ORIGINAL ARTICLES

Neurological outcome of methylmalonic acidemia

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Abstract

Objective—To assess the long term outcome of patients with methylmalonic acidemia in a cross sectional study.

Patients—All 35 patients with methylmalonic acidemia seen at Great Ormond Street Hospital for Children in London, UK between 1970 and 1996 were studied. They were divided into cobalamin responsive (n = 6) and non-responsive (n = 29), and early and late onset groups.

Results—There was a significant difference between cobalamin responsive and non-responsive groups in severity, survival, and incidence of neurological sequelae. Cobalamin responsive patients had mild disease, irrespective of age at presentation, their neurological complications were less severe, and they are all alive. The cobalamin non-responsive group comprised 19 early and nine late onset patients. The early onset patients had more severe disease at presentation and 14 have died; all late onset patients are alive. There was no significant difference in abnormal neurological signs, although early onset patients had a significantly reduced full scale intelligence quotient and poor cognitive outcome. In both groups, abnormal neurological signs continue to increase with age.

Conclusions—Cobalamin responsive patients have a better long term outcome. The outcome in the non-responsive patients, particularly the early onset group, remains poor and alternative treatments should therefore be considered early in this group.

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Methylmalonic acidemia is an inherited disorder of organic acid metabolism caused by a defect in the conversion of methylmalonyl-CoA to succinyl-CoA.¹ This reaction is catalysed by methylmalonyl-CoA mutase, which requires 5'-deoxyadenosylcobalamin as a co-factor. Patients with isolated methylmalonic acidemia may have a defect in the apoenzyme causing reduced (mut⁻) or absent (mut⁰) activity, or a defect in the synthesis of

5'-deoxyadenosylcobalamin (cblA or cblB).² Those with a defect in synthesis of adenosylcobalamin often respond to treatment with high doses of cobalamin with a reduction in the excretion of methylmalonic acid. Defects in cobalamin metabolism that affect the synthesis of both deoxyadenosyl- and methylcobalamin (cblC, cblD, and cblF) are characterised by methylmalonic acidemia and homocystinemia. These are not considered further here.

Patients with isolated methylmalonic acidemia commonly present in the first year of life with recurrent episodes of vomiting, failure to thrive, muscular hypotonia, and encephalopathy. Patients with the mut⁰ defect tend to present in the first month of life,³ while those with the other defects tend to present later. The early recognition and treatment of methylmalonic acidemia may have resulted in improved survival but there are long term sequelae. These include learning difficulties,⁴ the development of movement disorders such as acute pyramidal and extrapyramidal syndromes,⁵⁻⁸ and chronic renal failure.⁹⁻¹⁰

The long term outlook may also depend on the nature of the defect. However, biochemical markers such as plasma and urinary methylmalonate concentrations are highly variable and do not predict the outcome accurately. Even complementation group does not always predict the response to cobalamin.³ In general, patients with cblA defects usually respond to pharmacological doses of cobalamin and appear to do well.³⁻¹¹ Patients with no mutase activity (mut⁰) do not do well, and those with mut⁻ and cblB are in between.³⁻¹¹ However, these studies relied on a response to a questionnaire from physicians who referred cell lines for complementation analysis and therefore may have an inherent bias. Two other cross sectional studies about the outcome of methylmalonic acidemia have been published, but neither provided details of neurological findings.¹⁰⁻¹²

We studied the survival and neurological sequelae of methylmalonic acidemia and have found that these are determined largely by cobalamin responsiveness and the time of onset of symptoms.

Methods

All patients (n = 35) with methylmalonic acidemia who were seen and treated at Great

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Table 1 Summary of the neurological outcome of patients with methylmalonic acidemia

		Cobalamin non-responsive	
	Cobalamin responsive	Early onset	Late onset
Illness severity			
Hyperammonaemia at presentation	1/6	9/20	1/9
Severity score, median (≥ 95% CI*)	1 (1 to 2)	6 (5 to 7)	4 (1 to 6)
Neurological outcome			
Delayed early development‡	2/6	14/18	3/9
Full scale IQ, median (≥95% CI)	100 (77 to 102)	75 (65 to 84)	101 (83 to 125)
Abnormal neurological signs	2/6 1 spastic diplegia 1 dyspraxia	7/18 1 spastic terापaresis 1 dyspraxia 4 dystonia 1 complex‡	6/9 4 dyspraxia 1 dystonia 1 complex‡
Abnormal neuroimaging	1/3 1 pallidal LD	9/13 2 pallidal LD 3 hemispheric LD 4 cortical atrophy	2/6 2 pallidal LD

* $\geq$ 95% confidence interval for the median; †see text for details; ‡younger than 2 years.
LD, low density.

