Selective malabsorption of vitamin B₁₂ without proteinuria or structural renal tract anomaly

The first reports by Imerslund¹ and Gräsbeck² of children presenting with a megaloblastic anaemia due to vitamin B₁₂ deficiency but with normal gastric intrinsic factor activity (Imerslund-Gräsbeck syndrome or selective malabsorption of vitamin B₁₂) described associated proteinuria. In a review of 49 patients who had been examined for proteinuria, Visakorpi and Furuholm³ showed that 44 patients had persistent proteinuria. Urography in 40 of these patients showed a structural anomaly of the renal tract in eight. Here we describe another child with selective malabsorption of vitamin B₁₂ in whom there was no proteinuria and in whom no renal tract anomaly was shown on urography.

Case report

A 3½-year-old boy whose health had been normal until the age of 2 years presented with an 18-month history of difficult behaviour and tiring easily. He had had no abnormality of his faeces, and there was no history of consanguinity. His weight was 15 kg (between 25th and 50th percentile for his age). He was pale and irritable. There was no enlargement of the liver or spleen.

The results of preliminary investigations are shown in the table. The blood film showed anisopoikilocytosis, with oval macrocytes and neutrophil hypersegmentation. A bone marrow aspirate showed definite megaloblastic erythropoiesis and numerous giant metamyelocytes. There was increased stainable iron in the reticuloendothelial cells and in the erythroblasts. A urine sample taken without previous valine loading disclosed a methylmalonic acid concentration of 1.5 g/l. Consequently, daily physiological doses of one microgram hydroxocobalamin were given, and a reticulocyte response of 26% was noted on the fourth day. The one-hour gastric secretion after pentagastrin stimulation (6 µg/kg) was 30 ml, with pH 1.0, free acid 9 mmol (mEq)/l, total acid 16.4 mmol (mEq)/l, intrinsic factor activity before pentagastrin 17 U/ml, after pentagastrin 36 U/ml. The Schilling test showed impaired vitamin B₁₂ absorption with less than 1% excretion of a 1-µg ⁵¹Co-labelled oral dose in 24 hours, and this was uncorrected by the administration of an active preparation of hog intrinsic factor. A 24-hour urine collection showed no protein even after concentration and no abnormality on amino-acid chromatography. The results of the following investigations were normal: chest x-ray film, intravenous pyelogram, barium follow-through; serum calcium and phosphate, magnesium, and vitamin A concentrations; prothrombin time; urinary indican; and tests for ova and cysts in the faeces.

After an initial loading with hydroxocobalamin he was maintained on 1000-microgram hydroxocobalamin at three-monthly intervals. All test results became normal and his weight had risen to the 90th percentile one year after treatment was commenced.

Results of investigations

Investigation	Day 0	Day 4	Day 12	Day 19	Day 33
Haemoglobin (g/dl)	5.3	6.3	9.3	10.1	10.2
MCV (fl)	102	106	96	93	88
MCH (pg)	36.2	33.6	30.7	30.1	29.0
Reticulocytes (%)	2	26	6	2	2
Platelets ($\times 10^9$ /l)	126	160	920	475	450
Serum B ₁₂ (ng/l)	60				
Serum folate (µg/l)	13.0				
Serum iron (µmol/l)	19.5				5.1
Total iron binding capacity	58.5				51.0
Serum ferritin (µg/l)	138				
Parietal cell antibody	Neg				
Intrinsic factor antibody	Neg				
Haemoglobin F (%)	4.7		3.5		2.2
Lactate dehydrogenase (IU/l)	5160	3457		946	774
Total bilirubin (µmol/l)	16				
Serum haptoglobin (g/l)	2				

Conversion: SI to traditional units—Iron: 1 µmol/l $\approx$ 5.6 µg/100 ml. Bilirubin: 1 µmol/l $\approx$ 0.06 mg/100 ml.

Discussion

The diagnosis of specific malabsorption of vitamin B₁₂ was confirmed by the low vitamin B₁₂ concentration, the impaired absorption of vitamin B₁₂, and the failure of the Schilling test to correct with intrinsic factor; the presence of normal gastric acid and intrinsic factor; and the absence of serum parietal cell and intrinsic factor antibodies. The complete response to vitamin B₁₂; the lack of steatorrhoea; the normal barium follow-through result; serum folate, calcium, phosphate, magnesium, and vitamin A concentrations; and pro-

thrombin time rendered the possibility of a more general malabsorption syndrome (as in the case of Bell *et al**) improbable, and jejunal biopsy was considered unjustified. There was no evidence of fish-tapeworm infestation.

