Partial villous atrophy in nutritional megaloblastic anaemia corrected by folic acid therapy

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SYNOPSIS A patient with megaloblastic anaemia due to nutritional folate deficiency is described. Partial villous atrophy and malabsorption of xylose showed progressive improvement to normal with folic acid therapy.

Evidence of temporary malabsorption has been reported in a few patients with megaloblastic anaemia due to nutritional folate deficiency (Bickers and Sekinger, 1964; Winawer, Sullivan, Herbert, and Zamcheck, 1965; Siang, England, and O'Brien, 1966; Forshaw, 1969). The small intestinal mucosa in this condition is usually histologically normal but partial villous atrophy was observed in two Indian patients in Singapore by Siang *et al* (1966) and has been suspected in patients in Britain (Forshaw, 1968). However, no instance of the correction of such mucosal damage by folic acid has been recorded. A patient with nutritional folate deficiency in whom villous atrophy of the jejunum and evidence of malabsorption were corrected by folic acid therapy is therefore reported.

Case History

H.M., a woman aged 45 years, was admitted to the Manchester Victoria Memorial Jewish Hospital under Mr R. Hartley for cholecystectomy. She complained of nausea, vomiting, and loss of weight. She said that she had been vomiting intermittently since her only pregnancy 18 years before. At first she vomited only food but in recent years fluids, even water, were also returned and she had some anorexia. Barium meal examinations had been carried out three times in the last 10 years, with negative results, and a diagnosis of nervous dyspepsia made. Two and a half years ago she went to Dar es Salaam. While there her symptoms were no worse. On return to this country, four months before admission, nausea and anorexia worsened and she 'didn't keep a meal down'. Loss of weight became marked while abroad, and she estimated that she had lost 6 stone (12.7 kg) in the last two years. She had had occasional griping

abdominal pains recently, but had never had diarrhoea. Amenorrhoea had developed two years ago but curettage and hormone therapy (preparation unknown) restored regular menses until four months before admission, when amenorrhoea recurred. She took no more hormone tablets. She had taken Nembutal 200 mg nightly for some years and continued to take these capsules throughout the whole period of follow up.

On examination no abnormality was detected other than smoothness of the tongue and pallor. Her weight was 45 kg. A cholecystogram showed a non-functioning gallbladder. The discovery of anaemia led to postponement of the operation and the patient's referral to the Haematology Department.

INVESTIGATIONS

The haemoglobin was 6.6 g/100 ml, mean corpuscular haemoglobin concentration 31%, mean cell volume 123 μ . Bone marrow showed gross megaloblastic changes and increased iron stores. The serum iron concentration was 70 μ g/100 ml and the prothrombin activity 80%. The Schilling test was normal and a simultaneous folic acid absorption test without prior saturation gave only a small serum increment, indicative of either malabsorption or severe tissue folate deficiency. The results of other tests are shown in the Table.

PROGRESS

The patient's treatment started with daily intramuscular injections of 1 mg cyanocobalamin, the first being the 'flushing' dose of the Schilling test. An improvement in general well being was soon felt. More striking was the improvement in appetite, and by the third day she was eating all the normal ward diet without vomiting. Six injections of vitamin B₁₂

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Date	Weight (kg)	Haemoglobin (g/100 ml)	Serum Folate (ng/ml)	Serum Vitamin B ₁₂ (pg/ml)	Postabsorption Serum Folate (ng/ml) (Str. faecalis)	Schilling Test Urine Excretion (%)	Serum Ca P (mg/100 ml)	Alkaline Phosphatase (KA units/100 ml)	Five-hr Urine Xylose*	Faecal Fat (g/day)	
17.10.68	45	6.3	0.2	85	20 ¹	20	8.0	4.7	12	0.4	2.6
29.10.68		8.8			62						
23.12.68	52	13.6	30.0	105	99		9.2			1.1	
4. 8.69	57	11.7	25.0	65	90	24	8.8	3.6	8	1.4	4.0

Table Patient's data on presentation and following treatment

Normal serum folate 3.0-8.0 ng/ml

¹Patient unsaturated.

