

REVIEW

Benefits and risks of folic acid to the nervous system

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During three decades of neurological practice I have witnessed a remarkable change in attitudes to the benefits and risks of folic acid therapy in nervous system disorders. In the 1960s all that was known and taught was that folic acid was harmful to the nervous system, especially in precipitating or exacerbating the neurological complications of vitamin B12 deficiency. So deeply held was this view that the possibility of neuropsychological benefits from this vitamin was initially viewed with considerable scepticism.¹

During the 1970s and 1980s there was gradual and increasing recognition of the benefits of the vitamin in neuropsychiatric disorders associated with folate deficient megaloblastic anaemia.² Furthermore, the association of neurological disorders with inborn errors of folate metabolism³ and the potential for folic acid to prevent neural tube defects⁴ reinforced the importance of the vitamin in the developing brain. More contentious has been the significance of folic acid deficiency associated with neuropsychiatric disorders in the absence of anaemia which has been reported especially in some depressions and dementias, including Alzheimer's disease, commonly in elderly people.⁵ Interest in these associations, including cerebrovascular disease, has been reinforced in the 1990s by studies of blood homocysteine as a measure of functional folate deficiency.^{6,7}

Such is the new enthusiasm for the preventive potential of folic acid for neural tube defects and possibly for vascular disease that the United States FDA has authorised fortification of grains with folic acid since 1 January 1998,⁸ and similar suggestions are being made in the United Kingdom.⁹ Some of the advocates of these policies have cast doubt on or even dismissed the risks of folic acid to the nervous system.^{10,11} In 30 years we have moved from a view of all risks and no benefits to one of all benefits and little or no risks! The experience of a whole generation of physicians who painfully learned the risks of folic acid to the nervous system in the 1940s and 1950s,^{12,13} to which the risk of aggravating epilepsy was later added,^{13,14} is in danger of being overlooked, and a more balanced approach is needed.

BENEFITS**Megaloblastic anaemia**

Careful assessment shows that about two thirds of patients presenting to physicians or haematologists with megaloblastic anaemia due to either folic acid or vitamin B12 deficiency have

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nervous system complications responsive to appropriate vitamin therapy in proportion to the severity and duration of the disorder.² These manifestations of the two deficiency states, including cognitive impairment, overlap considerably but peripheral nerve and spinal cord (subacute combined degeneration) disorders are commoner with vitamin B12 deficiency and depression with folate deficiency. In 24 medical admissions with severe folate deficiency the most significant association was an organic brain syndrome, including depression, which was present in 71% compared with 31% of controls.¹⁵ Experience from the early part of the 20th century suggests that of the one third of patients with anaemia who have no neuropsychiatric disorder, most would go on to develop such complications if left untreated.¹

It has also been known since the beginning of that century that there is a poor correlation between the haematological and nervous system manifestations and that, less often, patients may present to neurologists or psychiatrists without any evidence of anaemia or macrocytosis.¹

Neuropsychiatric disorders without anaemia or macrocytosis

Clinical, biochemical, and pathological aspects

Over the past 35 years numerous studies have shown a high incidence of folate deficiency and a correlation with mental symptoms, especially depression and cognitive decline, in epileptic, psychiatric, and psychogeriatric populations.^{5–7,13,14} Most studies have utilised serum folate measurements but many have included the more reliable red cell folate, some have measured CSF folate and, more recently, plasma homocysteine. The number and quality of the psychiatric categories and ratings have varied and some have not included control groups. Nevertheless, a consistent pattern has emerged.

In epileptic patients anticonvulsant induced folate deficiency, as reflected in serum, red cell, or CSF folate concentrations were consistently correlated with various mental symptoms especially depression and cognitive impairment.^{5,14,16}

Studies of psychiatric populations showed an incidence of low serum or red cell folate between 8% and 33%, the higher figures in patients in hospital.⁵ The causes of the deficiency were mostly uncertain, but poor diet, alcohol, psychotropic drugs, and chronic illness were possible contributory factors. Folate deficiency was especially correlated with depression, a higher affective morbidity, and a poorer response to standard

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Abbreviations: SAM, S-adenosylmethionine

antidepressant treatment. Recently Bottiglieri *et al*⁷ have identified a subgroup of depressed patients with high homocysteine, low serum and CSF folate, and low CSF S-adenosylmethionine (SAM) and monoamine metabolites.

