Neuropsychiatric Disorders Associated With Nutritional Deficiencies
Incidence and Therapeutic Implications

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Summary

Deficiencies of various vitamins are associated with a variety of neuropsychiatric manifestations. Depression is a feature of deficiencies of folic acid, vitamin B2 (riboflavin) and vitamin B6 (pyridoxine), while vitamin B1 (thiamine) deficiency is associated with several psychosyndromes including alcoholism and schizophrenia. Data from recent studies of vitamin deficiency reveal that gross manifestations such as beri-beri (characteristics include Wernicke's encephalopathy and Korsakoff's syndrome) and pellagra (characteristics include fatigue, insomnia and encephalopathy) are now relatively rare in the Western world. However, milder and subclinical syndromes are still common. For example, the prevalence of low levels of vitamin B12 (cyanocobalamin) is has been estimated to be 5.8 to 26.1% in psychiatric patients, while that of folic acid is higher at 15 to 51% (derived from various studies).

Despite these apparent associations, whether deficiencies of vitamins are causal in neuropsychiatric disorders or a result of them is difficult to determine. For example, there is little direct evidence of a causal role for folic acid in neuropsychiatric disorders, except in the rare in-born errors of metabolism that present with neuropsychiatric abnormalities. It is known that folic acid deficiency is associated with the use of many therapeutic drugs, concomitant physical illnesses...
and chronicity of psychiatric illness. However, retrospective studies of the effects of folic acid replacement therapy in deficient patients, employing clinical and social outcome criteria, have shown an improvement in psychiatric symptoms over a period of 6 to 12 months in most patients. Controlled studies of folic acid replacement therapy are also encouraging. In a double-blind, placebo-controlled, add-on trial involving patients with endogenous depression and schizophrenia, the majority of folic acid-treated patients improved compared with placebo recipients.

The situation with regard to a causal role for other vitamins in neuropsychiatric disorders is even less clear. Obviously, more data are needed in this area to assist clinicians in determining the aetiology of episodes of depression and other neuropsychiatric disorders and, ultimately, their treatment.

It is well known that vitamin deficiency in patients with psychiatric illness, especially depression, is ubiquitous. This has been clearly demonstrated in studies of folic acid, vitamin B₁₂ (cyanocobalamin) and other B vitamins. Although the various haematological and neurological effects of vitamin B₁₂ deficiency were established by the mid 1960s, the psychiatric effects of this and other B vitamin deficiencies, especially folic acid, were largely unknown. By the mid 1960s, methods of assaying B vitamins with some precision became more generally available.

This review evaluates the evidence that deficiencies of folic acid, vitamin B₁₂, vitamin B₁ (thiamine), vitamin B₂ (riboflavin), vitamin B₆ (pyridoxine) and vitamin C (ascorbic acid) are frequently found in psychiatric and general practice. In this context, the term ‘deficiency’ is primarily used to describe a reduced vitamin level due to a nutritional inadequacy, as opposed to that conditioned by other factors such as drugs, physical illness, chronicity of illness and alcohol (ethanol) abuse.

It should be noted that accurate methods of assaying the concentrations of vitamins have only recently become established and that some are more specific than others. On the other hand, some methods are extremely sensitive and give rise to spurious false positive results. The adoption of more reliable techniques should remedy this situation.

1. Initial Investigations

When I first started to investigate folic acid and vitamin B₁₂ in 1965, I addressed 3 questions:

- Was the prevalence of folic acid (and vitamin B₁₂) deficiency in psychiatric patients more than could be expected by chance?
- If so, what were the relevant mental symptoms and psychiatric diagnoses associated with such deficiencies, and what other factors were associated with the deficiencies (e.g. malnutrition, other vitamin deficiencies, haematological abnormalities, chronicity of illness)?
- Did such vitamin deficiency have a primary or causal role in psychiatric illness (regardless of the initial aetiology of the deficiency, i.e. malabsorption, intestinal disease, etc.) or were vitamin deficiencies merely due to the impaired appetite and deceased food intake that can result from mental illness, or were the deficiency and mental symptoms linked in a vicious circle?

1.1 Assay Methods and Determination of Reference Range of Vitamins

In the mid 1960s, the lower limits of normal serum folic acid and vitamin B₁₂ levels were unknown, and there were no methods in use in clinical practice for measuring red blood cell folic acid levels or those of other vitamins.

Vitamin B₁ status was originally measured indirectly by estimating blood pyruvate levels. Subsequently, the Northwick Park Hospital laboratory,