Folate-responsive neuropathy: report of 10 cases

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British Medical Journal, 1976, 1, 1176-1178

Summary

Ten patients with severe neurological disease that was clinically indistinguishable from subacute combined degeneration of the spinal cord were found to have normal serum vitamin B12 levels. All were folate deficient. Specific folate treatment led to significant reversal of the neuropathy. These findings indicate the need to review orthodox concepts of the role of folic acid in maintaining the integrity of the nervous system.

Introduction

Neuropathic effects of folate deficiency have been widely reported. In some studies improvement in the neuropathy has coincided with folate administration and relapse has followed cessation of treatment indicating probable cause and effect. Despite this, folate deficiency is not universally accepted as a cause of neuropathy. Our purpose is to illustrate the neuropathic consequences of folate deficiency by describing a group of 10 patients with a characteristic clinical picture, manifesting as loss of tendon reflexes (knee and ankle), impaired or absent vibration sense, and bilateral extensor plantar responses indicating postero-lateral involvement of the spinal cord. The patients were severely deficient in folate.

Patients and methods

Neuropathic findings (absent knee and ankle jerks, loss of vibration sense, and extensor plantar responses) were first noted in an 83-year-old man (case 1) referred from local authority care with a diagnosis of senile dementia because of increasing confusion and difficulty in walking. He had become doubly incontinent. In addition to the neurological findings he had extensive involvement of the left tibia with Paget’s disease. Haemoglobin was 10·6 g/dl and mean cell volume 117 fl (117 am³). Serum B12 levels were normal (340 ng/l), but serum folate concentrations were low (1 µg/l). Specific treatment with folic acid resulted in unexpected and dramatic resolution of the psychosis and incontinence, and progressive, and ultimately complete, ambulation was achieved. Further neurological examination showed that there was loss of vibration sense in the legs, but pain and temperature appreciation was retained. The clinical disorder was therefore indistinguishable from subacute combined degeneration of the spinal cord but was folate-dependent.

The demonstration of a specific neurological lesion in folate-depleted subjects that was reversed by folate treatment would provide conclusive evidence for the neuropathic consequences of folate deficiency. To this end, nine other patients (seven men, two women) with similar neurological abnormalities were identified; they were either already in continuing care or had been referred to a geriatric assessment unit. The clinical details, referral diagnosis, dementia state, mobility, and the nature of intercurrent disease in these patients are shown in Table I. Blood was withdrawn for standard haematological and biochemical measurements. On the second aliquot the serum folate and vitamin B12 levels were measured microbiologically by the Lactobacillus casei and Lactobacillus wadsworthii assays respectively. Serum samples were assayed in duplicate. Equivalval values were repeated. The coefficient of variation of replicate measurements for these assays was similar (+/- 1%).

Treatment—Since the patients’ serum B12 levels were normal, a trial of oral folic acid (10 mg three times a day) could be carried out. Drug treatment was otherwise rigidly controlled. Two patients (cases 2 and 3) initially received several doses of chlorpromazine. Except in one patient (case 2) formal rehabilitation was not attempted, nor was it required subsequently. Psychiatric intervention was not required. Since all patients were severely disabled and spontaneous improvement was improbable, any response to folic acid would be apparent clinically and could be confidently ascribed to it. Acceptable objective criteria of response would be the restoration of tendon reflexes, the recovery of posterior column sensation, and regression of the extensor plantar responses.

Vitamin B12 metabolism—Since the patients’ clinical disorder was indistinguishable from subacute combined degeneration of the spinal cord, vitamin B12 metabolism had to be demonstrably normal in these patients before the pathogenetic role of folate-deficiency in their neuropathy could be accepted. We therefore looked not only for normal serum vitamin B12 levels but also for the presence of gastric parietal cell antibodies (six cases), and we measured the gastric acid response to pentagastrin stimulation (six cases). The absorption of labelled vitamin B12 (Dicocap test) was measured in six patients, but since the

<table>
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result was not relevant to their acute management and since the test procedure requires the administration of a therapeutically significant dose of vitamin B₁₂, this confirmatory test of normal B₁₂ metabolism was carried out only when maximum clinical improvement had occurred—that is, many months after their initial presentation.

