The adolescent and adult form of cobalamin C disease: clinical and molecular spectrum

C Thauvin-Robinet,[1] E Roze,[2,3] G Couvreur,[4] M-H Horellou,[5] F Sedel,[6] D Grabli,[6] G Bruneteau,[6] C Tonneti,[7] A Masurel-Paulet,[1] D Perennou,[8] T Moreau,[4] M Giroud,[4] H Ogier de Baulny,[9] S Giraudier,[7] L Faivre[1]

[1] Centre de Génétique, Hôpital d'Enfants, CHU, Dijon, France; [2] Service de Neurologie, Hôpital Saint Antoine, APHP, Paris, France; [3] CNRS UMR7102, Université Paris VI, Paris, France; [4] Service de Neurologie, Hôpital Général, CHU, Dijon, France; [5] Service d'Hématologie Biologique, Hôpital Hôtel-Dieu, APHP, Paris, France; [6] Fédération de Neurologie, CHU La Pitié-Salpêtrière, APHP, Paris, France; [7] Service d'Hématologie-Biologique, Hôpital Henri Mondor, Créteil, France; [8] Centre de Convalescence et de Rééducation, CHU, Dijon, France; [9] Service de Neuropédiatrie, Maladies Métaboliques, Hôpital Robert-Debré, APHP, Paris, France

Correspondence to:
Dr C Thauvin-Robinet, Centre de Génétique, Hôpital d'Enfants, 10 Bd maréchal de Lattre de Tassigny, 21034 Dijon Cedex, France; christel.thauvin@chu-dijon.fr

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ABSTRACT

Background: Cobalamin C disease is the most common inborn error of cobalamin metabolism with an autosomal recessive mode of inheritance and mutations within the *MMACHC* gene. Clinical features, including systemic, haematological and neurological abnormalities, usually occur in the first year of life. Adolescent and adult onset presentations are rare.

Methods: We report on the clinical, molecular and imaging features in three patients aged 40, 42 and 42 years at the last follow-up. We examine these cases together with eight previously described cases to determine the clinical and molecular features of the disease in adults.

Results: Mean age at onset of clinical symptoms was 26 years; clinical features included predominant neurological disturbances and thromboembolic complications. White matter abnormalities on brain MRI were sometimes observed. Most patients (eight of nine patients investigated) were compound heterozygotes for the 271dupA mutation and a missense mutation. Intramuscular or intravenous hydroxycobalamin therapy stopped the progression of the disease and resulted in a better clinical outcome and favourable biological status in 7/9 treated cases, while the two untreated patients died quickly.

Conclusions: As cobalamine C disease and related disorders of homocysteine metabolism are treatable conditions, homocysteinaemia should be included in the investigations of patients with progressive neurological deterioration, unexplained psychiatric disturbances or recurrent thromboembolic events.

Combined methylmalonic aciduria (MMA) and homocystinuria cobalamin C type (Cbl-c disease) secondary to *MMACHC* gene mutations are the most common inborn errors of cobalamin metabolism.[1 2] Clinical features, which usually occur in the first year of life, include failure to thrive, microcephaly, poor feeding, vomiting, hypotonia, mild to moderate developmental delay, speech delay and seizures.[3–7] More specific but inconstant features include haematological anomalies with macrocytic or microcytic anaemia, low vitamin B12 levels, thrombocytopenia and microthrombotic disease.[5 8–11] Whereas some cases have been described with onset in childhood,[4] only eight cases with adolescent and adult onset (>14 years of age) Cbl-c disease have been described in the literature.[12–19] Here we report on the clinical, metabolic and molecular spectrum of three new cases and follow-up of two previously reported cases of adolescent and adult onset Cbl-c disease.

CASE REPORT

Case No 1

A 39-year-old woman was referred to the neurological unit for the association of progressive neurological deterioration, acute mental confusion, myoclonus and visual hallucinations (global QI = 84 at 40 years of age in contrast with anterior QI = 90–95 at 15 years of age). Her family history was unremarkable. Clinical history revealed an episode of glomerulonephritis at 2 years of age and behavioural and learning difficulties since 15 years of age, despite normal intellectual development. Pulmonary embolism complicated by hemiplegia and depression occurred after childbirth at 18 years of age. This was followed by recurrent venous thromboses. Generalised seizures occurred from 31 years of age and a new episode of pulmonary embolism evidenced moderate C protein deficiency. Cerebral tomodensitometry showed cortical atrophy and leucoencephalopathy.

