Carbamazepine and folic acid in trigeminal neuralgia patients

A A Al-Musaed BDS MSc **J M Zakrzewska** MD FDSRCS **B J Bain** FRACP MRCPath
Joint Department of Maxillo-facial Surgery and Oral Medicine, Eastman Dental Hospital, 256 Gray's Inn Road, London WC1 and Department of Haematology, St Mary's Hospital Medical School, Praed Street, London W2

Keywords: trigeminal neuralgia; folic acid; macrocytosis; carbamazepine

Summary
The effect of carbamazepine monotherapy on the red cell folate level of 133 patients with trigeminal neuralgia was evaluated. The patient group had a significantly lower mean value of red cell folate levels compared with 110 controls. No significant correlation was found between the red cell folate levels and the mean cell volume or haemoglobin values in either the carbamazepine or control group. In addition no significant correlation was found between the red cell folate levels and drug dosage. Administration of folic acid supplements raised the mean value of red cell folate significantly. Dietary folate intake was assessed in 43 trigeminal neuralgia patients and 33 matched control patients and there was no significant difference between the groups. Patients taking carbamazepine should be advised on a well-balanced diet rich in folate as opposed to being given a routine prescription of folic acid.

Introduction

In recent years there has been an increased interest in the possible interplay between folic acid and anticonvulsant drugs. It has been recognized that anticonvulsants may interfere with the metabolism of folic acid with resultant megaloblastic anaemia[1,2]. Mannheimer *et al.*[3] were the first to describe megaloblastic anaemia in patients treated with phenytoin (diphenylhydantoin). The role of phenytoin, phenobarbitone and primidone in producing folic acid deficiency has been adequately documented by numerous investigators[4,5]. In addition, there have been several reports of low serum and/or red cell folate concentrations in patients on carbamazepine therapy but there are no convincing case reports of megaloblastic anaemia resulting from monotherapy with carbamazepine[6,7]. Most of the previous studies which reported folic acid deficiency were carried out in epileptic patients who were using anticonvulsants either as monotherapy or in various combinations on a long-term continuous basis. In the majority of these patients the subnormal folate concentrations were associated with minimal clinical and/or haematological abnormalities such as macrocytosis[8-10].

Shorvon in 1981[6] reported that two of 19 unselected epileptic patients had a red cell folate concentration below 150 μg/l following 1-3 years of carbamazepine therapy. A further report by Dellaportas *et al.*[11] observed that in a 2-year follow-up period only one of a group of 19 epileptic patients on carbamazepine monotherapy developed a serum folate level below 2.5 μg/l. In neither of these reports were there haematological features which could be related to the low red cell or serum folate concentration. Goggin *et al.*[7] in their study of a group of 50 epileptic patients reported a 17% incidence of a red cell folate of 120 μg/l or below. A negative correlation was reported between dose of carbamazepine and folate levels, but there was no correlation between red cell folate, duration of treatment and plasma concentrations of carbamazepine. The development of megaloblastic anaemia in patients on anticonvulsant therapy has also been ascribed to low dietary folate intake by some authors, but others have found no correlation between diet and folate levels[7,8]. The mechanisms responsible for folic acid deficiency in patients on anticonvulsant therapy remain uncertain with both malabsorption of folate and selective interference in certain pathways of folic acid metabolism having been suggested. With regard to carbamazepine there is evidence that at least the former mechanism operates[12].

In contrast to epileptics, patients who are suffering from trigeminal neuralgia tend to use anticonvulsant drugs in high doses over a long period, but on an intermittent basis. Folate levels in patients with trigeminal neuralgia who were on carbamazepine have not previously been assessed. The aim of the present study was to investigate the frequency of red cell folate deficiency in patients on carbamazepine, to establish whether any deficiency related to the dose of the drug, and to evaluate how many patients with subnormal red cell folate levels developed macrocytosis and/or megaloblastic anaemia. We also sought to determine whether macrocytosis alone could act as a predictor of low red cell folate since folate estimation is a time consuming investigation. In addition, the effect of folic acid supplementation in patients with subnormal red cell folate levels was evaluated.

