MEGALOBLASTIC ANAEMIA ASSOCIATED WITH ANTICONVULSANT THERAPY

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In 1954 Badenoch described two cases of megaloblastic anaemia which developed in epileptics while under treatment with phenytoin sodium and phenobarbitone, and subsequently 12 further cases have been recorded (Hawkins and Meynell, 1954; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954; Webster, 1954; Berlyne, Levene and McGlashan, 1955; Ryan and Forshaw, 1955; Vaishnava, 1955). Six of these patients were taking phenytoin sodium only, four patients were taking phenytoin sodium and phenobarbitone, and two patients were taking primidone in addition to phenytoin sodium and phenobarbitone (Chalmers and Boheimer, 1954; Berlyne et al., 1955). It is unlikely that the anticonvulsant drugs were responsible for the anaemia in two of these patients, one of whom probably had megaloblastic anaemia of pregnancy (Vaishnava, 1955) and the other probably had pernicious anaemia (Chalmers and Boheimer, 1954). More recently Girdwood (1956) and Girdwood and Lenman (1956) have described two cases in which megaloblastic anaemia developed during treatment with primidone and phenobarbitone, and Fuld and Moorhouse (1956) reported two cases in which the anaemia developed during primidone therapy alone. One case has been reported in which a severe megaloblastic anaemia developed during treatment with large doses of amylobarbitone and quinalbarbitone (Hobson, Selwyn and Mollin, 1956).

The present report is of another patient who developed megaloblastic anaemia during treatment with phenytoin sodium and phenobarbitone, and also of the subsequent progress of two of our original patients (Ryan and Forshaw, 1955). One of the original patients, who has continued to take 2 gr. phenobarbitone daily, has now been observed for over three years since stopping vitamin B12 therapy and the anaemia has not returned. The other patient, who has continued to take 3 gr. phenobarbitone daily, relapsed eight months after stopping folic acid treatment. She responded to a second course of folic acid treatment and a relapse has not occurred during the subsequent 10 months.

Case Report

A married woman, aged 60, was admitted to Whiston Hospital in August 1955. She had been feeling tired and depressed and had been breathless on exertion for about nine months. Her diet had been poor for many years. For about 12 years she had suffered from epilepsy. At first the epileptic attacks were infrequent and she did not take any anti-convulsant drugs, but more recently the attacks became more frequent and during the last year she had been taking 2 gr. phenobarbitone and 300 mg. phenytoin sodium daily. On examination she was thin (weight 7 st. 7 lb.), there was pallor of the skin and mucous membranes, and her temperature was 100°F. The tongue and gums were normal, the spleen was not palpable and there were no abnormal neurological signs. Both a chest X-ray and a barium meal X-ray were normal.

Laboratory Investigations

R.B.Cs. 1,500,000 per cu.mm.; Hb. 46 per cent. (6.7 g. per cent.); W.B.Cs. 3,000 per cu. mm. (normal differential count); P.C.V. 18 per cent.; M.C.V. 120 cu. µ; M.C.H.C. 37 per cent.; reticulocytes 0.2 per cent. Sternal marrow contained megaloblasts. Serum bilirubin 0.8 mg. per 100 ml. Serum calcium 11 mg. per 100 ml. Glucose tolerance test showed a normal curve. No excess of faecal fat. A fractional test meal showed hypochlorhydria.

Treatment

Folic acid 50 mg. was given daily by mouth for six weeks and then 20 mg. was given daily for three months. This produced a reticulocyte response of 15 per cent. and one month after starting treatment the blood count was as follows: R.B.Cs. 3,300,000 per cu. mm.; Hb. 73 per cent. (10.78 g. per cent.). Phenytoin sodium was stopped at the time of her admission to hospital but she has continued to take 2 gr. phenobarbitone daily. In October 1956, nine months after cessation of folic acid treatment she was feeling well, her weight had risen to 8 st. 10 lb. and the blood count was: R.B.Cs. 4,200,000 per cu.mm.; Hb. 85 per cent. (12.63 g. per cent.).
Discussion

During the last six years at Whiston Hospital three of the five cases of megaloblastic anaemia in which the known causes were not evident were taking phenytoin sodium and phenobarbitone, and this incidence suggests that the association is more than coincidental. However, in one of our cases in which there was a relapse eight months after stopping the phenytoin therapy, it is unlikely that the phenytoin was the cause of the anaemia. The aetiological relationship between anticonvulsant drugs and megaloblastic anaemia cannot be certain, therefore, until more cases are seen and adequately followed up.

Nineteen of the 20 cases, which have been reported, have been associated with either phenytoin sodium or primidone therapy, and therefore both of these drugs must be suspect. On the other hand, there has been only one case reported in which the anaemia developed during treatment with barbiturates. In view of the widespread consumption of barbiturates, it is less certain that these drugs may produce a megaloblastic anaemia.

The way in which these drugs could produce a megaloblastic anaemia remains obscure. The evidence favours a disturbance of folic acid metabolism for the response to folic acid therapy has been invariably good whereas there was no response in six of the 10 cases treated initially with vitamin B₁₂. In addition, the vitamin B₁₂ serum levels and the absorption of both vitamin B₁₂ and folic acid have been shown to be normal (Badenoch, 1954; Girdwood, 1956; Girdwood and Lenman, 1956).

In view of the general structural similarity of folic acid, phenobarbitone, primidone, and phenytoin Girdwood and Lenman (1956) suggest that the last two substances may possibly interfere in enzymatic processes involving folic acid as a cofactor. On the other hand, Broquist (1955) has found that phenytoin does not inhibit the growth of Streptococcus faecalis when tested in the presence or absence of purine bases and with high or low levels of citrovorum factor, and he concludes that phenytoin is not a specific folic acid antagonist.

It is possible that the metabolic defect may occur during the stage of conversion of folic acid conjugates in the food into folic acid. If this were the case, the suggestion of Mueller and Will (1955) that vitamin B₁₂ participates in the breakdown of folic acid conjugates into folic acid, would explain the occasional efficacy of vitamin B₁₂ therapy. Further work, however, is required in order to establish that anticonvulsant drugs can produce a megaloblastic anaemia, and to elucidate their mode of action.

Summary

One further case and the subsequent progress of two previous cases of megaloblastic anaemia, associated with phenytoin sodium and phenobarbitone therapy, are described. Although it is probable that both phenytoin sodium and primidone can produce a megaloblastic anaemia, this cannot be certain until more cases have been seen. The way in which these drugs could produce a megaloblastic anaemia remains obscure, and the possible mechanisms are discussed.

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BIBLIOGRAPHY