a final diagnosis when faced with SP.

According to the World Health Organization (WHO), vitamin B12 status is defined by serum levels using the following cutoff: > 221 pmol/L indicates vitamin "B12 adequacy" [5]. In our cohort, the serum levels of vitamin B12 and folate were all above the reference range of the normal population; thus, nutritional deficiency was excluded. Obviously, the biochemical parameters of our patients revealed both homocysteinemia and methylmalonic aciduria, which are direct evidence of MMA/HCY. Moreover, elevated serum levels of C_3 and increased C_3/C_2 and C_3/C_0 ratios were all substantive supporting findings [6]. Therefore, the comprehensive laboratory inspections of all our patients pointed to a diagnosis of MMA/HCY, which is supposed to represent a genetic disorder of intracellular cbl transport and processing resulting in deficient synthesis of MeCbl and AdoCbl [3, 7]. Cranial MRI was nonremarkable except for brain atrophy, as was the spinal MRI of 7 patients. Only case 8 showed an abnormal signal on cervical MRI. The radiological features were consistent with the clinical presentations that were dominated by gait disorder. Follow-up indicated that improvement occurred in all the patients after intramuscular cbl, oral betaine and folate, which supported the diagnosis of MMA/HCY. Five of the patients were verified as Cblc by genetic testing.

Clinical presentations specific for MMA/HCY include acute or chronic behavioural or psychiatric abnormalities, cognitive impairment, signs of peripheral neuropathy and ataxia that reflect subacute degeneration of the spinal cord and, in rare cases, venous thromboembolism in late-onset patients, including older children, adolescents and adults [3]. Our results indicate that spastic paraparesis is also one of the variable presentations of MMA/HCY and is occasionally accompanied by involvement of peripheral nerves and posterior columns of spinal cords. The main presentation of our patients was pyramidal signs. The motor neurons that form the pyramidal tracts are extraordinarily long cells that are particularly vulnerable to metabolic disorders because of their substantial energy and transport requirements [2]. Therefore, it is not surprising that MMA/HCY can provoke spastic paraparesis due to the demyelination of the pyramidal tracts because of a deficiency in *S*-adenosylmethionine (AdoMet). AdoMet is necessary to methylate the myelin basic protein and certain lipids of the myelin sheath [8]. Since MMA/HCY is treatable, early recognition and the initiation of therapy may prevent irreversible neurological damage. It is important to emphasize that metabolic screening should be performed in patients who present with progressive SP beginning at less than 30 years old, especially when accompanied by other neurological or extra-neurological features, including polyneuropathy, behavioural changes, cognitive impairment, psychosis, and seizures. Vitamin B12 levels should always be measured initially to rule out nutritional deficiency. Testing for urine methylmalonic acid and serum homocysteine levels is a simple but critical approach in suspected cases of MMA/HCY [3]. Serum C_3 and the ratios of C_3 to various other acylcarnitine species were used as secondary parameters to prompt a correct diagnosis [6]. If clinical and biochemical parameters are characteristic of MMA/HCY, it may be pragmatic to test first for cblC, the most frequent combined remethylation disorder, by searching for MMACHC gene mutations [3, 7].

In summary, we describe the clinical and biochemical characteristics of a cohort of MMA/HCY patients who

presented with SP that was easily confused with HSP. It should be noted that the small number of patients, the retrospective nature of data collection, the mainly descriptive characteristics of the data and the lack of molecular and enzymatic verification in three of our patients limit the findings of this study. Despite this, these data are still of value in highlighting the need for extensive investigation of intracellular cbl transport and processing as spastic paraparesis is a prominent component of this clinical picture. Raising awareness of this disorder could significantly improve patient outcomes and clinicians' perspectives by allowing the timely initiation of targeted treatment.

Compliance with ethical standards

Conflict of interest Authors declare no conflicts of interest.

Ethics approval and consent to participate All patients or their parents gave written informed consent. This study was in compliance with Ethics Guidelines and approved by the Ethics Committee of Peking Union Medical Collage Hospital. (PUMCH S-K764).

Consent for publication All authors read and approved the final manuscript. Consent for publication was obtained from all authors.

References

1. Victor P, Souza S De, Bocca W et al (2017) Hereditary spastic paraplegia: clinical and genetic hallmarks. Cerebellum 16:525–551
2. Sedel F, Fontaine B, Saudubray JM (2007) Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: A diagnostic approach. J Inherit Metab Dis 30:855–864
3. Huemer M, Diodato D, Schwahn B, Schiff M (2017) Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis 40:21–48
4. Trakadis YJ, Alfares A, Bodamer OA, Buyukavci M, Christodoulou J, Connor P (2014) Update on transcobalamin deficiency: clinical presentation, treatment and outcome. J Inherit Metab Dis 37:461–473
5. Hannibal L, Lysne V, Behringer S (2016) Biomarkers and algorithms for the diagnosis of vitamin B12 deficiency. Front Mol Biosci 3:27
6. Lindner M, Ho S, Ko S (2008) Newborn screening for methylmalonic acidurias—optimization by statistical parameter combination. J Inherit Metab Dis 31:379–385
7. Carrillo-carrasco N, Chandler RJ, Venditti CP (2012) Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. J Inherit Metab Dis 35:91–102
8. Powers JM, Rosenblatt DS, Schmidt RE et al (2001) Neurological and neuropathologic heterogeneity in two brothers with cobalamin C deficiency. Ann Neurol 49:396–400