Results

Haemoglobin, mean cell volume, and vitamin B₁₂ and folate levels are shown in table II. Serum folate concentrations were grossly reduced in all patients. The expected relation between macrocytic anaemia and folate deficiency was not observed. The normal range for MCV in this laboratory is 85-96 fl (85-96 μm²). Results of tests of vitamin B₁₂ metabolism are also shown in table II. All except one patient (case 3) had at least one additional normal value for vitamin B₁₂ metabolism. The low value for the Dicopac test in case 1 was due to malabsorption; the ratio of the two isotopes excreted was, however, normal. The low serum B₁₂ value in case 9 rose quickly and spontaneously to normal (274 μg/l) with folic acid. It was thought to be due to ileal dysfunction, which can occur in severe folate deficiency. Table III shows the response of these neuropathic patients to specific folate treatment. The neuropathy was completely reversed in three patients (cases 2, 7, and 8). In two others (cases 5 and 6) the only residual abnormality was incomplete recovery of vibration sense in the legs. In three others (cases 4, 9, and 10) significant improvement occurred. Two patients (cases 1 and 3) showed no improvement in the reflex and sensory abnormalities, even after 15 months' treatment in case 1. All patients experienced an improvement in mood, and in two patients (cases 2 and 3) psychosis dramatically resolved. The improvement in psyche was discernable within two weeks of starting treatment and preceded the improvement in reflex abnormalities by many weeks, and even months.

Discussion

Unequivocal recognition of the neuropathic role of folate deficiency is essential if the serious consequences of misdiagnosing this disorder are to be avoided. Folate deficiency has been described in association with diverse neurological lesions ranging from developmental abnormalities of the nervous system in the newborn to senile dementia. In the adult, however, available evidence is consistent. Two syndromes of folate deficiency neuropathy may be recognised: an encephalopathy giving rise to a confusional state usually diagnosed as senile dementia and a myelopathy variously diagnosed as atypical multiple sclerosis or clinically as spastic paraparesis. In other reports both abnormalities have been described in the same patient. Since folate treatment is effective, cheap, and, with one proviso, devoid of toxicity an empirical trial of this agent in obscure, chronic, neurological disorders would be justified. In patients with undiagnosed myelopathy with normal serum vitamin B₁₂ levels it is mandatory.

Our investigation differed from most in that the neuropathic consequences of folate deficiency were accepted from the outset; to illustrate this thesis several patients, mainly elderly and suffering from diffuse, severe, neurological disease, were studied. Patients with clinical evidence of cord involvement (myelopathy) were selected deliberately since the differential diagnoses of this finding are few, consisting of Friedreich's ataxia; tabaresis; the neuropathic syndrome associated with occult neoplasia; and, most importantly, subacute combined degeneration of the spinal cord classically associated with vitamin B₁₂ deficiency. All were excluded by appropriate testing. Acceptable evidence of the neuropathic effects of folate deficiency was then provided by showing in folate-deficient subjects a specific neurological disorder (posterolateral spinal cord involvement) responsive to, or reversed by, folate treatment (see table III).

It is important that impediments to accepting the neuropathic consequences of folate deficiency are understood so that this damaging controversy can be finally resolved. These stem from orthodox concepts of the physiological role of vitamin B₁₂ and folic acid, on the one hand, and from complex clinical attitudes to the treatment of chronic neurological disease, on the other. The dual control of haemopoiesis by vitamin B₁₂ and folic acid is established. A similar role in maintaining the nervous system is certainly accepted only for vitamin B₁₂. Since the cellular action of both vitamins is not at all understood, a similar role for folic acid cannot be excluded. Available evidence in fact suggests that folic acid does have such a role. There is selective concentration of folic acid (X3-5) in the cerebrospinal fluid (CSF) (brain) as compared with plasma. This contrasts with vitamin B₁₂, which is present in CSF in about one-tenth of its concentration in plasma. Clinical evidence also suggests a more fundamental and ubiquitous role for folic acid in maintaining the integrity of the nervous system. It has been reported as a cause of mental retardation and, more recently, in association with a reversible (with folic acid) schizophrenic state in an adolescent girl. Comparable clinical syndromes have not yet been reported in association with vitamin B¹² deficiency.
The clinical management of patients suffering from chronic neurological disease is notoriously difficult and tends to induce an attitude of therapeutic nihilism in medical and nursing staff alike. When such a condition is diagnosed the implicit assumption of inexorable progression of the lesion is accepted, hence the failure to review the patients in this series despite the eminently treatable nature of their disorder.

