Long term follow up of patients with transcobalamin II deficiency

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Abstract
Five cases of transcobalamin II deficiency presenting to our institution were reviewed. A delay in diagnosis often led to acute deterioration. Two patients have long term neurological sequelae. Minimal treatment in these patients may be dangerous. While haematological normality may be maintained, the adequate therapeutic dose of vitamin B-12 to allow normal neurological development and function is not easily determined and damage sustained early in life may be irreversible.

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Transcobalamin II is the plasma protein which transports B-12 into cells and its deficiency was initially described in 1971. Fewer than 40 cases have been reported in the literature, with little description of long term follow up.

Methods

Haematology files were used to identify all cases of transcobalamin II deficiency. Five patients were identified.

Results

CLINICAL DETAILS

All patients were born at term with no antenatal problems. Ages at presentation were 4, 5, 43, 5, and 11 weeks respectively. The most striking presenting feature in all patients was failure to thrive (significant crossing of centile lines). Pallor and poor feeding were prominent in all patients. Patients 2 and 3 had vomiting and diarrhoea. Patient 3 had marked irritability and perianal excoriation. Patient 4 had mouth ulcers, glossitis, gum bleeding, with irritability and seizure-like episodes.

LABORATORY FINDINGS

Three patients (1, 2, 4) had a normal haemoglobin concentration for age at diagnosis. Neutropenia (neutrophil count $<1 \times 10^9/l$) occurred in four patients (1, 2, 4, 5); thrombocytopenia (platelet count $<150 \times 10^9/l$) in two (1, 4). Red cell indices were abnormal in patient 3 only (raised mean corpuscular volume). Peripheral blood film changes were variable with no morphological changes in two (1, 4). All patients had a normal serum B-12 concentration. Four patients had raised urinary methylmalonic acid (MMA). This did not correlate with severity of neurological involvement. Patient 1 was misdiagnosed as having dihydrofolate reductase deficiency on the basis of deoxyuridine suppression test. Correct diagnosis was made at 2 years of age at another institution. This case has been reported.¹ Patients 2, 3, 4, and 5 were diagnosed as transcobalamin II deficient by functional assay and low or absent immunoreactive transcobalamin II concentrations.

INITIAL PROGRESS

Three patients (1, 2, 5) rapidly deteriorated after admission with marked lethargy and inability to maintain adequate oral intake, requiring nasogastric feeding. In patients 1 and 2 the haemoglobin concentrations decreased by approximately 40 g/l over one week. Patient 1 developed absolute neutropenia, patient 2 halved his white cell count over the same period.

TREATMENT AND INITIAL RESPONSE

Therapeutic regimens have varied (table 1). Clinical and haematological response to treatment was very rapid. Vomiting ceased and feeding returned to normal within a week. All patients had rapid weight gain. Normalisation of neutrophil and platelet counts, with reticulocytosis, usually occurred within days. Four patients with normal mean corpuscular volume at diagnosis showed significant reductions within the normal range.

Patient 2 had two interruptions to treatment: at 3 years of age it was stopped for two weeks; bone marrow showed slight megaloblastic change, and treatment was recommenced. At 4 years of age, oral vitamin B-12 was given on a trial basis (1000 µg three times per week). After two months the serum B-12 concentration was greater than 2400 pmol/l and there was no urinary MMA. However, peripheral blood pancytopenia and bone marrow megaloblastosis had

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Table 1 Maintenance treatment after diagnosis: dose and frequency of cobalamin at given ages

Patient No	500 µg (times/week)		1000 µg (times/week)		
	3	1	3	2	1
1	-	-	2-16 Years	-	16 Years onwards
2*†	-	-	6 Weeks-2 years	2-3 Years	3 Years onwards
3‡	-	-	-	11 Months-5 years	5 Years onwards
4	-	-	6 Weeks onwards	-	-
5	3-4 Months	4-5 Months	-	-	5 Months onwards

*Initial treatment 1000 µg daily for one week. †Two interruptions to treatment (see text).
‡Initial treatment of 1000 µg single dose. Presumed dietary deficient, so no further treatment for one month until true diagnosis confirmed.

Table 2 Clinical and laboratory features at most recent review

	Patient No				
	1	2	3	4	5
Duration of follow up (years)	19	12	8	8	0.5
Latest haemoglobin (g/l)	160	130	151	126	124
Latest mean corpuscular volume (fL)	81	86	81	82	74
Latest Arneith count	2.67	3.21	2.53	2.44	3.15
Weight (centile)	0-25th	>97th	25-50th	50th	>50th
Current frequency B-12 (1000 µg×per week)	1	1	1	3	1
Neurological status*	Abnormal	Normal	Normal	Abnormal	Normal
Other	-	-	Tonsillitis (4×per year)	Dental abnormalities	-

*Refer to text for details.

developed and intramuscular vitamin B-12 was recommenced.

FOLLOW UP

All patients continue to be monitored at this institution. Details of their current status are shown in table 2. Two patients have long term neurological sequelae. Patient 1 is now 19 years old, has spastic quadriplegia, seizures, intellectual delay, and behavioural problems. An electroencephalogram (EEG) in 1986 showed generalised and bilateral epileptiform activity.

Patient 4 is now 9 years old. Neuropsychological testing shows that while she functions within the average range of intelligence (IQ 94), there is wide variability with subtle cognitive defects, especially in information processing and organisation, and learning difficulties involving problems with reading. Social behaviour is inhibited. An EEG at one year showed mild asymmetry of slow components without focal features. These findings are consistent with a global cerebral insult in the perinatal period.

Discussion

There have been a number of reports of normal neurological outcome.^{2,3} Apart from patient 1 in this series, there have been three other reports of patients who had long term neurological sequelae.⁴⁻⁶ All of these were pre-treated with folate before commencing vitamin B-12 treatment.

Our patient 4 has significant long term neurological deficits despite early aggressive treatment with vitamin B-12 alone. She had neurological deficits when she presented at a young age. Patient 2, who presented at the same age with rapidly increasing lethargy and received similar aggressive early treatment (then reduced to 1000 µg weekly), has a normal neurodevelopmental outcome. Patient 3 (marked irritability at diagnosis) has been maintained on once weekly vitamin B-12 with normal outcome. Patient 5 has received minimal treatment: follow up is short and so neurological outcome remains uncertain.

Hakami *et al* reported one patient receiving 1000 µg every two weeks who failed to

maintain haematological normality.⁷ Arrabel *et al* showed 1000 µg weekly maintained haematological normality but 1000 µg twice a week lessened irritability in one patient of less than 1 year of age.²

The minimum level of vitamin B-12 treatment required for normal neurological development is not known in patients with transcobalamin II deficiency. We believe that during the first year of life, when neurological development is ongoing, 1000 µg vitamin B-12 three times a week would be prudent. After this time reduction to 1000 µg vitamin B-12 weekly could be considered depending on adequate monitoring of haematological and neurological status.

Monitoring is difficult. Urinary MMA is often used, yet it failed to appear when patient 3 developed severe pancytopenia on oral vitamin B-12. Blood counts looking for cytopenias, red cell indices, and morphological changes may not be a sensitive way to detect inadequate treatment. Significant deviations from previous clinical or haematological results should prompt early assessment of bone marrow morphology.

Minimal treatment in these patients may be dangerous. While haematological normality may be maintained, the adequate therapeutic dose of vitamin B-12 to allow normal neurological development and function is not easily determined and damage sustained early in life may be irreversible.

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