

MEGALOBLASTIC ANAEMIA DUE TO ANTICONVULSANT THERAPY

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Megaloblastic anaemia occurring during prolonged anticonvulsant therapy was first described by Mannheimer *et al.* in 1952. Subsequent studies (Reynolds, 1968; Klipstein, 1964; Malpas *et al.*, 1966) have established that such anaemia is due to a disturbance of folic acid metabolism and may be associated with a variety of anticonvulsants. Large-scale surveys have revealed that serum and red cell folate levels are commonly low in patients on anticonvulsant therapy, but a significant degree of anaemia is rare. According to Wintrobe (1967), less than 100 such patients have been reported. A case of severe megaloblastic anaemia complicating therapy with phenobarbitone and diphenylhydantoin sodium (phenytoin) is here described.

Case Report

A 41-year old married woman was admitted to St. Peter's Hospital, Chertsey, Surrey, in November 1970, complaining of increasing tiredness, shortness of breath and ankle oedema. Since the age of 10 she had been suffering from grand mal epilepsy which had been treated with phenobarbitone 60 mg. t.d.s. and phenytoin 100 mg. t.d.s. On this regime she had approximately one fit every two months. She was one of a pair of identical twins, and her sister had also developed epilepsy at the same age. The patient had undergone a cholecystectomy for gall stones in 1963, and had been successfully treated for iron deficiency anaemia in 1964. Menstruation had ceased in 1968. There had been no children from her 16-year marriage.

Her present symptoms had developed

insidiously. For two years she had noted increasing pallor and tiredness, but only over the last three months had she considered the possibility of physical illness. One month before admission she was given iron tablets without symptomatic improvement. Instead, she developed shortness of breath on exertion, extreme fatigue, dizziness, palpitations and ankle swelling. She also noted frequent headaches, and had increasing difficulty in thinking and remembering both recent and remote events, but did not complain of soreness of the tongue, paraesthesiae, unsteadiness in walking, gastro-intestinal disturbances, or loss of weight. Three days before admission, a doctor had given her cyanocobalamin 1000 μ g. intramuscularly, though no haematological investigations had been performed.

On examination she was a moderately obese dyspnoeic woman with striking pallor of the mucosae and skin, and there were several bruises on the extensor surfaces of the arms and shins. The tongue was normal. She had a regular full-volume pulse of 96 per minute, with a blood pressure of 120/60. The apex beat was 8 cm. to the left of the midline, and the impulse was hyperdynamic; there was an apical triple rhythm with a soft mid-systolic murmur; the jugular venous pressure was raised to 5 cm., and bilateral basal crepitations, a tender enlarged liver and sacral and ankle oedema were also observed. A firm enlarged spleen was felt 6 cm. below the left costal margin. Numerous round and flame-shaped haemorrhages and soft exudates were seen in the optic fundi. The remainder of the neurological examination was normal and in particular there was no evidence of pe-

ipheral neuropathy or cerebellar disturbances.

Immediate investigations gave the following results:

Haemoglobin 4.5 G/100 ml. (32%)

PCV 14%, MCHC 33%, MCV 115 cu.mm.

Reticulocytes 25%

White cell count 3000/cu.mm. (neutrophils 74%, eosinophils 2%)

Platelet count 65,000/cu.mm.

The blood smear showed marked anisocytosis, poikilocytosis, a few macrocytes, occasional erythroblasts, and some polysegmented neutrophil leucocytes.

Serum iron 75 μ g/100 ml. Total iron binding capacity 430 μ g/100 ml.

Serum folate assay (*Lactobacillus casei* method) 2.3 ng/ml. (normal range 6-20 ng/ml.)

Occult blood in faeces negative x 3.

Serum vitamin B₁₂ assay (*Lactobacillus leichmanii* method) more than 1000 pg/ml. (normal range 180 - 900 pg/ml.)

Vitamin B₁₂ absorption normal by the Schilling method.