In elderly or psychogeriatric populations the incidence of folic acid deficiency is even higher⁵ but again consistently associated with depression and cognitive decline.^{5 6 17 18} Clarke *et al*⁶ found a significant association between raised homocysteine, low folate (and vitamin B12) concentrations, and cognitive decline in a case-control study in 164 patients with Alzheimer's disease, 76 of whom were neuropathologically confirmed. In a neuropathological study of 30 elderly nuns from the same environmental and nutritional background, Snowdon *et al*¹⁹ found a remarkable correlation between serum folate and cerebral atrophy in subjects with or without histologically confirmed Alzheimer's disease, more so in the former. Among 18 separate nutritional factors atrophy correlated only with folate, as reported previously in CT and neuropsychological studies.¹⁸ In a prospective population based study for 3 years of 370 healthy elderly Swedish subjects over the age of 75 years the presence of folate or vitamin B12 deficiency doubled the risk of subsequently developing Alzheimer's disease.²⁰ The same group found that episodic memory impairment in elderly people is more clearly related to folate deficiency than vitamin B12 deficiency.²¹ Furthermore, correlations between folate concentrations and measures of cognitive impairment have been reported in a community of healthy elderly subjects, most of whom had "normal" folate concentrations,²² raising questions about what is an optimal nutritional environment for the nervous system?

Folate in CSF falls significantly with age,²³ as has also been noted for serum folate and plasma homocysteine. This may contribute to the high incidence of presumed folate deficiency in elderly and psychogeriatric patients. Studies of CSF folate²⁴ and its closely related metabolite in CSF, SAM²⁵ suggest that the lowest values are in dementia, including Alzheimer's disease.

The mechanisms of the effects of folates on mood and cognitive function probably involve the numerous methylation processes in the brain, including monoamine pathways, to which methyl folate donates its methyl group via SAM.²⁶ S-adenosylmethionine also has remarkable effects on mood.²⁷ Brain concentrations of this metabolite are significantly decreased in Alzheimer's disease.²⁸ Others suggest that the impact of folate deficiency on cognitive function is related to a vascular mechanism mediated by hyperhomocysteinaemia.^{6 29} Studies of the role of folic acid in the prevention of vascular disease, including stroke, are under way.

Treatment aspects

There are no clear guidelines for the appropriate formulation, dose, or duration of folate therapy for nervous system disorders. It is recognised that the response of neuropsychiatric disorders to vitamin therapy is usually very much slower than the haematological improvement and is often incomplete, depending on the severity and duration of the disorder. This is almost certainly due to the normal rapid turnover of blood cells by contrast with the slow or non-existent turnover of adult nervous system cells.¹³

There is an active transport system for folate, in the form of methyl folate, into the nervous system and a very efficient blood-brain barrier mechanism for limiting its entry,³⁰ perhaps for reasons concerned with risks to the nervous system. Thus, very little of a 5 mg dose of folic acid, which needs to be converted to methyl folate, will enter the nervous system.

There have been no controlled trials of folate therapy in anaemic subjects, as is also true of vitamin B12 deficiency, but appropriate treatment of the anaemia is often accompanied by variable degrees of improvement of associated neuropsychiatric disorders in either deficiency state.^{1 13 31} In non-anaemic

subjects there have been controlled trials and, apart from some short term studies—that is, 3 months or less—in epileptic subjects¹⁶; the trials have all been encouraging.