*5 g dose (Santini, Sheehy, and Martinez de Jesus, 1961), normal excretion > 1.2 g.

had been given before the microbiological assays were available. Three daily intramuscular injections of 15 mg folic acid were then given and the folic acid absorption test was repeated, this time with a normal result. The initial doses of vitamin B₁₂ and folic acid (1.8 mg) produced a reticulocyte response of 26% on the ninth day. The first jejunal biopsy was taken on the 12th day and was reported as follows: 'The villi are extremely stunted or club shaped; in areas the surface is flat. The brush border is indistinct and the nuclei of the surface epithelium are generally more oval than normal. Goblet cells and Paneth cells are normal. Polymorphs are numerous in the stroma and plasma cells are present in somewhat increased numbers' (Fig. 1). A dissecting microscope was not available but the specimen was re-embedded and cut at several angles of the chuck and the villous pattern was abnormal in every section.

Fig. 1. First jejunal biopsy showing marked flattening of the mucosal surface. H & E $\times 65$.

Treatment was continued with oral folic acid, 15 mg daily, to which oral iron was added two weeks later. She was discharged from hospital on the 21st day with a haemoglobin of 10.4 g/100 ml to live in the south of England. She returned after two months for review, when both the jejunal mucosa and xylose absorption had improved. She was feeling well. The second biopsy report read: 'A few stunted villi are still present but most appear normal, as does the surface epithelium in which the nuclei are narrow and peg-like. There is no stromal inflammatory infiltrate. Adenosine triphosphatase activity is normal. Fat droplets are present within the surface epithelium and in the underlying stroma, but not particularly in the region of the basement membrane' (Fig. 2). Iron therapy was stopped and folic acid continued for another seven months when she was seen again. She was eating a good diet and had gained further weight. She did, however, complain of some nausea and upper abdominal distension for the previous 10 days. Xylose absorption was normal. The jejunal biopsy was normal: 'dissecting microscope appearance of finger-like villi with some ridges. Section shows a normal villous pattern' (Fig. 3). Each biopsy had been taken with a Watson capsule from the jejunum between 10 and 15 cm from the ligament of Treitz.

Discussion

The patient described here had severe folate deficiency. On admission she had in addition subnormal serum vitamin B₁₂ and calcium levels with malabsorption of xylose, but not of vitamin B₁₂, folic acid, or fat. Jejunal biopsy showed partial villous atrophy. With vitamin B₁₂ and folic acid therapy xylose absorption and the jejunal mucosa became normal. Ten months after the start of treatment the only detectable abnormality was a low serum vitamin B₁₂ level. Because this was subnormal nine weeks after six injections of 1 mg cyanocobalamin and continuous oral folic acid and because

Fig. 2. Biopsy after two months' treatment. Considerable improvement in villous pattern. Frozen section, H & E $\times 65$.

Fig. 3. Normal jejunal biopsy after 10 months' treatment. H & E $\times 65$.

vitamin B₁₂ absorption was normal it is unlikely that it was due either to tissue deficiency or secondary to folate deficiency; nor is it likely that the gut improvement was due to vitamin B₁₂ therapy.

The differential diagnosis includes tropical sprue, idiopathic steatorrhoea, and nutritional folate deficiency with secondary jejunal villous atrophy. The first condition is unlikely because sprue does

not occur in East Africa, although doubtful cases have been described (Harries, 1964) and because the history preceded her stay overseas. A diagnosis of idiopathic steatorrhoea, in which evidence of malabsorption may be insignificant, is less easy to refute. It has been thought that a normal biopsy taken from the area of the ligament of Treitz virtually excludes the diagnosis of adult coeliac disease (MacDonald, Dobbins, and Rubin, 1965) and it is generally accepted that when the mucosal damage in this condition varies it is worst in the proximal small bowel (Cooke, 1968). For this reason subsequent biopsies were taken as close to the same site as possible. A multiple biopsy technique (Roy-Choudhury, Cooke, Banwell, and Smits, 1967) showed that there may be considerable variation in the severity of the lesion in parts of the proximal jejunum within a few centimetres of each other, and of particular importance was the finding of one normal area in each of six patients. But, as Roy-Choudhury and his colleagues (1967) stressed, a normal biopsy in untreated adult coeliac disease was rare, being found in only three of 88 specimens from 23 new patients. In view of these figures, the failure to obtain a typical biopsy picture of subtotal villous atrophy and the sequence of improving biopsy findings without the use of a gluten-free diet were considered to be very strong evidence against a diagnosis of adult coeliac disease.

