Unusual presentation of more common disease/injury

Vitamin B₁₂ deficiency: an unusual cause for recurrent generalised seizures with pancytopeniaKushal Naha,¹ Sowjanya Dasari,¹ G Vivek,² Mukhyaprana Prabhu¹¹Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India²Department of Cardiology, Kasturba Medical College, Manipal, Karnataka, India

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Summary

We report the case of a 70-year-old man with pancytopenia and new-onset recurrent generalised seizures. Detailed evaluation yielded a diagnosis of vitamin B₁₂ deficiency. He was treated with parenteral vitamin B₁₂ supplementation and antiepileptic drugs. Seizures are an unusual manifestation of vitamin B₁₂ deficiency and possible mechanisms of epileptogenesis are discussed.

BACKGROUND

Vitamin B₁₂ deficiency is known to produce a variety of neuropsychiatric manifestations¹ including peripheral neuropathy, subacute combined degeneration of the spinal cord, optic atrophy, dementia, psychosis and mood disturbances. This case highlights seizures as yet another complication of vitamin B₁₂ deficiency.

Although unusual, this condition is nevertheless completely reversible with appropriate therapy; thus awareness of this possibility can spare the occasional patient prolonged therapy with antiepileptic drugs. Moreover, certain commonly employed antiepileptic drugs are themselves known to lower vitamin B₁₂ levels. Paradoxically, initiation of therapy with these drugs in a patient with underlying vitamin B₁₂ deficiency can further exacerbate the problem, leading to poor control of seizures and unmasking other neurological and haematological manifestations of vitamin B₁₂ deficiency.

Vitamin B₁₂ deficiency should be ruled out in all patients with otherwise unexplained seizures, especially when associated with suggestive features such as a macrocytic anaemia, as seen in our patient.

CASE PRESENTATION

A 70-year-old previously healthy man presented with six episodes of generalised seizures over the past 24 h. There was no history of previous seizures, head injury or substance abuse. He had not received any epileptogenic drugs recently.

On admission, the patient was drowsy and confused. He was haemodynamically stable. General physical examination revealed severe pallor. There was no significant lymphadenopathy, no bleeding spots and no organomegaly. Cutaneous stigmata of vitamin B₁₂ deficiency, in the form of knuckle hyperpigmentation, icterus and hair depigmentation were not seen. Neurological examination showed hyper-reflexia in upper and lower limbs. Plantar response was bilaterally mute. Fundal examination and tests for proprioception and vibration sensation could not be performed as the patient was not cooperative.

INVESTIGATIONS

Routine laboratory tests showed pancytopenia (haemoglobin 4.4 g/dl; total count 3600 cells/mm³; platelets 75 000 cells/mm³). There was no dyselectrolytaemia (sodium 137 mEq/l; potassium 4.1 mEq/l; calcium 8 mg/dl; magnesium 2.1 mg/dl; albumin 3.4 g/dl). Blood sugars performed at admission and repeated over the course of hospital stay were normal. EEG was abnormal showing bilateral asymmetric non-synchronous frontal slow wave discharges (1–2 Hz). MRI showed diffuse periventricular white matter changes (see figure 1A–C). Further work-up for the cause of pancytopenia revealed low serum vitamin B₁₂ levels (98.43 pg/ml). Serum folate levels were normal (4.97 ng/ml). A peripheral blood smear also showed macro-ovalocytes and hypersegmented neutrophils consistent with vitamin B₁₂ deficiency. Bone marrow study showed features of megaloblastic anaemia with trilineage dyspoiesis. Gastric biopsy was suggestive of atrophic gastritis.

DIFFERENTIAL DIAGNOSIS

- ▶ Vitamin B₁₂ deficiency secondary to atrophic gastritis, complicated by recurrent seizures.

TREATMENT

The patient was initially started on phenytoin in consultation with neurologists, as well as parenteral vitamin B₁₂ supplementation. Subsequently, he was switched to valproic acid, after considering the possibility of phenytoin induced lowering of vitamin B₁₂ levels (see the discussion below).

OUTCOME AND FOLLOW-UP

Complete recovery was noted as there were no further episodes of seizure. Pancytopenia also responded to therapy with brisk reticulocytosis. The patient was discharged on long-term vitamin B₁₂ supplementation. Valproic acid was rapidly tapered and stopped over the next 3 months, and the patient remained seizure-free 1 year after the index illness. A cerebral MRI performed approximately 18 months later at another hospital for vague complaints

Figure 1 MRI of brain (fluid attenuated inversion recovery sequence, axial section) showing diffuse periventricular white matter changes (A). MRI of brain (T2 sequence, axial section) showing diffuse white matter changes (B and C).

of fatigue, was reported as normal indicating probable reversal of white matter changes seen in the first MRI. Unfortunately, the actual images could not be obtained and the patient refused a repeat MRI at our hospital in view of financial constraints. Blood parameters including complete blood counts, and serum B₁₂ and folate levels were entirely normal. Electroencephalography was also done and was normal.

