ANTICONVULSANTS AND MEGALOBLASTIC ANAEMIA

By

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THE development of megaloblastic anaemia as a complication of anticonvulsant therapy is now well recognized, and a total of thirty cases has been recorded.

Badenoch (1) reported the first detailed studies of megaloblastic anaemia developing in epileptic patients treated with phenobarbitone and epanutin, whilst Fuld and Moorhouse (6) reported the association with primidone (Mysoline) alone. In all the cases reported, the anaemia responded to folic acid therapy, whilst anticonvulsant drugs were continued.

Girdwood and Lenman (7) drew attention to the similar chemical structure of phenobarbitone, epanutin, primidone and folic acid. They suggested that the anticonvulsant, by acting as a competitive co-inhibitor in a tissue enzyme system involving folic acid, could produce a megaloblastic anaemia. This suggestion was, to some extent, confirmed by Chanarin, Elmes and Mollin (3), who demonstrated a normal clearance rate of intravenous folic acid in a patient with megaloblastic anaemia due to primidone. In other "folic acid deficiency" anaemias, due to pregnancy or intestinal malabsorption, the rate of clearance was increased because of depleted tissue stores of folic acid in these anaemias.

The elucidation of the mechanism by which the anaemias are produced, does not explain why only a small number of patients, treated with anticonvulsants, develop this complication. Individual factors, such as diet and duration of anticonvulsant therapy, may be important. Only full reporting of all cases with this complication will allow assessment of these factors.

Two further cases of magaloblastic anaemia due to anticonvulsants are reported.

Case 1. A 24-year old female epileptic presented in a psychiatric out-patient department, with symptoms of "anxiety" and progressive increase in frequency of epileptic seizures. Anticonvulsant therapy had consisted of phenobarbitone gr. 1 twice daily for six years, with the addition of primidone 750 mg. daily during the past 2½ years. The patient's diet had been conspicuously lacking in protein and fresh vegetables, because of her poor economic circumstances. She was admitted to a psychiatric unit in a general hospital for investigation.

Physical examination was normal apart from obvious anaemia. There were no haemorrhagic manifestations or abnormal neurological findings. Laboratory investigations: R.B.C. 1·9 million per cu.mm.; Hb. 8·5 g. per 100 ml.; M.C.V. 138 c.microns. Serum vitamin B12 was 160 $\mu\mu$g./per ml.; free acid was present on gastric analysis; fat balance and liver function tests were normal. Bone marrow puncture was megaloblastic.

Oral folic acid, 10 mg. twice daily, produced complete recovery from the anaemia. Six months later, the patient was in good physical health and there had been a marked reduction in the frequency of fits.

Case 2. A 45-year old, well-nourished, male, high-grade defective epileptic had lived in an epileptic hospital from 1934–55. He was then transferred to a mental hospital because of aggressive behaviour. Anticonvulsant therapy had consisted of phenobarbitone gr. iii. and phenytoin sodium gr. iii. daily for ten years, with the addition of primidone 250 mg. daily during the last three years.

A "pyrexia of unknown origin" of T.102° F. first drew attention to the haematological abnormalities. The patient was obviously anaemic, but made no complaints. Physical examination was normal with no neurological signs or haemorrhagic manifestations. Laboratory investigations: R.B.C. 1·4 million per cu.mm.; Hb. 36 per cent.; W.B.C. 2,300 per cu.mm. (46 per cent. polymorphs); M.C.V. 130 c.microns; P.C.V. 17 per cent. Bone marrow was megaloblastic. Liver function and fat balance tests were normal. Chest X-ray and urine examinations revealed no abnormality. Repeated attempts to perform a F.G.A. failed owing to the disturbed mental state of the patient. Tubeless gastric analysis was performed with the quinium resin test (Denborough, Retief and Witts (5)). This revealed the presence of free hydrochloric acid in the stomach.

Treatment consisted of oral folic acid 10 mg. b.d. this produced a 16 per cent. reticulocyte response on the sixth day.

There had been a progressive clinical improvement in the patient's haematological condition. Six months after the commencement of folic acid treatment, the blood count showed R.B.C.s 5·3 million per cu.mm.; W.B.C.s 7,000 per cu.mm.; Hb. 100 per cent. Anticonvulsant therapy has been continued throughout at the same dosage.

Discussion

Increase in frequency of epileptic seizures was observed in both the above cases. Failure to recognize the anaemia could lead to further increases in dosage of anticonvulsant drugs in an attempt to control the epileptic seizures, and it is possible that this, in turn, would further increase the severity of the anaemia. Deaths directly related to megaloblastic anaemias due to anticonvulsant drugs have been reported by Benians and Hunter (2) and Kidd and Mollin (8).

Haemoglobin estimations were carried out on a further fifty epileptics in mental hospital, who had been treated with anticonvulsants for from three to twenty years. No other significant anaemias were discovered. An annual haemoglobin estimation is a simple method of detecting this complication of anticonvulsant therapy at an early stage.

A review of all reported cases of this type of anaemia reveals that where primidone has been incriminated the average duration of therapy has been one and a half years, whereas with phenytoin sodium this has been five years. This discrepancy could be explained by the closer structural similarity of primidone to folic acid (Dawson and Johnson (4)).

"Tubeless gastric analysis", using the quinium resin test (Denborough, Retief and Witts (5)), is a reliable method of demonstrating free acid in gastric contents. It cannot give quantitative estimates of gastric acidity, but it is useful for the detection of achlorhydria in such conditions as pernicious anaemia and gastric carcinoma. In disturbed and unco-operative patients in mental hospitals, the estimation of gastric acidity by the "tube" method may frequently be impossible. Where this investigation is of importance, the method of "tubeless gastric analysis" forms a useful alternative, requiring only the giving of resin by mouth and the collection of urine specimens.

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