It was difficult to obtain a satisfactory dietary

history because, although the patient apparently took a reasonable diet for some years, she claimed that she vomited all foods. This could not have been strictly true but her previous history clearly indicated that she had had some gastric disturbance for many years. Psychiatric factors are frequently responsible for nutritional folate deficiency in this country. Her obvious loss of weight supported the story of more recent anorexia and, with the correction of the one abnormal absorption test, a diagnosis of nutritional folate deficiency was made.

The taking of contraceptive drugs has been associated with true jejunal atrophy (Watson and Murray, 1966) but in this patient the hormone therapy was not thought to be of aetiological significance because her condition continued to deteriorate for four months after its withdrawal.

There are a number of reports of abnormal absorption tests in folate deficiency either due to malnutrition (Bickers and Sekinger, 1964; Winawer *et al*, 1965; Siang *et al*, 1966; Forshaw, 1969) or to anticonvulsant therapy (Reynolds, Hallpike, Phillips, and Matthews, 1965). The malabsorption has been of either vitamin B₁₂ or xylose or both; in one patient there was also steatorrhoea (Siang *et al*, 1966). Tests repeated after folic acid therapy have been normal (Bickers and Sekinger, 1964; Reynolds *et al*, 1965; Forshaw, 1969). The small bowel is usually normal in nutritional folate deficiency (Gough, Read, McCarthy, and Waters, 1963) though in some patients minor cellular and histological changes have been observed (Forshaw, Moorhouse, and Harwood, 1964; Winawer *et al*, 1965; Siang *et al*, 1966; Wheby, Swanson, and Bayless, 1968) and in two Indians in Singapore (Siang *et al*, 1966) there was partial villous atrophy. Unfortunately a biopsy after treatment was not taken from any of the 11 patients with malnutrition recorded as having an abnormal jejunum.

The mucosal damage of sprue usually regresses with folic acid therapy (O'Brien and England, 1966; O'Brien, 1968). It has been suggested that this improvement indicates the aggravating effect of folate deficiency on the underlying lesion (Wheby *et al*, 1968). Bowel improvement might therefore be expected in some other patients with folate deficiency and an abnormal mucosa, though this does not occur in coeliac disease (Butterworth, 1968). Cooke, Fone, Cox, Meynell, and Gaddie (1963) reported a series of 20 cases of folic acid deficiency which are of interest in this respect. The cause of the deficiency was unknown, though two suffered from malnutrition and subsequent follow up has shown only two to have coeliac disease (Cooke, 1970). Sixteen biopsied initially had minor jejunal changes and the six biopsied again after treatment showed change

towards normality. It is reasonable to accept that such regular improvement was due to folic acid, the only therapy common to all patients.

Chanarin (1969) stresses the difficulty in differentiation between malnutrition and sprue in areas where both are rife, and where one condition may be superimposed on the other. But this case, and those with temporary malabsorption reported from elsewhere, demonstrate that a similar problem may be encountered in non-tropical areas, which would not be resolved by the obtaining of a single abnormal jejunal biopsy.

There are several possibilities why this patient had a more abnormal jejunal mucosa than others with nutritional deficiency, including such factors as the severity and duration of the deficiency, the taking of the first biopsy soon after admission to hospital, and the presence of additional but unknown aetiological agents. The last is supported by the unusual finding of a marked polymorph mucosal infiltrate and the persistently subnormal serum vitamin B₁₂ level. Correction of the mucosal damage was effected, however, by folic acid treatment.