It was also important to assess whether dietary folate might account for any observed low red cell folate levels as patients with trigeminal neuralgia are generally elderly and when in severe pain are unable to eat normally. Impaired intellectual function and depression in epileptic patients have been attributed to phenytoin induced folic acid deficiency[13] and have been shown to respond to folic acid therapy[14]. We did not investigate the intellectual function or mood in our mainly elderly patients as they are more complex than assessing haematological parameters. Also many patients with trigeminal neuralgia are depressed as a consequence of the severe pain they are suffering.

Correspondence to Dr Joanna Zakrzewska

0141-0768/92/
010019-04/$02.00/0

Materials and methods

Patient group

The group was selected at random among patients with trigeminal neuralgia who were coming up for their regular outpatient reviews at the oral medicine department, Eastman Dental Hospital. Patients were included in the study if they had a diagnosis of classical paroxysmal trigeminal neuralgia and had been on carbamazepine continuously for at least 3 months and had used it intermittently for the last 3 years. They had no severely debilitating diseases and liver function tests, serum vitamin B_{12} and serum ferritin levels were normal.

One hundred and thirty-three patients were assessed (50 men, 83 women) their ages ranged from 24 to 87 years (mean 60±14 years). All patients were assessed clinically for symptoms and/or signs of megaloblastic anaemia. A history of previous folic acid supplement or previous prolonged use of drugs, particularly drugs which may interfere with folate metabolism, was noted. Patients with trigeminal neuralgia alter the drug dosage frequently therefore the dosage considered was that which patients were taking at the time of investigation. It was recorded in mg/kg/day.

Control group

The control group who were matched for sex and age were drawn at random from patients of the same department. They were free of oral lesions which could interfere with their eating habits and showed normal liver function tests, serum vitamin B_{12} and serum ferritin levels.

One hundred and ten control patients were assessed (47 men, 63 women); their ages ranged from 34 to 82 years (mean 58±14).

Routine haematological investigation including haemoglobin (Hb), mean cell volume (MCV) and red cell folate (RCF) level were carried out on all patients and controls.

A subsequent group of 25 patients taking carbamazepine for trigeminal neuralgia who showed low RCF levels were given folic acid supplements in a dose of 5 mg three times a day for 2 weeks then 5 mg daily for another 2 weeks; haematological investigations were then repeated.

The haematological indices were determined on a Coulter S plus IV automated blood counter and the red cell folate levels were estimated using radioassay techniques. The results were compared with the 95% reference ranges for these tests established in our laboratory.

Dietary intake was recorded for 43 patients and 33 controls using a diet questionnaire which was completed over 3 days after the collection of the blood sample. These were analysed according to standardized diet tables looking in particular at folate content.

Results

The red cell folate levels in patients and controls are shown in Figure 1 and Hb, MCV and red cell folate values of both groups are summarized in Table 1.