Chest x-ray — slight enlargement of the heart with evidence of pulmonary congestion.

Blood urea and serum electrolyte levels, liver function tests, electrocardiogram and urine analysis were all normal.

Later investigations showed a mildly diminished red cell survival time using the 51 Cr-labelled red cell method. The 3-day stool fat content and xylose absorption test were normal.

A provisional diagnosis of megaloblastic anaemia following long-term anticonvulsant therapy was made. Marrow examination was not performed because of recent vitamin B₁₂ medication. It was decided to observe the response to this and to continue with oral iron therapy but not to add folic acid to the treatment immediately. The marked reticulocytosis and rising haemoglobin level which occurred during the first week following admission is shown in *fig. 1*. It will be seen that during the second week there was no further rise in the haemoglobin level. Treatment with folic acid 5 mg. t.d.s. was now added. This was followed by a well-marked reticulocytosis. In the first three weeks of folic acid therapy, the

haemoglobin level rose from 6.3 g/100 ml. to 10.5 g/100 ml., at which stage she was discharged from hospital. Treatment by folic acid 5 mg. t.d.s., phenobarbitone 60 mg. t.d.s., sulthiame 200 mg. q.d.s. and diazepam 10 mg. nocte was continued.

Initially, treatment was also given for congestive cardiac failure with satisfactory results. As regards anticonvulsant therapy, phenytoin was discontinued on admission to hospital and sulthiame (Osplot) in increasing doses substituted. There was a deterioration in epileptic control, three nocturnal fits occurring in the first two weeks. When folic acid treatment was started at the end of the second week, fits became even more frequent and on one occasion status epilepticus supervened but was controlled by intramuscular paraldehyde. Eventually good control was re-established using phenobarbitone 60 mg. t.d.s. and sulthiame 200 mg q.d.s. together with diazepam 10 mg. at night.

When last seen at the outpatient clinic on 24th April 1971 she was well with a haemoglobin level of g/100 ml.

Discussion

Circumstantial evidence leaves little doubt that this patient initially had a megaloblastic type of anaemia, although it is unfortunate that a diagnostic marrow examination was not performed. The peripheral blood picture which showed severe anaemia, macrocytosis, leucopenia, polysegmented neutrophil leucocytes and thrombocytopenia was characteristic, and the response to cyanocobalamin and later to folic acid therapy, in the presence of a low serum folate level, was confirmatory. The red cell survival studies excluded serious haemolytic disease as a cause of splenomegaly, and in any case considerable splenomegaly may occur in uncomplicated megaloblastic anaemia. At outpatient follow-up some weeks later there had been a marked decrease in the size of the spleen. Retinal haemorrhages may occur with severe anaemia of any type but are particularly associated with the megaloblastic anaemias and the leukaemias, and may be related to the associated