This patient represents a new case of selective malabsorption of B₁₂ without proteinuria. The fault is thought to be in the ileal transport of B₁₂, ileal receptors for intrinsic factor being present in the one patient so tested.⁵

¹ Imerslund, O, *Acta Paediatrica Scandinavica*, 1960, **49**, suppl 119.

² Gräsbeck, R, *et al*, *Acta Medica Scandinavica*, 1960, **167**, 289.

³ Visakorpi, J K, and Furuholm, U, *Modern Problems in Pediatrics*, 1968, **11**, 150.

⁴ Bell, M, *et al*, *Archives of Disease in Childhood*, 1973, **48**, 896.

⁵ Mackenzie, I L, *et al*, *New England Journal of Medicine*, 1972, **286**, 1021.

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Tetracycline for acne vulgaris and possible teratogenesis

Most doctors are especially cautious about administering drugs to a patient who is pregnant. Nevertheless, the non-gravid woman who is endeavouring to conceive or having unprotected intercourse is easily overlooked when it comes to such discriminative prescribing. One form of treatment that merits careful consideration in relation to this latter group of patients is that of prolonged tetracycline therapy for acne vulgaris. The problem with this medication is that if such a patient conceives she may continue tetracycline from six to eight weeks or even longer into her pregnancy.¹ We report such a case and the subsequent delivery of a malformed baby.

Case report

A 33-year-old primigravida, married for eight years without conceiving, became pregnant while taking the tetracycline, clomocycline sodium, 170-340 mg daily, and this treatment was maintained for eight weeks after her last period. The patient's menstrual cycle had sometimes been irregular, but early clinical assessments of uterine size were commensurate with a diagnosis of pregnancy dating from her last menstrual period. She had been in contact with rubella at 16 weeks, but her seronegative status, which was shown by antibody tests, was not converted by this apparent exposure.

The infant, a live boy, weighed only 1928 g at birth and showed multiple abnormalities. He had low set ears, prominent epicanthic folds, and micrognathia with mandibular hypoplasia. Deformity of both scapulae was demonstrated radiologically. Generalised contraction of the joints in flexion (arthrogryposis) was present with deficient muscle development. The fingers of both hands showed abnormal flexion of the metacarpophalangeal joints and extension of the interphalangeal joints with the second finger overlapping the third finger of the left hand. Cardiomegaly, genital hypoplasia, and severe club feet completed the anomalies. The baby died, aged 14 days, from respiratory complications. Analysis of the baby's chromosomes by gross morphology was normal, but detailed analysis by special banding techniques was not possible on the specimen received. Parental chromosome analysis was normal.

Comment

There are few reports² of malformations in the human fetus attributable to tetracycline, but consideration of several clinical and experimental observations must engender fears of possible human teratogenesis. Tetracycline is a general inhibitor of cell metabolism and has even been employed in cancer chemotherapy.

Abnormal skeletal development has occurred in chick embryos exposed to this agent and transplacentally acquired tetracycline has produced appreciable inhibition of fetal growth in rats.³ Chromosomal aberrations and a reduction in the mitotic index have been found on adding tetracycline to human lymphocyte cultures⁴ and in premature infants transient inhibition of skeletal growth has been observed during the short-term administration of tetracycline.⁵ It is several years since Carter and Wilson² reported a case of bilateral congenital deformity of the hands (absence of ring and little fingers and allied metacarpals, with webbing of the index and middle fingers) in an infant whose mother had received tetracycline early in pregnancy but their cautionary advice against the prenatal use of tetracycline seems as pertinent as ever.

Although no definite conclusions can be reached regarding the role of tetracycline in this case, the incomplete fibrous ankylosis and bone changes are of interest given the tendency for this agent to localise in developing skeletal tissues.³ Moreover, although arthrogryposis has been attributed to prolonged intrauterine pressure, possibly this disorder may originate early in embryonic life before such a factor can operate.⁵

Hence it is advisable that women who are trying to conceive or having unprotected intercourse should either not receive prolonged tetracycline treatment for acne, or should use contraception while taking it, and that the medication should be stopped as soon as possible in an unplanned pregnancy.¹

¹ Greene, G R, *New England Journal of Medicine*, 1976, **295**, 512.

² Carter, M P, and Wilson, F, *British Medical Journal*, 1962, **2**, 407.

³ Cohan, S Q, Bevelander, G, and Tiamsic, *American Journal of Diseases of Children*, 1963, **105**, 453.

⁴ Westland, M M, *Journal of the American Medical Women's Association*, 1967, **22**, 719.

⁵ Warkany, J, and Kirkpatrick, J A, jr, in *Textbook of Pediatrics*, by Nelson, Gaughan, and McKay, p 1349. Philadelphia, Saunders, 1969.