Ormond Street Hospital for Children in London, UK between 1970 and 1996 were studied. The diagnosis was established by the continuing profound increase in urinary methylmalonate and methylcitrate, and raised methylmalonate in the blood, with normal plasma vitamin B-12 concentrations and no detectable plasma homocystine. In most patients the diagnosis was confirmed by enzyme studies on cultured skin fibroblasts. Once the diagnosis was made, all patients were treated with a low protein diet and were subsequently given a trial of intramuscular injections of cyanocobalamin or hydroxycobalamin, 1 mg daily for five days. The response to this was assessed by urinary methylmalonate measurements, and in the responsive patients (a consistent decrease in urinary methylmalonate excretion of 50% or more) cobalamin injections were continued.

All living patients under the age of 16 were recalled for detailed examination by a paediatric neurologist and for psychometric testing. The case notes of those patients who had died before assessment ($n = 14$) and those who did not attend for reassessment ($n = 4$) were reviewed in detail and we recorded neurological complications, measured intelligence quotient (IQ), and age at death. Psychometric testing was carried out using the WISC III or the British ability scales. Early development (before the age of 2 years) was assessed using either the Bayley scales of infant development or the Ruth Griffiths developmental scales; development was termed delayed if the general quotient was less than 70 for either scale. Neuroimaging was performed when clinically indicated (usually when abnormal neurological signs were found). Early studies used cranial computed tomography while later studies used magnetic resonance imaging.

A clinical severity score was calculated for each patient. This score is based on IQ, appetite, protein tolerance, growth, and number of episodes of metabolic decompensation.⁹ The maximum score obtainable is 9 (severe disease) and the minimum 0 (mild disease).

Urinary organic acids were analysed by gas chromatography, then high performance liquid chromatography, and more recently, by gas chromatography mass spectroscopy.¹³

DATA ANALYSIS

Survival curves were estimated using the product limit method of Kaplan and Meier and were compared using the logrank test. The hazard plot was constructed using the cumulative hazard ratio (that is, the relative risk of an end point occurring at any given time), calculated using the proportional hazards model,¹⁴ at time points where abnormal neurological signs were noted to be present. Because of small numbers, comparisons between groups were made using non-parametric methods (Mann-Whitney U test or Kruskal-Wallis analysis of variance with continuous data, and Fisher's exact test for those with categorical data). All statistical calculations were made using SPSS for Windows software.

Results

Patients were divided into groups based on responsiveness to cobalamin, and age at presentation. Those who presented in the first month of life were classified as early onset, and those who presented after the first month were classified as late onset. There were 22 early onset patients, of whom two were cobalamin responsive, and 13 late onset patients, of whom four were cobalamin responsive.

The median date of diagnosis was 1985. Subsequently, some patients with cobalamin non-responsive methylmalonic acidemia were treated with carnitine. There was no difference in illness severity, survival, or neurological complications between patients diagnosed before ($n = 17$) and those diagnosed after 1985, nor between those treated with carnitine ($n = 13$) and those not treated with carnitine.

ILLNESS SEVERITY

There was a significant difference between cobalamin responsive and non-responsive patients in the severity of the illness. Cobalamin non-responsive patients had a greater severity

Figure 1 Magnetic resonance images of the brain in a girl with late onset methylmalonic acidemia following an episode of metabolic decompensation complicated by the development of dystonia. (A) axial and (B) coronal T2 weighted images showing high signal confined to the globus pallidus; (C) sagittal T1 weighted image showing low signal from the globus pallidus (arrows).

score (median difference (95% confidence limits) of 3.6 (2.0 to 5.2), $p < 0.001$) and more encephalopathic episodes (median difference 4.4 (2.4 to 6.3), $p < 0.001$).