A placebo controlled trial in depression utilising 15 mg daily of folic acid for 4 months showed improvement in mood and neuropsychological function.³² In a double blind placebo controlled trial 200 µg of folic acid for 1 year improved affective morbidity in lithium treated manic depressive patients.³³ Similarly, the addition of 500 µg of folic acid to fluoxetine for 10 weeks significantly improved antidepressant response, mainly in women.³⁴ In a double blind placebo controlled trial, Godfrey *et al*³⁵ utilised 15 mg of methyl folate in addition to standard psychotropic medication and reported significant and increasing clinical and social recovery of folate deficient depressed and schizophrenic groups over 6 months. Methyl folate (50 mg) was as effective as a standard antidepressant drug trazodone (100 mg daily) in elderly depressed patients with mild to moderate dementia.³⁶

In summary, the main improvements are in mood, arousal, and cognitive and social function and may continue up to 1 year or more after the start of therapy.¹⁴ There is evidence that the nervous system response is related both to the dose and the duration of treatment as well as the folate status of the patient. However, given the restricted entry of folate into the nervous system, small doses over prolonged periods may be preferable to large doses in the short term, especially in view of the risks. Clearly, however, there is a need for more clinical trials to clarify issues of formulation, dose, and duration.

Neural tube defects

There is a well documented relation between folate status and intake and the risk of neural tube defects, although most pregnant women with low folate do not have babies with neural tube defects. Intervention studies have shown that periconceptional preventive treatment with folic acid of 400 µg or higher significantly reduces the risks of such defects.^{4 9} Since 1995 young women planning pregnancies have been advised to take 400 µg of folic acid and this educational policy has significantly reduced the incidence of neural tube defects in the United Kingdom to 181 cases in 1998, although some of this reduction is due to terminations. It has been estimated that fortification of flour in the United Kingdom by 240 µg of folic acid per 100 g of flour would prevent a further 74 cases (41%).⁹ Although it is assumed that folic acid overcomes genetically determined defects in folate metabolism that interfere with normal neural tube development, the exact mechanisms are not clear. It is recognised that other factors contribute to neural tube defects and about one third are not preventable with folic acid.⁹

Inherited disorders of folate transport and metabolism

Five well established and four putative inherited disorders have been reviewed (table 1).³

These rare disorders are often associated with variable and overlapping neurological disorders, including developmental delay associated with cognitive impairment, motor and gait abnormalities, behavioural or psychiatric symptoms, seizures, subacute combined degeneration, neuropathy, signs of demyelination or failure of myelination and vascular changes on MRI or at postmortem. The age of onset of the neurological symptoms ranges from the neonatal period to early adult life.

Ogier de Baulney *et al*³⁷ have reviewed the clinical features of three separate subgroups presenting either in infancy, in late infancy and early childhood, and in late childhood or early adulthood. Usually large parenteral doses of folic acid or folic acid are required, sometimes supplemented with another methyl donor, betaine, but with more apparent improvement in young adults than in infants or young children, some of whom are unresponsive.³⁷

Table 1

Inherited disorders of folate transport and metabolism ³ :	
Definite	
Methylene-H4 folate reductase deficiency	
Functional methyltetrahydrofolate (methyl-H4 folate): homocysteine methyltransferase (methionine synthase) deficiency caused by cobalamin E (cblE) or G(cblG) disease	
Glutamate formiminotransferase deficiency	
Hereditary folate malabsorption	
Putative	
Dihydrofolate reductase deficiency	
Methenyl-H4 folate cyclohydrolase deficiency	
Cellular uptake defects	
Primary methyl-H4 folate:homocysteine methyltransferase deficiency	
Nervous system clinical features ³⁷ :	
(a) Neonatal and early infancy (<3 months):	
Poor feeding	
Lethargy	
Hypotonia/hypertonia	
Seizures	
Coma	
(b) Late infancy and early childhood (>3 months-<10 years):	
Slow development	
Lethargy	
Mental deterioration	
Encephalopathy	
Seizures	
Spastic paresis (subacute combined degeneration)	
Extrapyramidal signs	
Neuropathy	
(c) Late childhood and early adulthood (>10 years):	
Previous mild retardation	
Mental deterioration	
Behaviour disturbance	
Encephalopathy	
Myelopathy (subacute combined degeneration)	
Neuropathy	

