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 Baunly,9 S Giraudier,7 L Faivre1

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 cobalamin 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 thromboembolic complications.

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 5 More specific but inconstant features include haematological anomalies with macrocytosis or microcytic anaemia, low vitamin B12 levels, thrombocytopenia and microthrombotic disease.3 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. Generalized 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 leukoencephalopathy.

Clinical examination revealed severe and diffuse myoclonus, dysarthria, dysmetria, adiadochocinesis and tetraparesis. Cerebral MRI showed leukoencephalopathy 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 betaine (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, logorrhea 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.
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 leuencephalopathy (fig 1C, D). Spinal cord MRI revealed a diffuse abnormal high 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 reported17)
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 reported17)
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

<table>
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<tr>
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<td>AdoCbl and MetCbl deficiency</td>
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<td>Encephalopathy</td>
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<td>–</td>
<td>Death</td>
<td>–</td>
<td>38</td>
<td>Treatment</td>
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</table>

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.

Before the present report, adolescent and adult onset Cbl-c disease had been described in only eight cases in the literature (table 1). 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. 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). Spinal cord lesions in two of the three cases screened for this feature were similar to abnormalities observed in cobalamin deficiency.

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. 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 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. Intracutaneous 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. 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. Indeed, none of the patients had abnormal haematological results and serum vitamin B12 levels were also normal (9/9 cases).


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