Clinical examination revealed severe and diffuse myoclonus, dysarthria, dysmetria, adiadochocinesia and tetraparesis. Cerebral MRI showed leucoencephalopathy with corpus callosum agenesis and bilateral ventricular dilatation (fig 1A, B). Metabolic investigations showed high plasma homocysteine, low plasma methionine and increased urinary MMA levels (see table 1). Impaired synthesis of adenosylcobalamin and methylcobalamin in cultured skin fibroblasts, complementation studies and *MMACHC* gene sequencing analysis confirmed Cbl-c deficiency.

One month later, after starting combined daily treatment with intramuscular hydroxycobalamin (1 mg), oral folinic acid (10 mg) and oral betaïne (6 g), she presented with pain and distal dystonia of the left hand. She progressively recovered partial autonomy and her ability to walk, but had persistent dysarthria, logorrhoea and arterial hypertension. At this time, intramuscular delivery of hydroxycobalamin was replaced by oral administration. Nine months later, her cognitive disorders had almost disappeared, but distal dystonia was persistent. Metabolic investigations showed persistent high plasma homocysteine (135 μmol/l) and increased MMA levels (2556 mmol/mol creatinine) with a normal level of plasma methionine. These unsatisfactory metabolic results led to the prescription of intravenous hydroxycobalamin (2 mg): intramuscular injections were contraindicated because of antivitamin K treatment. A few months later, she died suddenly at home.

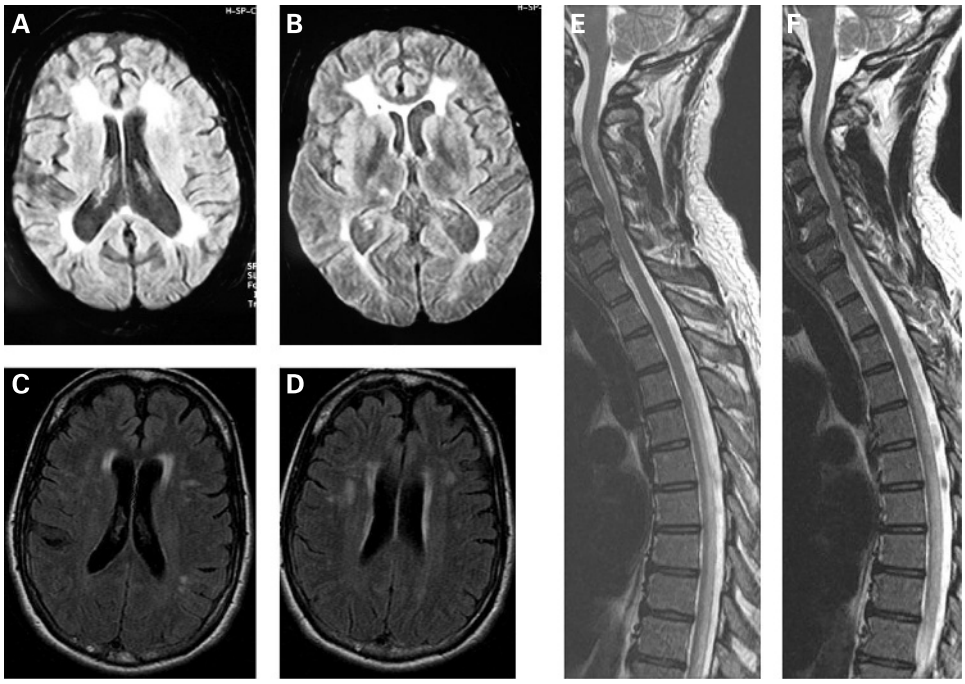

Figure 1 (A, B) Cerebral MRI of patient No 1 showing severe leucoencephalopathy with corpus callosum agenesis and bilateral ventricular dilatation. (C, D) Brain MRI of patient No 2 showing a mild periventricular leucoencephalopathy. (E, F) Spinal cord MRI of patient No 2 showing a diffuse abnormal high signal on T2 weighted sequences involving the posterior columns and pyramidal tracts at the cervical and dorsal levels, suggestive of subacute combined degeneration of the spinal cord.