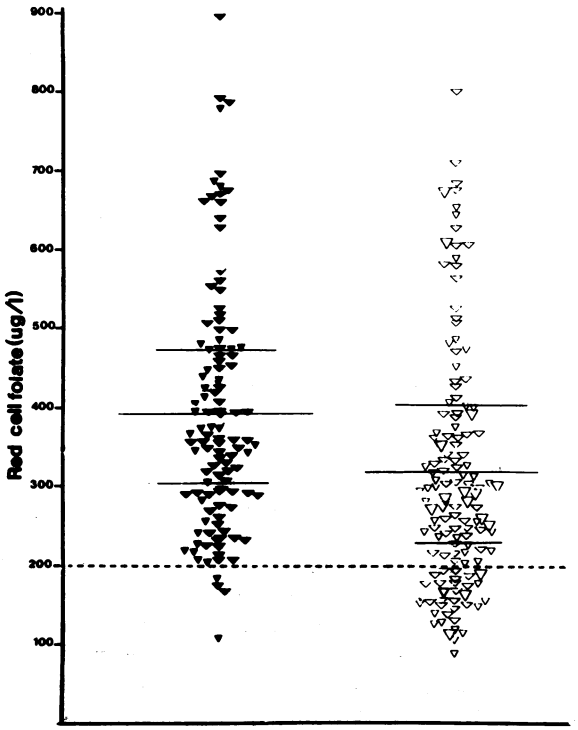

Figure 1. The red cell folate levels in 110 controls (▼) and 135 patients (▽) with trigeminal neuralgia on carbamazepine (solid lines indicate the geometric mean and 95% confidence limits; the dotted line is the lower limit of the reference range)

The patient group had a significantly lower mean value of red cell folate levels than the control group ($P<0.05$). Among the patient group 33 (24%) had red cell folate level below the lower limit of the reference range (200-800 μg/l).

Of the 133 patients only three (2%) showed MCV values exceeding the upper limit of the reference range (82-99 fl); two of them, both of whom had normal Hb concentrations, demonstrated concurrent subnormal red cell folate levels. In the third patient the red cell folate level and the Hb concentration were normal.

Three of the 33 patients with a low red cell folate (9%) showed a low Hb concentration with no other haematological abnormalities being detected.

Of 110 controls, four (4%) had subnormal red cell folate levels. Two (2%) controls had elevated MCV values but neither of them had a low red cell folate level. One control subject had a Hb concentration below normal.

No significant correlation was found ($P>0.05$) between the red cell folate levels and the MCV values in either the carbamazepine ($r=0.1137$) or control group ($r=0.0429$). Furthermore, no significant correlation was found ($r=0.168$; $P>0.05$) between the red cell folate levels and the drug dosage.

Table 1. The mean values of haemoglobin, MCV and red cell folate levels in patients and controls

	Patient group	*Control group*	*Significance of difference*
Mean haemoglobin concentration (g/dl)	13.7±1.2	13.9±1.2	>0.05
Mean MCV value (fl)	91.9±4.2	89.7±6.6	>0.05
Mean red cell folate levels (μg/l)	321.7±43.8	392.6±153.9	<0.05

Following the administration of folic acid supplements to the 25 patients, the mean value of the red cell folate levels rose dramatically in all except one patient who had a very low red cell folate prior to treatment. However, the mean MCV values and the Hb concentrations were unchanged after treatment.

Mean dietary folate intake was below the recommended daily allowance (300 μg) in both the patient and control groups (being 64.5±52.6 μg/day and 61.7±50 μg/day respectively). However, there was no significant difference ($P>0.05$) between the dietary folate intake in the two groups. Moreover, no significant correlation was found between red cell folate levels and dietary folate intake in either the patient ($r=-0.0393$) or the control ($r=0.1325$) groups.

Discussion

Patients with trigeminal neuralgia being treated with carbamazepine monotherapy were found to have significantly lower red cell folate levels than control patients. The incidence of subnormal levels was 24% compared with 4% in the control group ($P<0.05$). Two previous studies of epileptics receiving carbamazepine monotherapy found 12.2% and 17% respectively to have low folate levels[7,11]. The greater frequency of low levels which we observed may be because patients with trigeminal neuralgia tend to use higher doses of anticonvulsants than do epileptic patients. Some studies of epileptics on other anticonvulsant drugs have found a much higher incidence of low serum and/or red cell folate levels than we observed in trigeminal neuralgia patients. Frequencies as high as 53% and 59% have been reported[4,15]. This may be because many patients were receiving polytherapy. However, carbamazepine may have a less potent effect on red cell folate than phenytoin; this is supported by the greater reduction of red cell folate concentrations observed in a group of epileptics on phenytoin who were studied by the same assay and in the same laboratory as the current group of patients taking carbamazepine[16]. Goggin *et al.*[7] showed a significant negative relationship between carbamazepine dose and red cell folate levels in those patients who were on monotherapy but a similar relationship in those on phenytoin did not reach statistical significance. We did not observe any correlation between the dose of carbamazepine and red cell folate levels. The discrepancy may be attributable to the fact that epileptic patients are on constant doses of the relevant drugs while patients with trigeminal neuralgia continually change their dose regimens and are intermittent users.