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Long-term colchicine prophylaxis in familial Mediterranean fever

Small doses of colchicine will prevent the attacks in most patients with familial Mediterranean fever (FMF, recurrent polyserositis).¹ Nevertheless, long-term administration of colchicine raises the problems of chromosomal abnormalities² and azoospermia³ which may occur and are of great importance in children and in adults wanting to have children. The present report summarises the results of treatment in 47 patients, 24 of whom have received colchicine for between one and four years.

Patients

The 47 patients with typical FMF who are included in this study had extensive routine laboratory investigations before they were started on colchicine (0.5 mg per 25 kg body weight divided in one to three daily doses) and at six-month intervals thereafter. Both men and women were advised to stop treatment three months before trying to achieve pregnancy; 26 were male and 21 female, the youngest being 9 years old and the oldest 60. Before colchicine treatment, the attacks had appeared at intervals of less than one month in 21 patients, every two to three months in 20, and at intervals longer than three months in six. Only one patient had renal amyloidosis proved by kidney biopsy.

Of the patients, 35 received colchicine in a daily dose of 1.0 mg, seven 0.5-0.75 mg, and five 1.5 mg colchicine and 1.0 g aspirin daily. Twenty-four patients (51%) received treatment for one year or more, while the total

period of observation amounted to 60 patient-years. Complete remission of symptoms was achieved in 46 cases, the remaining patient continuing to have mild attacks. Colchicine had no effect on the acute attack, and one or two, usually milder, attacks appeared in some cases during the first weeks of treatment. Transient failure due to underdosage (four cases) and to lack of compliance (eight cases) was not infrequent. Patients who voluntarily discontinued treatment after prolonged absence of symptoms had recurrence of attacks sometimes as early as two to three days after stopping the tablets. A 17-year-old girl told us that she could induce attacks by stopping treatment for 48 hours whenever she wished.

The only adverse reactions to colchicine were mild diarrhoea and abdominal pain, which occurred in three patients and disappeared after readjustment of the dose. Periodic examination of the urine, blood count, and blood chemistry showed no abnormal changes. Enhancement of growth was seen in all patients below the age of 16 who were treated for six months or more (see table). Three pregnancies occurred in the wives of three men and one in a woman while under treatment. The latter underwent transabdominal amniocentesis during the 15th week of gestation. She had received 1.0 mg colchicine daily for 46 months before conception and during the first trimester of her pregnancy. Chromosomal analysis of cultured amniotic fluid cells showed no aneuploidy or chromosomal breakage. Colchicine was discontinued and she remained symptom free during the rest of the pregnancy, but had a severe attack five days after the delivery. Her child, as well as the children of the three men, was born healthy with no congenital anomalies. Two additional men and one woman discontinued medication before the onset of pregnancies which have not yet come to term.

Effect of colchicine on growth in five young patients treated for six months or more

Case No	Age	Sex	Duration of treatment (months)	Initial height (cm)	Growth (cm)
1	16	M	12	139	12
2	16	M	12	165	7
3	14	F	12	133	7
4	11	M	6	127	5
5	12	F	6	135	7

Comment

Not only did colchicine improve FMF in our patients, but there were also no alarming untoward adverse effects. Furthermore, stunted growth, a neglected sign in FMF children, was dramatically corrected in five cases. These results are in keeping with studies of long-term colchicine prophylaxis in gouty arthritis,⁴ while the results of cytogenetic studies were no different from those in control subjects (to be published). Our observations also indicate no effect of long-term colchicine treatment on fertility, teratogenicity, or chromosomal integrity.

The effect of colchicine on amyloidosis is still unknown. The incidence of amyloidosis in FMF is controversial and figures ranging between nil and 26% have been reported. Probably amyloidosis is more frequent in Sephardic Jews with a heavy genetic load and much rarer in sporadic cases, in Ashkenazi Jews, and in Armenians. Zemer *et al* reported reduction in albuminuria in six patients with FMF receiving colchicine for six to twelve months.⁵ Since amyloidosis leads to death in an average of seven years, the effect of colchicine on its incidence is of crucial importance. The possibility of its prevention is, however, a strong argument in favour of starting long-term colchicine treatment in patients with FMF.

¹ *British Medical Journal*, 1975, **2**, 60.

² Ferreira, N R, *Lancet*, 1968, **2**, 1304.

³ Merlin, H E, *Fertility and Sterility*, 1972, **23**, 180.

⁴ Yu, T F, and Gutman, A B, *Annals of Internal Medicine*, 1961, **55**, 179.

⁵ Zemer, D, *et al*, *New England Journal of Medicine*, 1976, **244**, 170.

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