Case No 2

A 42-year-old man was referred for neurological and psychiatric deterioration. His family history was unremarkable. He had experienced depression for 1 year following hip surgery. Neurological examination showed apraxia, ataxia, spasticity and myelopathy. Brain MRI showed mild periventricular leucoencephalopathy (fig 1C, D). Spinal cord MRI revealed a diffuse, abnormal, high intensity signal on T2 weighted sequences involving the posterior columns and pyramidal tracts at the cervical and dorsal levels (fig 1E–F). Such abnormalities were suggestive of subacute combined degeneration.

Routine laboratory investigations, including haemoglobin, platelet count and level of vitamin B12, were normal. Metabolic investigations revealed high plasma homocysteine and high urinary MMA levels (table 1). Impaired synthesis of adenosylcobalamin and methylcobalamin in cultured skin fibroblasts and *MMACHC* gene sequencing confirmed Cbl-c deficiency. Electromyography and fundoscopy were normal. Previous asymptomatic pulmonary embolism and spleen infarcts were diagnosed by vascular investigations. A few weeks after starting combined daily treatment with oral folinic acid (10 mg) and betaine (9 g) and intravenous hydroxycobalamin, the clinical, psychiatric and cognitive disturbances had disappeared and he progressively recovered partial autonomy and his ability to walk. The high intensity signal of the spinal cord disappeared within 6 months of treatment with hydroxycobalamin, folinic acid and betaine

Case No 3

A 40-year-old woman was referred for recurrent venous thrombosis. Her family history was unremarkable. Past medical history revealed glomerulonephritis at 23 years of age and deep iliac venous thrombosis at 33, 39 and 40 years of age. She did not present any neurological or psychiatric disturbances. Neurological examination and cerebral MRI were normal.

Investigations revealed normal red cell and platelet counts; metabolic investigations showed high plasma homocysteine, low plasma methionine and increased urinary MMA levels (table 1). Impaired synthesis of adenosylcobalamin and methylcobalamin in cultured skin fibroblasts and *MMACHC* gene sequencing analysis confirmed Cbl-c deficiency.

Combined daily treatment with intramuscular hydroxycobalamin (1 mg), oral folinic acid (10 mg) and oral betaine (16 g) was started and resulted in decreased plasma homocysteine (74 μmol/l) and normal plasma methionine levels. Oral hydroxycobalamin (1 mg/day) rapidly replaced intramuscular injections because of anticoagulant therapy, but this led to an increased level of plasma homocysteine (183 μmol/l). Intravenous hydroxycobalamin (2.5 g/month) was therefore introduced. Nine months of this protocol led to normal plasma homocysteine levels. Unfortunately, it had to be replaced again by intracutaneous hydroxycobalamin because of allergy. This modification led to a new increase in plasma homocysteine levels (101 μmol/l). During the 2 years after introduction of this treatment, she did not present any recurrence of thromboembolic complications.

Case No 4 (follow-up of case No 1 previously reported[17])

Five years after combined daily treatment with intramuscular hydroxycobalamin (1 mg), oral folinic acid (10 mg), oral L-carnitine (3 g) and oral betaine (9 g), follow-up revealed persistent moderate myelopathy. Metabolic investigations showed satisfactory results with decreased hyperhomocysteinaemia and urinary MMA levels, and normal plasma methionine levels. The patient had recurrent miscarriages, probably secondary to placental thrombosis. She also had two uneventful pregnancies with anticoagulation therapy, leading to two healthy children.