Since patients with trigeminal neuralgia are often elderly and may alter their eating habits because of severe pain it could be postulated that low red cell folate levels are a consequence of poor dietary intake rather than carbamazepine therapy. Our results do not support this hypothesis. Although the trigeminal neuralgia patients had a mean folate intake considerably below the recommended daily requirements this was also true of the age-matched control patients who did not have low folate levels. Furthermore there was no correlation between red cell folate levels and dietary intake of folate in either group. It therefore appears likely that the low folate levels in the trigeminal neuralgia patients are an effect of carbamazepine therapy rather than being due to the disease itself.

It is important to establish whether low red cell folate levels in patients receiving carbamazepine for trigeminal neuralgia are likely to be associated with macrocytosis and megaloblastic anaemia and are therefore an indication for folic acid treatment.

We did not find either macrocytosis or anaemia to be more common in the patient group than in the control group and nor did red cell folate level correlate with either MCV or Hb. Three (2%) of 133 patients and two (2%) of 110 control patients had an MCV which fell above the upper limit of the reference range (82-99 fl). Two of the three macrocytic trigeminal neuralgia patients but neither of the macrocytic control patients had a concurrent low red cell folate. Only one of the five macrocytic patients was anaemic and that was a control patient. The three trigeminal neuralgia patients and two control patients having a MCV above the 'upper limit of normal' although defined as macrocytic are not necessarily abnormal since 2.5% of healthy subjects are expected to fall above the upper limit of a 95% reference range.

Mean haemoglobin concentrations did not differ between the trigeminal neuralgia and control groups. Three trigeminal neuralgia patients (2%) and one control patient (1%) had a Hb below the lower limit of normal but none of these subjects was macrocytic; as for the MCV these numbers are no greater than the percentage of healthy subjects expected to fall below the 'lower limit of normal' for Hb.

We did not consider it justified to carry out a bone marrow aspirate on either trigeminal neuralgia or control patients with only minor abnormalities of MCV or Hb so we cannot totally exclude megaloblastic erythropoiesis. However, such a possibility seems unlikely. In order to exclude megaloblastic erythropoiesis without resorting to an invasive test we carried out a study of the effect of folic acid therapy in a subsequent group of trigeminal neuralgia/carbamazepine patients with low red cell folate levels. Although the red cell folate levels rose significantly following a month's therapy there was no change in either MCV or Hb. A month's therapy should be adequate to allow detection of significant changes since, in patients with anticonvulsant-induced folic acid deficiency, a haematological response is seen within a week of starting folic acid therapy[17].

Conclusion

Until now it has been our practice to monitor red cell folate levels every 6 months in patients receiving carbamazepine for trigeminal neuralgia and to prescribe folic acid therapy when red cell folate levels are found to be low. Since the current study has not demonstrated any haematological abnormalities which can be related to the observed low red cell folate levels this may not be necessary. The administration of folic acid therapy is not without risks, particularly in the elderly, since haematological effects of concomitant vitamin B_{12} deficiency may be masked allowing neurological lesions to progress. A further longitudinal study is needed to establish whether or not megaloblastic anaemia is a risk if carbamazepine therapy is continued for a period of years without folic acid supplementation. Meanwhile in view of our findings that patients commonly have a low intake of folic acid, those taking carbamazepine should be advised on a well-balanced diet rich in folate.

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(Accepted 22 May 1991)