

Congenital isolated folic acid malabsorption

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SUMMARY We report a case of congenital isolated malabsorption of folic acid, the first in a boy. Only seven previous cases have been reported, and we discuss two aspects—namely, the tendency to infection, with evidence of impairment of both cellular and humoral immunity, and the absence of neurological disturbances.

Congenital isolated malabsorption of folate is a rare and specific disorder, causing megaloblastic anaemia in early childhood, which can be corrected by administering very high doses of folic acid orally or by parenteral administration of physiological doses. The case reported here is the first in a boy.

Two additional aspects will be emphasised: our patient (a) showed no neurologic disturbances and (b) suffered from a tendency to infections apparently due to partial immunodeficiency.

Case report

A five month old Moslem boy was admitted to hospital with recurrent infections, severe anaemia, and failure to thrive. He was the seventh child of healthy parents, who were first cousins. Two of their seven children had died during the first year of life without definite diagnosis.

The patient was born after a full term pregnancy with a weight of 3500 g. He was breast fed for one month only and then fed on SMA formula. From the fourth month of life the child began to suffer from recurrent infections, especially of the upper respiratory tract, lungs, ears, and gastrointestinal tract. On admission his general condition was very poor; he was very pale and feverish (38.2°C). He showed failure to thrive in both weight (5050 g) and height (59 cm). Bilateral otitis media and bronchopneumonia were present. On first admission, the haemoglobin was 9.0 g/dl, packed cell volume 27%, and white blood cell count 12 800/mm³, with normal differential count and mild thrombocytopenia of 100 000/mm³. Tests on urine and all other biochemical tests yielded normal results.

The most striking clinical disturbance was severe and chronic anaemia during the fifth and sixth months of life, with haemoglobin concentrations

ranging from 4.5 to 9.2 g/dl and packed cell volume between 15% and 29% and with mean corpuscular volume of 100 μ^3 . The peripheral blood smears showed macrocytosis and hypersegmentation of polymorphonuclear cells; the leucocyte count was in the range of 7000–12 000/mm³ and thrombocytes 100 000–200 000/mm³, with reticulocytes 0.2–1.0%. Coombs tests yielded negative results, and both a Motulsky test and electrophoresis of haemoglobin showed normal results. These data together with the macrocytosis found in the peripheral blood smear were compatible with a diagnosis of megaloblastic anaemia, which was confirmed by the findings of megaloblastic changes in the bone marrow.

The megaloblastic anaemia was found to be due to folic acid deficiency, as indicated by the low concentrations of folic acid in red blood cells (15–50 ng/ml, while the normal value is above 250 ng/ml) serum (<1 ng/ml, while normal is above 5 ng/ml) and cerebrospinal fluid (<1 ng/ml, while normal is 15 ng/ml). Blood concentrations of vitamin B₁₂ were 700–800 pg/ml and urine orotic acid concentration was normal too. The folates were determined by the microbiologic assay of Grossowicz *et al.*¹ using *Lactobacillus casei* as test organism. The diet of the mother during lactation and the child's diet were found to be normal; the possibility of dietary folate

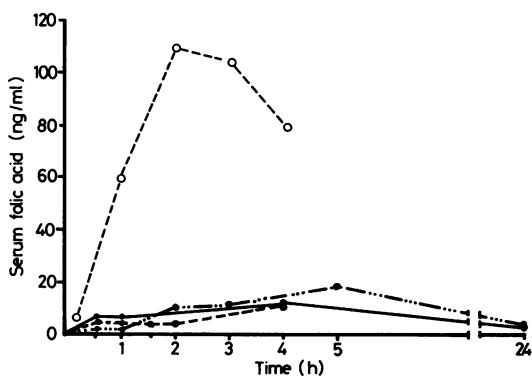


Figure Oral folic acid loading tests, assayed with *Lactobacillus casei*,¹ in the patient aged 9.5 months (● --- ● = 5 mg folic acid; ● — ● = 10 mg folic acid; ● ··· ··· ● = 10 mg folic acid) and in a control aged 9 months (○ --- ○ = 5 mg folic acid).

Table Concentrations of serum folate before and after treatment with folic acid

Body fluids	Before treatment (ng/ml)	After oral administration (ng/ml)	After intravenous administration (ng/ml)
Serum	<1.0	<1.0	1.7
Whole blood	30-50	20-90	420
Cerebrospinal fluid	1.0	1.0	4.0

deficiency was thus excluded. The diagnosis of malabsorption of folate was confirmed by the unchanged concentrations of serum and red blood cell folate after oral loading tests of 5 mg and 10 mg folic acid, respectively, as well as of 10 mg folinic acid (5-formyltetrahydrofolate), as shown in the Figure, and by reaching normal concentrations of red blood cell folate after intravenous administration of 5 mg folic acid (Table). Treatment consisted of three consecutive daily doses of 5 mg each of folic acid given intravenously and then observation for three weeks before being discharged in good condition.