Case No 5 (follow-up of case No 2 previously reported[17])

Over the following 6 months of treatment, the patient developed deep venous thrombosis and persistent psychotic features associated with complete tetraparesis. Because of antivitamin K therapy, intravenous hydroxycobalamin was used. After 6 weeks of combined treatment with intravenous hydroxycobalamin (2.5 mg twice a month), oral folinic acid

Table 1 Clinical features in the three new cases with late onset cobalamin C disease and follow-up of two previously reported cases and a review of the literature

	Present reported cases			Follow-up of two previously reported cases		Literature review					
	Case 1	Case 2	Case 3	Case 4[17]	Case 5[17]	Powers[14]	Powers[14]	Bodamer[15]	Brunelli[16]	Boxer[18]	Tsai[19]
Family history	–	–	–	+	+	+	+	–	–	+	–
Age at onset (y)	18	41	33	24	16	32	16	19	16	38	teens
Age at diagnosis (y)	39	42	40	25.5	16	32	44	20	16	42	36
Sex	F	M	F	F	F	M	M	M	M	M	F
Thromboembolic disease	+	+	+	–	+	–	+	+	+	–	–
Neurological disturbances											
Encephalopathy	+	+	–	–	–	–	+	+	+	+	–
Myoclonia	+	–	–	–	–	–	–	–	–	–	–
Seizures	+	–	–	–	–	–	–	–	–	+	–
Neuropathy	–	–	–	–	+	+	–	+	–	–	+
Myelopathy	+	+	–	+	+	+	–	+	–	–	–
Mental retardation	–	–	–	–	–	–	–	–	–	–	–
Psychiatric disturbances	+	+	–	–	+	–	+	–	+	–	+
Renal complications											
Glomerulopathy	–	–	+	–	–	–	–	–	+	–	–
Microangiopathic nephropathy	+	–	–	–	–	–	–	–	–	–	–
Optic pallor	+	–	–	–	–	+	+	–	NA	NA	NA
Outcome	Death					Death	Death		Death		
Age at follow-up (y)	40	42	42	26	17	34	45	20	21	43	38
Biological findings at diagnosis											
Plasma homocysteine*	172	228	288	125	205	NA	NA	27.9	134	309	57
Plasma methionine†	7	1067	12	10	7	NA	NA	NA	7.3	12	N
Urine MMA‡	1708		1209	3330	3890	NA	NA	1722	1100	NA	NA
Metabolic studies											
AdoCbl and MetCbl deficiency	+	+	+	+	+	NA	+	NA	NA	+	+
CblC complementation study	+	NA	NA	+	+	NA	+	+	+	+	+
Cerebral MRI/TDM											
White matter abnormalities	+	–	–	–	+	+	+	–	NA	+	–
Cortical atrophy	+	–	–	–	+	–	–	–	NA	–	–
Medullar lesions	NA	+	NA	–	NA	NA	NA	NA	NA	NA	+
Treatment	+	+	+	+	+	–	–	+	+	+	+
Mutations (base pair)	C457T	271dupA	271dupA	271dupA	271dupA	271dupA	271dupA	271dupA	NA	NA	271dupA
	A365G	C565A	A365G	T347C	T347C	G440C	G440C	G482A			G482A
Mutation (amino acids)	R153X	R91KfsX14	R91KfsX14	R91KfsX14	R91KfsX14	R91KfsX14	R91KfsX14	R91KfsX14	NA	NA	R91KfsX14
	H122R	R189S	H122R	L116P	L116P	G147A	G147A	R161Q			R161Q

AdoCbl, adenosylcobalamin; CblC, cobalamin C; MetCbl, methylcobalamin; MMA, methylmalonic acid; NA, not available; TDM, tomodensitometry.
*Normal range 6–14 μmol/l; †normal range 11–29 μmol/l; ‡normal range <5 mmol/mol creatinine.

(10 mg), oral L-carnitine (3 g) and oral betaine (9 g), clinical improvements were noticeable with the recovery of arm function and the disappearance of psychotic features and lethargy.

Four and a half years after initiation of hydroxycobalamin therapy, she presented with severe neuropathy and myelopathy. Cerebral and spinal MRI showed decreased white matter abnormalities. Neurophysiological studies showed severe axonal non-demyelinating polyneuropathy. Metabolic results were satisfactory with moderate plasma homocysteine (20 μmol/l), increased plasma methionine (4 μmol/l) and decreased urinary MMA (190 μmol/mmol creatinine) levels.

