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MEGALOBLASTIC ANAEMIA FOLLOWING ANTICONVULSANTS

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Two cases of megaloblastic anaemia occurring in epileptics who had been taking phenobarbitone and phenytoin were reported by Badenoch (1954), who suggested that the anticonvulsants might have played a part in the production of the anaemia. Other cases have been reported by Hawkins and Meynell (1954), Chalmers and Boheimer (1954), and Rhind and Varadi (1954).

In April, 1954, we first encountered a megaloblastic anaemia in a patient who had been receiving phenytoin and phenobarbitone. In the absence of any obvious cause we speculated whether anticonvulsant drugs could have had any causative relationship. Our suspicions were strengthened when in July a further epileptic patient under our care developed a megaloblastic anaemia which had no obvious cause. The cases reported recently, together with the cases we now record, seem to indicate that megaloblastic anaemia may arise after the prolonged use of anticonvulsant drugs, and that this anaemia is probably due to phenytoin.

Case 1

A man aged 28 was admitted to Prestwich Hospital with an epileptic psychosis in August, 1952. He had suffered from major and minor fits for seven years and had been taking both phenytoin and phenobarbitone for at least eighteen months. At the time his anaemia was detected he was taking phenytoin 1½ gr. (100 mg.), and phenobarbitone, ¾ gr. (50 mg.), thrice daily. He was a good eater and was on a full mixed diet. There was no history of steatorrhoea.

On April 23, 1954, he was noted to be pale and he complained of weakness. Physical examination revealed nothing beyond pallor of skin and mucous membranes and a loud apical systolic murmur. A blood count showed: haemoglobin, 50%; red cells, 2,660,000 per c.mm.; white cells, 6,800 per c.mm. (polymorphs 48%, lymphocytes 50%, monocytes 2%). Anisocytosis and poikilocytosis were present. A fractional test meal revealed a small quantity of free acid. Sternal marrow puncture revealed megaloblastic erythropoiesis, the predominant cells being early and intermediate megaloblasts. The white-cell series showed early forms, some of which were larger than normal.

On May 4 vitamin B_{12} was started (100 μg. daily), but in spite of this his blood picture continued to deteriorate and there was no reticulocyte response. By May 10 the blood count was: haemoglobin, 25%; red cells, 1,800,000 per c.mm.; white cells, 3,200 per c.mm.; and reticulocytes, 3%. His physical condition was unaltered. He had a smooth tongue but no active glossitis, a loud apical systolic murmur, and high pulse pressure (B.P. 110/50). There was no evidence of subacute combined degeneration of the cord or any clinical evidence of steatorrhoea or liver disease.

On May 10 he was put on oral folic acid, 5 mg. four times a day. On the 11th his reticulocytes were 5%, and by the 13th they had reached 8%. In addition to folic acid, 20 mg. daily, he received a crude liver preparation ("hepatex T," 4 ml. daily) from May 11 to 13. Otherwise he was maintained solely on folic acid.

On the 13th he was transferred to the Manchester Royal Infirmary under the care of Dr. J. F. Wilkinson. His reticulocytes reached a peak of over 30%, and on his return to Prestwich Hospital on June 2 his haemoglobin had reached 70%. By July 9 the blood count showed: haemoglobin, 90%; red cells, 5,000,000 per c.mm.; white cells, 13,600 (normal differential).

He was discharged home in August, his mental state having improved. He remained on phenytoin and phenobarbitone throughout his illness, and at the time of discharge was taking folic acid, 20 mg. daily.

Case 2

A 26-year-old male epileptic had suffered from epilepsy following a head injury at the age of 5 which had left him with a left hemiparesis. He was also suffering from an epileptic psychosis. He had been on phenobarbitone and phenytoin since 1950. In May, 1954, he was put on to primidone, 0.25 g. thrice daily, in addition to phenytoin, 1½ gr. (100 mg.), and phenobarbitone, ½ gr. (32 mg.), thrice daily to obtain better control of his fits. He was a good eater and was on a full mixed diet. There was no history of steatorrhoea.

Physical examination on August 24, 1954, revealed intense pallor, a left hemiparesis, an apical systolic murmur, and a blood pressure of 140/70 mm. Hg. He had mild hypertrophy of the gums but no significant glossitis. There was no evidence of subacute combined degeneration of the cord or any clinical evidence of steatorrhoea or liver disease. A blood count showed: haemoglobin, 28%; red cells, 1,620,000 per c.mm., white cells, 3,600 per c.mm. (polymorphs 31%, lymphocytes 64%, monocytes 3%, eosinophils 3%). Anisocytosis, poikilocytosis, punctate basophilia, Howell-Jolly bodies, and Cabot rings were obvious in the blood film. Sternal marrow puncture showed a megaloblastic marrow, early and intermediate megaloblasts predominating. No abnormality was noted in the white-cell series.

A fractional test meal with histamine showed free acid present. There were no fat globules in the faeces, and faecal-fat estimation showed total fat 28%, with a normal split/unsplit ratio. The glucose-tolerance test showed normal

absorption of glucose (fasting blood sugar, 85 mg. per 100 ml.; 30 minutes, 150 mg.; 60 minutes, 170 mg.; 90 minutes, 140 mg.; 120 minutes, 80 mg.). Liver-function tests were normal (serum bilirubin, 0.4 mg. per 100 ml.; serum alkaline phosphatase, 7.5 King-Armstrong units; thymol turbidity, 2 units; thymol flocculation, 0; colloidal gold, 0).