RISKS

Vitamin B12 deficiency

In the search for the missing principal in pernicious anaemia folic acid was synthesised in 1945, 3 years before the isolation of vitamin B12 in 1948.¹ From 1946 onwards into the 1950s there were numerous reports that, whereas folic acid seemed to improve anaemia, the vitamin not only failed to prevent the neurological complications of pernicious anaemia but actually precipitated or aggravated the neurological manifestations.^{1 12 13 38-40} The reasons for this latter suspicion were the frequency and the severity of the neurological deterioration which seemed in some to have an "explosive" onset.

Although the initial improvement in the anaemia and rapidly evolving neurological problems, especially subacute combined degeneration, were the most striking findings, longer follow up showed that haematological remission with the vitamin was usually suboptimal and temporary and that after 3 or 4 years, haematological relapse was as common as neurological relapse.^{12 13 40} Furthermore, there were some reports of brief temporary improvement in neurological symptoms before the later more obvious deterioration—that is, both the blood and the nervous system showed evidence of remission and relapse with folic acid.^{38 39} The fact that the haematological remission and neurological relapse were the most striking features can readily be explained by fundamental differences in the nature of the blood and nervous system.¹³

These painful lessons of the dangers of folic acid in the presence of unrecognised vitamin B12 deficiency were widely accepted in the ensuing decades, reinforced by the occasional lapse of good practice. However, in the past few years, as the benefits of folic acid to the nervous system have been more widely accepted, these risks have been questioned and

doubted, mainly by advocates of food fortification with folic acid to prevent neural tube defects and vascular disease. Dickinson¹⁰ suggests that folic acid is intrinsically safe for the nervous system, neither causing nor accelerating neurological deterioration. The most he accepts is that by "correcting" the anaemia of pernicious anaemia, folic acid could allow the "natural" progression of the neurological disorder by "masking" and delaying the diagnosis. Oakley¹¹ does not even accept that there is any risk from masking, as any theoretical risk could be prevented by an educational programme. Both authors are critical of the physicians of the 1940s and 1950s for not undertaking controlled clinical trials. They accept that it would be unethical to do so now, as alternative effective treatment for vitamin B12 deficiency is available, but they overlook the fact that in the 1940s a Nobel prize winning treatment in the form of liver therapy was already widely used. The contrast between the benefits of liver therapy and the risks of folic acid to the nervous system in pernicious anaemia was all too apparent to our predecessors. Furthermore, it is inaccurate to suggest that folic acid "corrects" the anaemia as what was reported was usually a suboptimal temporary remission followed by relapse.^{12 40}

Are the risks to the nervous system in the presence of vitamin B12 deficiency related to the dose of folic acid administered? Most of the early studies involved pharmacological doses of 1 to 30 mg daily of the vitamin and some authors suspected that the risks were related to the dose.^{9 12} Is there a minimum safe dose? Savage and Lindenbaum³¹ reviewed reports of 38 patients with vitamin B12 deficiency treated with 1 mg or less of folic acid, 30% of whom showed a significant haematological response. Of 25 patients treated for seven to 19 days, none developed nervous system disorder, whereas of 12 treated for 90 to 930 days six did so. Isolated examples of a reticulocyte response and neurological deterioration were seen with doses of folic acid as low as 0.3 to 0.5 mg daily. As in the case of the benefits of folic acid, and for the same reasons, the duration of folic acid therapy may be as important as the dose of the vitamin.