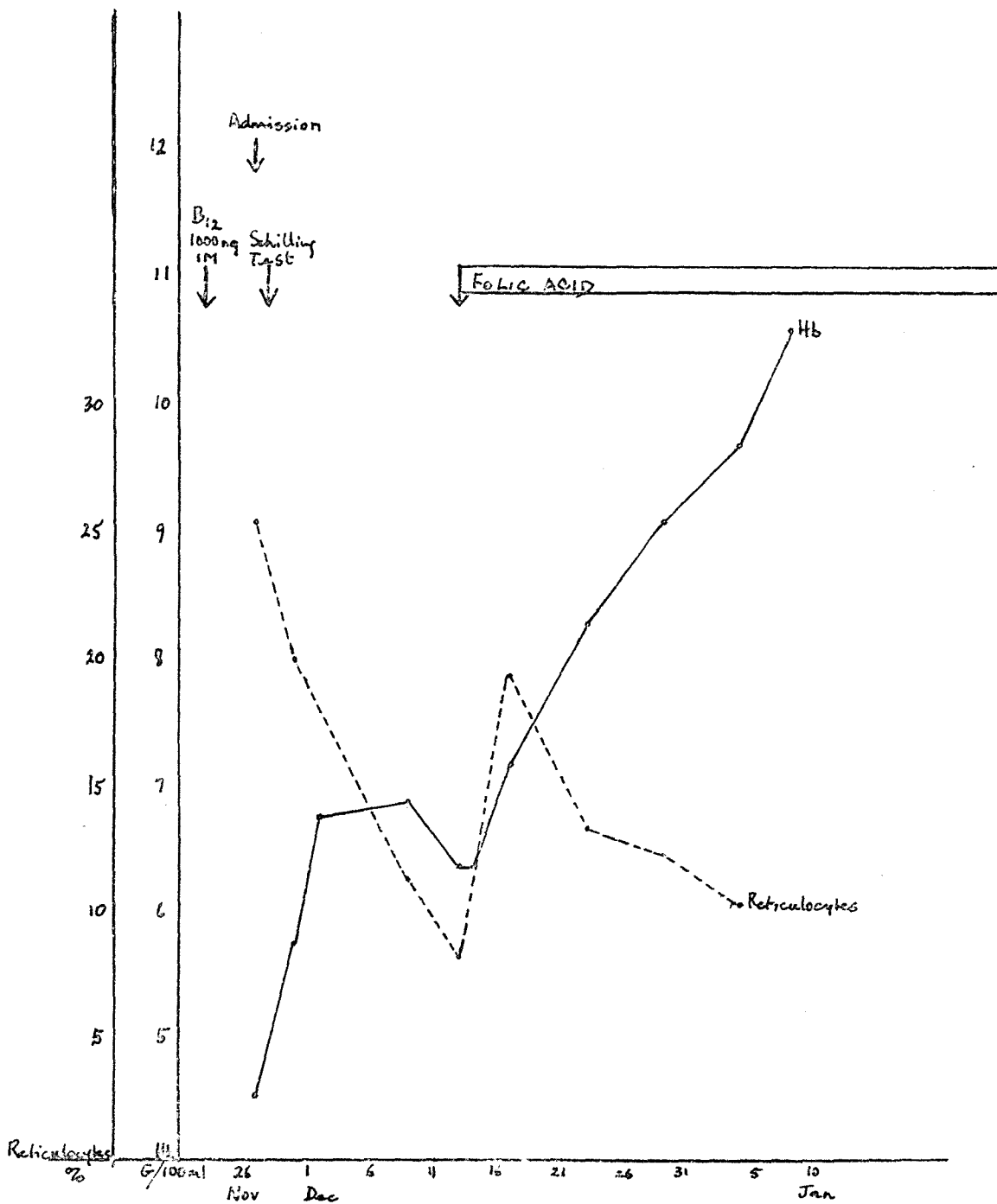


Figure 1

thrombocytopenia. The partial response to vitamin B₁₂ therapy in the presence of a normal vitamin B₁₂ absorption was consistent with folate deficiency. There was no evidence of other causes of folate deficiency such as poor nutrition, malabsorption, liver disease or severe haemolytic disease. She had never been exposed to drugs of the cytotoxic folate-antagonist group. There can be little doubt that anticonvulsant drugs, in the combination of phenobarbitone and phenytoin, were responsible for this patient's haematological picture.