On August 25 he was started on vitamin B_{12} (100 μg. intramuscularly daily). By the 28th he had still shown no reticulocyte response (reticulocytes remaining stationary at 1%). As the blood picture was deteriorating (haemoglobin, 24%; red cells, 1,300,000 per c.mm. on the 28th) and he was having occasional major fits, he was started on folic acid, 10 mg. twice daily.

On August 30 the reticulocytes were 3%, but on the 31st they rose to 12%. By September 2 a reticulocyte response of 30% had been achieved. The blood picture improved rapidly until on October 12 it showed: haemoglobin, 90%; red cells, 4,980,000 per c.mm.; white cells, 7,800 per c.mm. (normal differential count). The patient is now in good general health and is being maintained on folic acid, 20 mg. daily. He has continued on phenytoin and phenobarbitone throughout, primidone having been discontinued when his anaemia was first noted.

Discussion

Megaloblastic erythropoiesis is found in pernicious anaemia, the sprue syndrome, abnormalities of the gastro-intestinal tract, nutritional deficiency, diphyllobothrium infestation, and, rarely, in liver disease. Recently, megaloblastic anaemia has been reported in patients who had been receiving anticonvulsants (Badenoch, 1954; Hawkins and Meynell, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954).

Our two cases were encountered among the epileptic patients in a large mental hospital. The type of patient restricted full investigation, but in both cases the well-known causes of megaloblastic anaemia did not seem to be present. Free acid was found in the gastric juice, there was no evidence of nutritional deficiency or of steatorrhoea or liver disease, and there was nothing to suggest organic disease or previous surgical intervention in the gastro-intestinal tract. Both cases responded well to folic acid, but the clinical impression was that vitamin B_{12} was ineffective.

In Case 1 no reticulocyte response was obtained after six days' treatment with vitamin B_{12}. In Case 2 there was no reticulocyte response five days after commencing vitamin B_{12}, although a response appeared on the sixth day (three days after the start of folic acid treatment). In both cases a good reticulocytosis followed the use of folic acid, and with this drug alone the blood picture was restored to normal and maintained at this level. Both cases had been on phenytoin and phenobarbitone for a period of years, and both continued to receive these drugs during their illness.

Vitamin B_{12} resistance has been reported in all the other cases except one of those reported by Badenoch (1954). Folic acid produced a favourable response in the other recorded cases.

The mechanism of this type of anaemia is obscure. There are numerous instances of the effects of the hydantoins, particularly methoin, upon bone marrow, but only agranulocytosis and aplastic anaemia have been reported in the past (Jones, 1951; MacArthur, 1952). Phenobarbitone rarely causes marrow damage, although a few cases of agranulocytosis have been recorded (Watkins, 1933). Primidone was given to one of our cases, and Chalmers and Boheimer had one of their patients on the drug. Serious blood dyscrasias, however, do not seem to have been recorded in trials so far with this drug, though the fact that it is a dione and a relatively new addition to therapeutics suggests that we may see such results in the future.

Phenytoin would appear to be responsible for the megaloblastic anaemia in these cases. It was the only drug used in the case recorded by Hawkins and Meynell, and it had been used in all other cases reported, although, in these, other drugs had been given in conjunction with phenytoin. If phenytoin is responsible it is remarkable that no previous cases of this type of anaemia associated with the drug have been recorded, for it has been in use since 1938. There is the possibility that previous cases have been dismissed as idiopathic megaloblastic anaemias and the relationship to phenytoin has not been recognized. Another possibility has been suggested by Hawkins and Meynell, to the effect that anaemia may appear only if the patient has taken the drug for a long time. Their patient had been on phenytoin for 13 years. However, most of the recorded cases were on phenytoin for much shorter periods, although the length of time on the drug has been more in the nature of years than months. A further interesting point is that, whilst the number of epileptics on phenytoin is enormous, this complication appears to be a rarity. At this hospital 75 other epileptics receiving anticonvulsant drugs have been screened so far, but none has shown any evidence of anaemia, though in age, type of epilepsy, food, and living conditions, in addition to anticonvulsant medication, they closely resemble the two recorded cases.

Hawkins and Meynell suggest that phenytoin may either affect absorption of haematopoietic factors or act as a folic acid antagonist. In only one case, that of Rhind and Varadi, has there been evidence of malabsorption, and even this was inconclusive. The normal vitamin B_{12} serum levels in those cases in which this has been determined (Badenoch, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954), and the excellent response to folic acid, suggest that this anaemia is essentially a folic acid deficiency, whatever its precise mechanism. It is extremely difficult to produce a folic acid deficiency in the experimental animal, but, in man, megaloblasts have occasionally been found in the bone marrow in cases of acute leukaemia treated by aminopterin (Stickney, 1952). Wintrobe (1951) reports that in pigs a vitamin B_{12} refractory megaloblastic anaemia can be produced, but only by reducing dietary vitamin B_{12}, excluding folic acid from the diet, and giving a folic acid antagonist in conjunction with succinylsulphathiazole. This porcine anaemia responds promptly to folic acid and resembles the anaemia in the cases on phenytoin reported here.

Whatever the mechanism, it seems essential that epileptics treated with anticonvulsants be watched for the possible advent of this anaemia. The severity of the condition and the excellent response to folic acid make this imperative. Further work will be necessary to elucidate the precise mechanism involved and to produce means of preventing this complication.

Summary

Two cases of megaloblastic anaemia which developed after the prolonged use of anticonvulsants are recorded. Both cases responded well to folic acid, and the evidence suggested that they were refractory to vitamin B_{12}. The literature is briefly reviewed and possible causative mechanisms of this anaemia are discussed.

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