All six cobalamin responsive patients had mild disease, and its severity did not depend on age at presentation. Two patients presented following an episode of metabolic decompensation that required ventilatory support. No patient subsequently decompensated. All patients had good metabolic control and tolerated a normal diet, and all had a low severity score.

The cobalamin non-responsive patients included 20 early onset (13 female) and nine late onset patients (four female). The early onset patients had a more severe illness at presentation, with episodes of severe acidosis, hyperammonaemia (up to 1800 μM), and six collapsed, requiring intensive care and ventilatory support. Acidosis was persistent in two

infants who died during the first week of life. Most late onset patients presented in their first year with either an episode of metabolic decompensation and subsequent developmental delay, or feeding difficulties with failure to thrive and vomiting. Two patients who had an affected sibling in the early onset group were diagnosed antenatally. These and two others were treated prospectively from birth. Despite this, all four children died; the two longer survivors (three and seven years) both had poor growth and high severity scores.

The cobalamin non-responsive group suffered recurrent episodes of metabolic encephalopathy and some were admitted frequently for management of acidosis and dehydration. Anorexia and feeding difficulties were seen in 25 of 27 of cobalamin non-responsive patients. All patients in the early onset group, and five of nine in the late onset group required partial or full nasogastric or gastrostomy feeding. There

Figure 2 Hazard plot showing the cumulative hazard of developing abnormal neurological signs with age in cobalamin non-responsive methylmalonic acidemia. There is no significant difference between the early onset group (dashed line) and the late onset group (solid line). Crosses show censored patients.

was no significant difference between the groups with regards to protein intake, which varied between 1.0 and 1.8 g/kg/day. One third of the cobalamin non-responsive patients had poor growth with weight and height below the third centile.

SURVIVAL

Survival differed significantly between the cobalamin responsive and non-responsive patients and, in the latter group, between the early and late onset presenters. The cobalamin responsive patients and the late onset non-responsive patients are all alive. In contrast, 14 patients in the early onset cobalamin non-responsive group have died. The median survival (95% confidence limits) of this group was 6.4 years (3.6 to 9.1). Six of the early onset non-responsive patients died in the first year of life and eight died between 15 months and 7 years of age. Two early onset patients received an orthotopic liver transplant at the age of 8 and 9 months, respectively. One died 24 hours after the procedure from cardiovascular instability and persistent metabolic acidosis. The other developed a movement disorder postoperatively and is developmentally delayed. She has severe anorexia and several complications related to the transplant, including an episode of acute rejection and chronic renal disease. In the late onset group one patient received a successful combined liver and kidney transplant at the age of 13½ years because of end stage renal failure. More than one year later he remains well on a normal diet.

NEUROLOGICAL OUTCOME

Table 1 summarises the neurological outcome of the patients. The cobalamin responsive group had fewer complications than the cobalamin non-responsive group (2 of 6 and 22 of 24, respectively, $p = 0.031$); also the neurological complications were less severe in the cobalamin responsive group. In the cobalamin responsive group one patient developed mild spastic diplegia and developmental delay following an encephalopathic episode at the age of 1 year, before which he had been normal. One was mildly developmentally

Key messages

- Survival and neurological outcome in methylmalonic acidemia is determined by the biochemical response to pharmacological doses of cobalamin and the age of onset of symptoms.
- Early onset, cobalamin non-responsive patients have greater disease severity, a median survival of six years, and a poorer neurological and cognitive outcome.
- Cobalamin non-responsive patients have an increased risk of developing new neurological symptoms and signs with age; these develop following episodes of acute metabolic decompensation.

delayed and had dyspraxia, autistic features, and abnormal low density in the white matter on cerebral imaging.

In the patients who were cobalamin non-responsive, there was no significant difference between the early and late onset groups with respect to the proportion with abnormal neurological signs (7 of 18 and 6 of 9, respectively, $p = 0.13$), but early onset patients had a reduced full scale IQ (median difference 26, $p = 0.03$) and a poor neurological and cognitive outcome (table 1). One patient developed a deteriorating, disabling complex movement disorder (dystonia, chorea, and supranuclear ophthalmoplegia), which followed frequent episodes of metabolic decompensation.