DISCUSSION

Here we report on three new cases and the 5 year follow-up after treatment of two previously described patients with adolescent and adult onset Cbl-c disease.[17]

Before the present report, adolescent and adult onset Cbl-c disease had been described in only eight cases in the literature (table 1).[12–19] Mean age at diagnosis was 32 years and at follow-up was 33.5 years. Diagnosis was suspected because of neurological anomalies (7/11 cases) or thromboembolic complications (2/11 cases). In 2/11 cases, the diagnosis was suspected at autopsy because of neuropathological findings suggestive of a methylation defect, and because of a family history.[14] The clinical courses were characterised by sudden neurological deterioration in adults with normal early development. Neurological disturbances occurred in 9/11 cases, including myelopathy (6/11 cases), encephalopathy (6/11 cases), neuropathy (4/11 cases) or psychiatric disturbances (6/11 cases). The clinical features were restricted to the nervous system in 4/11 cases. Whereas neuroradiological investigations were not always contributive, white matter involvement seemed to be a common finding in adult onset forms (5/10 cases).[17] Spinal cord lesions in two of the three cases screened for this feature were similar to abnormalities observed in cobalamin deficiency.[20]

Thromboembolic complications were frequent (7/11 cases), and remained the main cause of mortality or morbidity (3/4 cases). Indeed, sustained plasma homocysteine elevation was an established independent risk for vascular disease, including thrombosis.

Optic pallor was rare, occurring in 3/8 patients. Contrary to the early onset form, retinopathy has never been described in adult onset patients. Considering renal involvement (3/11 cases), glomerulopathy was described in adults only whereas renal complications also included thrombotic microangiopathy in the infant form. Adolescent and adult onset presentation was also characterised by the absence of haematological symptoms.[4] Indeed, none of the patients had abnormal haematological results and serum vitamin B12 levels were also normal (9/9 cases).

Hypomethioninaemia and methylmalonic aciduria can be corrected by treatment with hydroxycobalamin. Parenteral administration of hydroxylamine stopped the progression of the disease and resulted in a better outcome (7/9 cases). Two patients died under treatment: one of cerebrovascular complications with poor compliance with therapy[16] and the second with a case of suspected pulmonary embolism following intravenous hydroxycobalamin treatment that did not lead to a satisfactory decrease in homocysteine levels (case No 1). In both cases, treatment with anticoagulation drugs precluded intramuscular injections. Infracutaneous administration was less effective, and intravenous injections had to be performed in hospital units because of allergic risks. The two untreated patients died of profound venous thrombosis and severe infections 1–2 years after the onset of symptoms.[20–23]

Molecular diagnosis by *MMACHC* gene sequencing analysis was performed in 9/11 cases, and showed that all patients except one were compound heterozygous for the 271dupA mutation and a missense mutation in the late onset form.[2 24]

In conclusion, because Cbl-c deficiency can be diagnosed easily by amino acid chromatography, and neurological and vascular improvements can be obtained with simple hydroxycobalamin therapy, the disease should be considered in the diagnosis of patients with progressive neurological deterioration, psychiatric disturbances and/or recurrent thromboembolic disturbances.

Competing interests: None.

