The association of protein-losing enteropathy with cobalamin C defect

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Summary: We report a male infant with cobalamin C defect whose clinical course was complicated by diarrhoea suggestive of a protein-losing enteropathy, failure to thrive, macrocytosis and thrombocytopenia which resolved with hydroxocobalamin treatment. Protein-losing enteropathy has not previously been reported in association with cobalamin C defect and, if unrecognized, could cause considerable morbidity.

Cobalamin in its methylcobalamin form is a coenzyme in the remethylation of homocysteine to methionine, and as 5-deoxyadenosylcobalamin acts as a coenzyme in the conversion of L-methymalonyl-CoA to succinyl-CoA within mitochondria. Deficiencies of these two coenzymes result in the combined metabolic abnormalities of methylmalonic aciduria, homocystinuria and hypomethioninaemia (Ribes et al 1990; Fenton and Rosenberg 1995).

Cobalamin C defect (McKusick 277400) is a rare inborn error of vitamin B12 metabolism that characteristically presents in the neonatal period or early infancy with failure to thrive, developmental delay, hypotonia and haematological abnormalities including macrocytic anaemia and megaloblastosis. Onset in adolescence has been documented with impaired intellect, neurological dysfunction and psychosis (Fenton and Rosenberg 1995). In addition, a pigmentary retinopathy often develops (Mitchell et al 1980). Urinary amino and organic acid profiles will show the signature metabolites of homocystine and methylmalonic acid. The diagnosis is confirmed by complementation studies using cultured skin fibroblasts (Bartholomew et al 1988). The multisystemic nature of the condition is exemplified by the uncommon association of haemolytic uraemic syndrome and gastritis (Geraghty et al 1992; Russo et al 1992). We describe here an infant with cobalamin C defect whose initial clinical course was complicated by a severe protein-losing enteropathy. Protein-losing enteropathy, which has not been previously reported in cobalamin C defect,
may be due to temporary functional abnormalities of the upper gastrointestinal tract.

**CASE REPORT**

This boy, the only child of first-cousin Iraqi parents, was born after an uneventful pregnancy at 38 weeks gestation, and had a birth weight of only 2550 g (<10th centile). Feeds were difficult to establish because of a poor suck and he required nasogastric tube feeds for the 48 h. His discharge weight on day 8 was 2400 g. He continued to feed poorly with consequent failure to thrive, and required hospitalization at 4 weeks of age following a 3-day history of vomiting, diarrhoea and lethargy. Weight on admission was only 300 g over his birth weight. Examination revealed a poorly nourished, lethargic and hypotonic infant with hepatomegaly and peripheral oedema.

Admission investigations revealed a borderline low haemoglobin of 10.5 g/dl (normal range 10.5–13.5) and thrombocytopenia, platelet count $100 \times 10^9$/L (see Table 1). A peripheral blood film had a leukoerythroblastic picture, with macrocytes and promyelocytes. Biochemical evaluation demonstrated elevated urinary and plasma methylmalonic acid and homocystine, with low plasma methionine. Serum and red blood cell folate and vitamin $B_12$ levels were above the normal range. A presumptive diagnosis of cobalamin C deficiency was made and the patient was started on hydroxocobalamin (500 $\mu$g i.m./day), betaine (0.5 g twice a day) and folinic acid (7.5 mg twice a day). The doses were decided on the basis of our experience with other children with cobalamin C defect and other homocystinurias. A bone marrow aspirate was performed to exclude an acute promyelocytic leukaemia. This showed granulocytic hyperplasia with giant metamyelocytes and erythroid hypoplasia with dyserythropoiesis and megaloblasts.

A stool $\alpha_1$-antitrypsin level, performed because of hypoalbuminaemia (15 g/L) and persistent diarrhoea, was found to be grossly elevated, 25.5 g/kg (normal range <1.5). Liver and renal function were normal, with no proteinuria. Serological investigations excluded both a congenital or recent viral infection, and no bacterial pathogens were isolated on stool, blood or urine cultures. An endoscopy was not performed in our patient because his clinical course was very unstable, becoming complicated by severe pulmonary oedema. He required admission to the intensive care unit where he was closely monitored and treated with fluid restriction, diuretic therapy, albumin, and platelet and blood transfusions. The protein-losing enteropathy resolved rapidly with the stool $\alpha_1$-antitrypsin down to the normal range within 10 days of commencing hydroxocobalamin.

At 25 months of age the patient remains well on treatment with hydroxocobalamin, betaine and folic acid. He exhibits moderate global developmental delay. In the last 12 months he has developed a pigmentary retinopathy. Follow-up biochemistry demonstrates elevated plasma homocysteine and methylmalonic acid, suggesting incomplete correction of the biochemical defect, despite an increased dose of betaine (1.5 g/day). Owing to parental refusal to give daily intramuscular injections, he receives hydroxocobalamin 750 $\mu$g i.m. three times per week.