Megaloblastic anaemia is a well-recognised but rare complication of long-term treatment with phenobarbitone, phenytoin and primidone. Evidence of megaloblastic haemopoiesis is commonly seen in patients undergoing anticonvulsant therapy. A macrocytic blood picture has been recorded in 11-33% of patients on anticonvulsant treatment (Malpas *et al.*, 1966; Ibbitson *et al.*, 1967; Hawkins and Meynell, 1958) and megaloblastic changes on bone marrow examination in 38% (Reynolds *et al.*, 1966). Serum vitamin B₁₂ levels are almost always in the normal range in these patients, though the levels are often lower than in control subject (Malpas *et al.*, 1966). On the other hand, evidence of a disturbance of folate metabolism is commonly found. Serum folate levels of less than 5 µg/100 ml. in up to 80% of patients on anticonvulsant therapy have been reported (Ibbitson *et al.*, 1967; Reynolds *et al.*, 1966). FIGLU tests are of no value in detecting this type of folate deficiency (Reynolds *et al.*, 1966). On this evidence it has become generally accepted that disturbed folic acid metabolism is commonly associated with prolonged anticonvulsive treatment. This induced folate deficiency rarely leads to megaloblastic anaemia, and rather more commonly according to some (Reynolds *et al.*, 1966), to such other manifestations as mental, emotional and behavioural deterioration, florid psychiatric disturbances, peripheral neuropathy, intestinal malabsorption and secondary infertility (Hughes Jones, 1968).

The mechanism of the disturbance of folic acid metabolism is obscure. It is

usually considered to be due to a competitive interaction between the anticonvulsant drug or drugs and folic acid (Klipstein, 1964; Hawkins and Meynell, 1958; Reynolds, 1970). It has also been suggested that the drugs may interfere with folate absorption (Hoffbrand and Necheles, 1968). There is no evidence that the mechanism involves liver enzyme induction, which is known to occur with some drugs, particularly phenobarbitone (Conney, 1967).

Anticonvulsant-induced anaemia invariably responds to treatment with folic acid in pharmacological doses (Wintrobe, 1967). There may also be a partial or complete response to treatment with vitamin B₁₂. This is understandable in view of the close association of folic acid and vitamin B₁₂ in basic biochemical processes. In our patient vitamin B₁₂ therapy led to a dramatic reticulocytosis but a small rise only in the haemoglobin level. A further marked and persistent rise followed the exhibition of folic acid therapy.

The institution of folic acid therapy in patients with anticonvulsant-induced folate deficiency may in turn cause certain problems. An increase in the frequency or severity of epileptic attacks may be induced, and status epilepticus has been observed (Chanarin *et al.*, 1960; Wells, 1968). It has been suggested that the anticonvulsant action of phenobarbitone and phenytoin may be at least in part due to their effect on folic acid metabolism (Reynolds *et al.*, 1966), the low serum folate level contributing to adequate control of the epilepsy. It is possible that the temporary deterioration which occurred in our patient may have been related to the initiation of folic acid therapy as well as the discontinuation of phenytoin. It is uncertain whether in patients with anticonvulsant-induced anaemia, the offending anticonvulsants should be discontinued and others substituted in addition to folic acid administration. It is usually recommended that the dose of these drugs should be reduced to the lowest compatible with adequate epileptic control, as there is some evidence that folate deficiency is related to the dose (Hawkins and Meynell, 1958) and dura-

tion (Klipstein, 1964) of anticonvulsant therapy. In our patient sulthiame, which does not appear to interfere with folic acid metabolism, was substituted for phenytoin but phenobarbitone had to be continued to control her epileptic attacks.

It is self evident that folate deficiency resulting from anticonvulsant therapy, when it causes such serious sequelae as megaloblastic anaemia or peripheral neuropathy, must be treated, but does folate deficiency *per se* require treatment? Is there a case for the routine administration of folic acid supplements in all patients on long-term anticonvulsant treatment? The answer must depend on how far the anticonvulsant action is indeed dependent on disturbed folate metabolism. It would seem that, in the present state of our knowledge, supplementary treatment with folic acid should be restricted to those patients in whom psychiatric or neurological disturbances are present, or who have developed megaloblastic anaemia. All epileptic patients on anticonvulsant therapy must therefore be monitored for neurological, psychiatric and haematological deterioration, so that folic acid supplements may immediately be given if the deterioration, which often develops insidiously, can be traced to folate deficiency.

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