REFERENCES

1. **Rosenblatt DS,** Shevell MI. Inherited disorders of cobalamin and folate absorption and metabolism. In: Fernandes J, Saudubray JM, Van Den Bergh G, eds. *Treatment of metabolic diseases*. Berlin: Springer-Verlag, 1996:247–58.
2. **Lerner-Ellis JP,** Tirone JC, Pawelek PD, *et al*. Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. *Nat Genet* 2006;**38**:93–100.
3. **Mitchell GA,** Watkins D, Melançon SB, *et al*. Clinical heterogeneity in cobalamin C variant of combined homocystinuria and methylmalonic aciduria. *J Pediatr* 1986;**108**:410–15.
4. **Rosenblatt DS,** Aspler AL, Shevell MI, *et al*. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). *J Inherit Metab Dis* 1997;**20**:528–38.
5. **Andersson HC,** Marble M, Shapira E. Long-term outcome in treated combined methylmalonic academia and homocystinemia. *Genet Med* 1999;**1**:146–50.
6. **Biancheri R,** Cerone R, Rossi A, *et al*. Early-onset cobalamin C/D deficiency: epilepsy and electroencephalographic features. *Epilepsia* 2002;**43**:616–22.
7. **Briddon A.** Homocysteine in the context of cobalamin metabolism and deficiency states. *Amino Acids* 2003;**24**:1–2.
8. **Brandstetter Y,** Weinhouse E, Splaingard ML, *et al*. Cor pulmonale as a complication of methylmalonic academia and homocystinuria (cbl-C type). *Am J Med Genet* 1990;**36**:167–71.
9. **Geraghty MT,** Perlman EJ, Martin LS, *et al*. Cobalamin C defect associated with hemolytic–uremic syndrome. *J Pediatr* 1992;**120**:934–7.
10. **Russo P,** Doyon J, Sonsino E, *et al*. A congenital anomaly of vitamin B12 metabolism: a study of three cases. *Hum Pathol* 1992;**23**:504–12.
11. **Patton N,** Beatty S, Lloyd IC, *et al*. Optic atrophy in association with cobalamin C (cblC) disease. *Ophthalmic Genet* 2000;**21**:151–4.
12. **Ben-Omran TI,** Wong H, Blaser S, *et al*. Late-onset cobalamin C disorder: a challenging diagnosis. *Am J Med Genet* 2007;**143**:979–84.
13. **Al-Memar AY,** Preece A, Ross C, *et al*. Combined methylmalonic aciduria and homocystinuria: a defect in cellular metabolism and a treatable cause of dementia. *J Neurol Neurosurg Psychiatry* 1998;**65**:420(abstract).
14. **Powers JM,** Rosenblatt DS, Schmidt RE, *et al*. Neurological and neuropathologic heterogeneity in two brothers with cobalamin C deficiency. *Ann Neurol* 2001;**49**:396–400.
15. **Bodamer OA,** Rosenblatt DS, Appel SH, *et al*. Adult-onset combined methylmalonic aciduria and homocytinuria (cblC). *Neurology* 2001;**56**:1113.
16. **Brunelli SM,** Meyers KE, Guttenberg M, *et al*. Cobalamin C deficiency complicated by an atypical glomerulopathy. *Pediatr Nephrol* 2002;**17**:800–3.
17. **Roze E,** Gervais D, Demeret S, *et al*. Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. *Arch Neurol* 2003;**60**:1457–62.
18. **Boxer AL,** Kramer JH, Johnston K, *et al*. Executive dysfunction in hyperhomocystinemia responds to homocysteine-lowering treatment. *Neurology* 2005;**64**:1431–4.
19. **Tsai ACH,** Morel CF, Scharer G, *et al*. Late-onset combined homocystinuria and methylmalonic aciduria (*cblC*) and neuropsychiatric disturbances. *Am J Med Genet Part A* 2007;**143A**:2430–4.
20. **Hemmer B,** Glocker FX, Schumacher M, *et al*. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. *J Neurol Neurosurg Psychiatry* 1998;**65**:822–7.
21. **Bartholomew DW,** Batshaw ML, Allen RH, *et al*. Therapeutic approaches to cobalamin-C methylmalonic academia and homocystinuria. *J Pediatr* 1988;**112**:32–9.
22. **Ribes A,** Briones P, Vilaseca MA, *et al*. Methylmalonic aciduria with homocystinuria: biochemical studies, treatment, and clinical course of a Cbl-C patient. *Eur J Pediatr* 1990;**149**:412–15.
23. **Andersson HC,** Shapira E. Biochemical and clinical response to hydroxycobalamin versus cyanocobalamin treatment in patients with methylmalonic academia and homocystinuria (CblC). *J Pediatr* 1998;**132**:121–4.
24. **Morel CF,** Lerner-Ellis JP, Rosenblatt DS. Combined methylmalonic aciduria and homocystinuria (*cblC*): Phenotype–genotype correlations and ethnic-specific observations. *Mol Genet Metab* 2006;**88**:315–21.