A particular difficulty with the therapeutic use of folic acid is that it can precipitate subacute combined degeneration of the cord in subjects with occult or undiagnosed vitamin B₁₂ deficiency. This is not a reason for withholding folic acid in patients with obscure neurological disease, but rather underlines the need for precise diagnosis. In practice this fear of folate's toxicity is deeply entrenched in the clinical conscience and has proved a powerful disincentive to its prescription. This is all the more unfortunate since available tests permit precise diagnosis of disorders of vitamin B₁₂ metabolism. In difficult cases it would be proper to give both to affected patients. Finally, since it takes several months for folate-induced subacute combined degeneration of the cord to develop, a short-term trial (up to four weeks) of folic acid may be conducted in doubtful cases if the techniques, some of which may be esoteric, for distinguishing between the two deficiencies are not readily available to the clinician.

The diagnosis of folate deficiency poses several problems. There are no tests comparable to the Dicopac test in disorders of B₁₂, nor are there parallel markers of folate dysfunction such as antibody studies etc. At present diagnosis depends on showing low folate concentrations in serum or in the red cell. The red cell concentration would be regarded by some workers as a better index of tissue folate deficiency than the serum level. Unfortunately red cell folate values are reduced in some patients with vitamin B₁₂ deficiency and cannot be confidently used to discriminate between the two possibilities—a critical consideration in this particular study. It must be accepted that a low serum folate concentration does not necessarily indicate whole body folate deficiency, since the plasma folate compartment is labile and has a rapid turnover. In chronic or long-standing folate deficiency, however, the serum folate concentration represents a true equilibrium state, and low values indicate folate deficiency. The patients in this study were all considered to be suffering from long-standing dietary folate deficiency. The reasons for this have to be carefully elucidated but were not the main purpose of this study.

When the complex interactions between chronic folate deficiency, haemopoiesis, and neurologic function are considered several points emerge. Table II shows that there may be complete dissociation between the haematological and neurologic effects and indicates a greater vulnerability of the nervous system to long-standing folate deficiency. The important corollary to this is that a normal haemoglobin level does not exclude the diagnosis of a severe folate-dependent neuropathy. Macrocytosis is a sensitive indicator of occult folate deficiency (table II), but this effect is masked by concurrent iron deficiency, making the diagnosis even more difficult. This problem is illustrated by one of our patients (case 2), who presented with iron deficiency anaemia (nutritional). When this was corrected obvious macrocytosis of the red cells developed. It is interesting, and perhaps clinically significant, that the neurological lesion (spastic paraparesis) progressed rapidly over this same period.

We thank Professor Sir W Ferguson Anderson for his interest in this study and Dr R L C Cummings for haematological guidance. The department of audiovisual services, Stobhill General Hospital, prepared the tables.

References


Deep venous thrombosis of the legs after strokes

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Part I—Incidence and predisposing factors

Summary

Forty out of 76 patients (53%) who had suffered a cerebrovascular accident developed deep venous thrombosis of the paralysed leg, as detected with the ¹²⁵I-fibrinogen technique. A further five also had thrombosis in the non-paralysed leg. A study of many predisposing risk factors provided no help either in elucidating the cause of venous thromboembolism or in identifying patients at risk of DVT as a complication of cerebrovascular accidents.

Introduction

The observation that deep venous thrombosis (DVT) may occur in the paralysed leg of patients after cerebrovascular accidents, or strokes, is not new. In 1810 Ferriar described the clinical signs of DVT in a patient whose leg had been "previously affected by a paralytic stroke" and the necropsy appearance of a thrombus in the deep veins of a paralysed leg was clearly described by Lobstein in 1833. Despite these early observations...