In summary, folic acid directly interferes with the natural history of both the anaemia and the nervous system manifestations of vitamin B12 deficiency. It has been suggested that it does so by aggravating the methyl folate trap/block.⁴¹ Experimental studies with vitamin B12 deficient fruit bats have confirmed that pretreatment with folic acid or formyl tetrahydrofolate speeds up the appearance of nitrous oxide induced subacute combined degeneration.⁴² The risk to the nervous system is probably related to both the dose and the duration of vitamin therapy. It is also the case that in the absence of controlled trials, which will never be undertaken, the exact risks of different doses and durations of therapy will be difficult to quantify.

Epilepsy

A new risk emerged in epileptic patients in the 1960s and 1970s.^{13 14 16} After several reports of exacerbation of seizures associated with vitamin treatment of antiepileptic drug induced folate deficiency, there is abundant experimental evidence in several species that folates have powerful excitatory properties, especially when applied directly into the nervous system.^{16 43} In laboratory animals intravenous sodium folate will only induce seizure activity in very large doses, but if the animal is already vulnerable to seizures or the blood-brain barrier is damaged locally, for example by a heat lesion, the dose of intravenous sodium folate required to produce an epileptogenic effect is much reduced.^{44 45} If the blood-brain barrier is circumvented by intraventricular⁴⁴⁻⁴⁶ or intracortical⁴⁷ administration all folate derivatives are highly convulsant. For example, sodium folate is 100 times more epileptogenic than comparable nanomolar concentrations of sodium glutamate.^{44 45} Folate induced models of epilepsy can

be used to study basic mechanisms and antiepileptic drug actions.^{47,48} Furthermore, folic acid enhances the electrical kindling model of epilepsy⁴⁹ and the vitamin can even be used to kindle seizures directly.⁵⁰

The mechanism of the excitatory properties of folates is uncertain, but there is some evidence that they may do so by blocking or reversing GABA mediated inhibition.^{16,51-54} Epileptic phenomena induced by folates resemble those induced by disinhibitory compounds—that is, bicuculline, strychnine, penicillin, and picrotoxin, but differ in many respects from those induced by direct excitatory drugs—that is, kainic acid, carbachol, neostigmine.^{55,56}

Because of the normally efficient blood-brain barrier mechanism which limits the entry of the vitamin into the nervous system, the risk to epileptic patients is small, especially in the short term. However, damage to the blood-brain barrier—for example, due to trauma—may lead to local accumulation of folate and patients with partial epilepsies may, therefore, be at slightly greater risk. There is some evidence that higher doses and prolonged therapy increase the risk.^{13,57,58} Perhaps prolonged therapy with the vitamin kindles seizures in patients.^{50,57} However, in some epileptic patients an additional mechanism is the enhanced metabolism of phenytoin leading to a fall in blood concentrations of this drug.⁵⁹

Arousal and mood

A little studied occasional side effect of folate therapy in pharmacological doses—5 mg daily or more—is increased arousal, overactivity, sleeplessness, and the rare precipitation of hypomania in predisposed persons,⁶⁰ as can occur with any antidepressant drug and has also been noted with the closely related metabolite, SAM.⁶¹

SUMMARY

Folates, especially in the form of methyl folate, are important to the nervous system at all ages, perhaps in part related to numerous CNS methylation reactions. Neural tube defects in the foetus, inborn errors in childhood, and depression/cognitive impairment in elderly people are all areas of current interest.

There is evidence from open and controlled trials of replacement therapy with folic acid and methyl folate of an effect of the vitamin on mood, arousal, cognitive, and social function. The vitamin has significant risks in patients with vitamin B12 deficiency or epilepsy which are related to both the dose and duration of treatment. It is difficult to define a safe dose of the vitamin in these situations, and a low dose over many years may not be without risk. The vitamin interferes with the natural history of both the anaemia and the neurological complications of vitamin B12 deficiency.

The potential benefits of the vitamin in the prophylaxis of neural tube defects are well established, but its role in the prophylaxis of mood disorders and dementia, including Alzheimer's disease and cerebrovascular disease, require evaluation. Long term prophylactic studies will help to clarify and quantify the benefits and risks associated with this important vitamin for the nervous system at all ages.

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