A gastrointestinal evaluation made to reveal other defects of absorption in the intestine gave normal results in loading tests of glucose and fat. The sweat test yielded normal results as did tests of the pancreatic enzymes lipase, amylase, and trypsin in the duodenal juice. Small intestine biopsy examination revealed normal mucosa; *Giardia lamblia* was not found. The diagnosis of isolated malabsorption of folic acid was thus established.

In connection with the recurrent infection an immunological evaluation was performed; normal concentrations of IgG (1002 mg/100 ml) and a fairly high concentration of IgM (326 mg/100 ml) were found. IgA was undetectable. Of the family members tested (parents and three siblings), all showed normal concentrations of immunoglobulins. On the other hand, cellular immunity was decreased in both T cells (E rosettes forming and response to phytohaemagglutinin and concanavalin A) and B cells (surface Ig and response to pokeweed mitogen). C₃ complement concentration was normal (184 mg/100 ml) and immune complexes were not found.

The failure to thrive that was seen in the infant on first admission continued during the three consecutive admissions to hospital. These failures could be explained, in part at least, by the anaemia and recurrent infections, which became milder after the age of 6 months when the child's general condition improved considerably. Because of this improvement, his parents, who were not particularly cooperative, refrained from bringing the child to hospital

unless his condition worsened considerably. No psychomotor retardation was observed in the child. On the last admission, at the age of 14 months, the child arrived in a very neglected condition and with severe anaemia. He immediately received a blood transfusion but died unexpectedly of severe bilateral pneumonia, which did not respond to aggressive antibiotics and other treatment, before a regular course of treatment with parenteral folic acid could be established.

Discussion

Congenital malabsorption of folic acid is a rare and specific defect of the absorption of this vitamin from the gastrointestinal tract in the absence of malabsorption of any other nutrient.² It has been shown, in the few cases described by others, that the defect persisted after considerable doses of folate were given orally.²⁻⁴ This was also the case with our patient, who responded only to parenteral folate. All seven cases described in the published reports were girls; recently, an X linked defect was hypothesised.⁵ Our case in a boy supports the possibility of autosomal or multifactorial inheritance.

In contrast to the cases described by others,²⁻⁴ ours is unique in that there were no signs of mental retardation or any convulsive disorders. Correction of serum folate concentrations was accompanied by correction of cerebrospinal fluid folate concentrations to the normal serum:cerebrospinal fluid ratio of 1:3, which indicates that no transport defect of folate through the blood-brain barrier occurred.

The immunological work performed because of the recurrent infections revealed partial deficiency in both humoral and cellular immunity. The findings of decreased T cell function in folate deficiency were reported even though increased tendency to develop infections was not present.⁵ Corbeel *et al* described a case showing a tendency to infections.⁶ The only immune deficiency found by them, however, was a low concentration of immunoglobulins. Whether a correlation between folate deficiency and a tendency to recurrent infections is a common finding cannot be answered before a follow up of more cases of this rare disorder is undertaken. This also holds true regarding the question of whether there is more than one type of congenital folate malabsorption.

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Tachycardia and heart failure after ritual circumcision

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SUMMARY Four newborn babies developed acute heart failure a few hours after circumcision at 8 days. During this procedure, a sponge soaked in epinephrine was applied to the circumcision site and left there for several hours. Treatment was with digoxin and diuretics and signs of heart failure disappeared within 24-72 hours.

Circumcision is the operation most often performed on males in Israel and the United States.

We describe a complication of this procedure that has not hitherto received publicity.

Case reports

The four babies described here were admitted to the paediatric intensive care unit a few hours after ritual circumcision, which was performed at 8 days of age. All were born normally at term after normal pregnancies, and there were no postnatal complications.

On admission the clinical signs in each baby were similar, consisting of pallor, central cyanosis, tachycardia, tachypnoea, and grunting respirations (Table).

Their heart rates were over 200 beats per minute and the liver was enlarged in three patients. The electrocardiogram (ECG) of all four patients showed rapid sinus tachycardia with a right ventricular strain pattern. Their chest x ray films were in keeping with an acute heart failure and showed cardiac enlargement with mild pulmonary oedema. Metabolic acidosis was present in three patients. Cardiac muscle enzymes were measured in two patients and were normal. Blood lactic acid concentration was investigated in case 1 and was raised at 145 mg/dl (normal range 5.7-22.0 mg/dl). Three patients had raised serum glucose concentrations (above 6.2 mmol/l) during the first hours of admission. Echocardiography was performed in all patients and yielded normal results. Serum electrolyte concentrations were within normal limits and blood, urine, and cerebrospinal fluid cultures yielded negative results.

Table *Clinical and laboratory findings in the four babies*

Case No	Skin colour	Respiratory rate (breaths/min)	Heart rate (beats/min)	Liver edge below costal margin (cm)	Right ventricular strain	Serum cardiac enzymes (U/l)
1	Pale	80	230	6	+	
2	Mild cyanosis	120	220	2	-	CPK 30 LDH 200
3	Pale cyanosis	70	200	3	+	
4	Normal	88	230	4	+	CPK 20 LDH 250

CPK=Creatine phosphokinase (normal 5-130 U/l); LDH=Lactic dehydrogenase (normal 150-370 U/l).