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References

- Bickers, J. N., and Sekinger, D. J. (1964). Radioisotopes in the diagnosis of hematologic manifestations of gastrointestinal disease. *Amer. J. dig. Dis.*, **9**, 634-640.
- Butterworth, C. E., Jr. (1968). Absorption and malabsorption of dietary folate. *Amer. J. clin. Nutr.*, **21**, 1121-1127.
- Chanarin, I. (1969). *The Megaloblastic Anaemias*, p. 777. Blackwell, Oxford.
- Cooke, W. T. (1968). In *Progress in Gastroenterology*, vol. 1, edited by G. B. J. Glass, p. 307. Grune and Stratton, New York and London.
- Cooke, W. T. (1970). Personal communication.
- Cooke, W. T., Fone, D. J., Cox, E. V., Meynell, M. J., and Gaddie, (1963). Acute folic acid deficiency of unknown aetiology: temperate sprue. *Gut*, **4**, 292-298.
- Forshaw, J. (1968). Faecal fats and the coeliac syndrome. *Lancet*, **1**, 1204-1205.
- Forshaw, J. (1969). Effect of vitamin B12 and folic acid deficiency on small intestinal absorption. *J. clin. Path.*, **22**, 551-553.
- Forshaw, J., Moorhouse, E. H., and Harwood, L. (1964). Megaloblastic anaemia due to dietary deficiency. *Lancet*, **1**, 1004-1008.
- Gough, K. R., Read, A. E., McCarthy, C. F., and Waters, A. (1963). Megaloblastic anaemia due to nutritional deficiency of folic acid. *Quart. J. Med.*, **32**, 243-256.
- Harries, J. R. (1964). Tropical sprue in the African. *E. Afr. med.*, **41**, 180-187.
- MacDonald, W. C., Dobbins, W. O., and Rubin, C. E. (1965). Studies of the familial nature of celiac sprue using biopsy of the small intestine. *New Engl. J. Med.*, **272**, 448-456.
- O'Brien, W. (1968). Acute military tropical sprue in Southeast Asia. *Amer. J. clin. Nutr.*, **21**, 1007-1012.
- O'Brien, W., and England, M. W. J. (1966). Military tropical sprue from South-east Asia. *Brit. med. J.*, **2**, 1157-1162.
- Reynolds, E. H., Hallpike, J. F., Phillips, B. M., and Matthews, D. (1965). Reversible absorptive defects in anti-convulsant megaloblastic anaemia. *J. clin. Path.*, **18**, 593-598.
- Roy-Choudhury, D. C., Cooke, W. T., Banwell, J. G., and Smits, B. (1967). Multiple jejunal biopsies in adult celiac disease. *Amer. J. dig. Dis.*, **12**, 657-663.

- Santini, R., Jr., Sheehy, T. W., and Martinez-de Jesus, J. (1961). The xylose tolerance test with a five-gram dose. *Gastroenterology*, **40**, 772-781.
- Siang, S. C., England, N. W. J., and O'Brien, W. (1966). Megaloblastic anaemia in Asians in Singapore. *Trans. roy. Soc. trop. Med., Hyg.*, **60**, 668-675.
- Watson, W. C., and Murray, D. (1966). Lactase deficiency and jejunal atrophy associated with administration of conovid. *Lancet*, **1**, 65-67.
- Wheby, M. S., Swanson, V., and Bayless, T. M. (1968). Jejunal crypt cell marrow morphology in tropical sprue. *Ann. intern. Med.*, **69**, 427-434.
- Winawer, S. J., Sullivan, L. W., Herbert, V., and Zamcheck, N. (1965). The jejunal mucosa in patients with nutritional folate deficiency and megaloblastic anemia. *New Engl. J. Med.*, **272**, 892-895.

ADDENDUM

The patient was seen in May 1970 by Dr Habershon of Maidenhead. Her haemoglobin was 14.6 g/100 ml, serum folate 1.5 ng/ml and serum vitamin B₁₂ 280 pg/ml. She had no haematinics for the previous 8 months.