In contrast, patients with late onset cobalamin non-responsive disease had a better prognosis with less severe long term neurological sequelae (table 1). However, one patient developed a deteriorating complex movement disorder (dystonia, myoclonus, and pyramidal tract signs). Despite less severe neurological disease overall, cranial imaging abnormalities in the late onset group were similar to the early onset group (fig 1).

In both the early and late onset cobalamin non-responsive groups, abnormal neurological signs continued to increase with age (fig 2). In all patients, new neurological symptoms and signs developed following episodes of acute metabolic decompensation.

Discussion

Because of the poor correlation between outcome and biochemical or enzyme characteristics we have chosen to divide our patients into simple clinical groups on the basis of age at presentation and the response to pharmacological doses of cobalamin. Here we have shown that this approach is useful and of predictive value.

With improved survival, long term complications of methylmalonic acidemia have been increasingly recognised. These include neurological sequelae such as developmental arrest and regression, seizures, focal neurological signs such as spasticity, and movement disorders.^{6 10 12} Cobalamin responsive patients are generally considered a distinct group with a better prognosis.³ Here we confirm that cobalamin responsive patients

undoubtedly have a better long term prognosis with milder disease, but are still at risk of developing neurodevelopmental problems. The early onset cobalamin non-responsive patients have the worst prognosis. Despite medical treatment these patients may die, and survivors usually have serious neurological sequelae. These patients may have severe developmental delay, global learning difficulties, and dystonia. The late onset cobalamin non-responsive patients have an intermediate prognosis, with improved survival, but also have significant neurological abnormalities, developmental delay, and dyspraxia.

Cranial imaging findings in methylmalonic acidemia include deep cerebral hemisphere lucencies, with selective involvement of the posterior limbs of the internal capsules, and diffuse loss of brain substance.¹⁵ Bilateral globus pallidus lucencies have also been described.^{5,8} In a review of cranial imaging abnormalities in the organic acidemias, Brismar *et al* report white matter changes with delayed myelination and isolated necrosis of the globus pallidus as a common feature in patients with methylmalonic acidemia.¹⁶ In our study we report similar imaging findings in all groups, although they are more common in the early onset cobalamin non-responsive patients.

The increasing risk of neurological complications with increasing episodes of encephalopathy in the cobalamin non-responsive group suggests that encephalopathic episodes may be the cause of the neurological complications of methylmalonic acidemia. Treatment of the cobalamin responsive group prevents further episodes of encephalopathy and any neurological disability remains static. The cobalamin non-responsive group, in contrast, develops a deteriorating neurological disease with new symptoms and signs after encephalopathic episodes.

The occurrence of dystonia and the imaging findings suggest that the globus pallidus is selectively vulnerable to disordered metabolism of the propionate pathway. Similar findings have also been noted in propionic acidemia.¹⁷ Methylmalonic acid can cause a secondary deficiency of cytochrome *c* oxidase and succinate dehydrogenase,^{18,19} and primary deficiencies of this enzyme also cause hypodensity of the basal ganglia.²⁰ This suggests that mitochondrial disturbance may contribute to the neurological complications. In addition, we have noted that persistently high blood lactate concentrations during metabolic decompensation carry a poor prognosis (unpublished observations). However, other mechanisms in addition to direct toxicity are also likely to play a part in the pathogenesis of the neurological complications. Episodes of acute encephalopathy may be accompanied by pronounced hypovolaemia secondary to electrolyte loss caused by methylmalonic aciduria, and this will be exacerbated by renal disease.⁹

Despite changes in treatment and better understanding of methylmalonic acidemia over the past decade, the overall outcome of these patients—particularly the early onset group—remains unchanged, disappointing, and unsatisfactory; our findings are broadly similar to those of others.¹² All cobalamin non-responsive patients are at risk of developing a progressive neurological disease. Medical treatment including diet is likely to remain the mainstay of treatment for the cobalamin non-responsive patients, but alternative treatments such as liver transplantation should be considered for the early onset patients in view of the poor prognosis. Liver transplantation is not without risk, including the development of neurological complications at the time of transplant, but nevertheless should be considered early to prevent further illness.

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