DISCUSSION

The metabolic importance of vitamin B₁₂ and folate stems principally from their central role in one carbon metabolism,² where they are essential for the functioning of several coenzymes. In this metabolic pathway, a single carbon unit is transferred from serine or glycine to tetrahydrofolate (THF) producing methylene-THF, which is then utilised directly to synthesise the pyrimidine thymidine. Alternatively, methylene-THF may be oxidised to formyl-THF and diverted to the purine synthesis pathway, or reduced to methyl-THF which participates in the formation of methionine, and ultimately S-adenosyl methionine, a universal methyl group donor. The latter step involving carbon transfer from methyl-THF to methionine is catalysed by vitamin B₁₂-dependent methionine synthase; this step regenerates THF and completes the metabolic cycle of folate. The concept of methyl-folate trapping arises from the fact that conversion of methylene-THF to methyl-THF is irreversible; B₁₂ deficiency in such a situation can lead to progressive accumulation of otherwise metabolically inactive methyl-THF (figure 2).

Although associated occasionally with seizures in infants³ where it has an important role in genomic methylation, vitamin B₁₂ rarely produces seizures in adults.^{4–6} Various mechanisms have been proposed for the neurological manifestations of vitamin B₁₂ deficiency. Dysfunction of the B₁₂-dependent enzyme methionine synthase is known to result in deficient or abnormal synthesis of myelin sheaths within the central nervous system. While this explains the development of peripheral neuropathy and subacute combined degeneration of the cord, it cannot directly explain epileptogenesis. However, Akaike *et al*⁷ demonstrated that demyelinated neurones are more susceptible to the excitatory effects of glutamate, providing a link between demyelination and the development of seizures, analogous to the pathogenesis of paroxysmal symptoms in multiple sclerosis.⁸

We would like to postulate an alternative mechanism, based on the dual observations by Reynolds⁹ that vitamin B₁₂ deficiency can elevate serum folate levels via the methyl-folate trap, and that all folate derivatives are highly epileptogenic,^{10–11} especially when administered directly into the central nervous system. Intravenous folate derivatives must be present in very high levels to produce this effect, but much lower concentrations are needed if the blood–brain barrier has been disrupted by prior neurological insult. Therefore, by producing high serum folate levels, vitamin B₁₂ deficiency could directly produce an epileptogenic effect (figure 3). The exact mechanism by which folate derivatives produce seizures is yet to be elucidated; possibly it occurs by direct reversal of gamma-aminobutyric acid-mediated inhibition.¹²

This hypothesis is similar to that proposed by Meng *et al*,⁶ who suggested that high serum levels of homocysteine seen in B₁₂ deficiency could produce seizures. This theory is supported by animal studies^{13–14} demonstrating the epileptogenic potential of homocysteine.

While our patient presented with generalised tonic-clonic seizures, complex partial seizures have also been reported in a patient with vitamin B₁₂ deficiency.⁵ However, unlike that case, our patient had both neurological and haematological manifestations of B₁₂ deficiency.

We conclude that vitamin B₁₂ deficiency is a rare but reversible cause of epilepsy that should be ruled out before

Figure 2 Folate cycle and the folate trap. Failure of vitamin B₁₂-mediated conversion of methyl-tetrahydrofolate (THF) to THF (red cross), results in progressive accumulation of methyl-THF (red outline), ultimately resulting in epileptogenesis.

Figure 3 Hypothesised mechanism of seizures in vitamin B₁₂ deficiency.

labelling a patient with an idiopathic seizure disorder. It is also important to note that several antiepileptic drugs have been found to lower vitamin B₁₂ levels including carbamazepine and phenytoin.¹⁵ Therefore paradoxically in such cases, early tapering and cessation of antiepileptic drugs is important to avoid future recurrence of seizures.

Learning points

- ▶ Recurrent seizures are an unusual but recognised complication of vitamin B₁₂ deficiency.
- ▶ Vitamin B₁₂ deficiency should be ruled out in all patients presenting with unexplained seizures.
- ▶ Most antiepileptic drugs lower vitamin B₁₂ levels, hence care should be exercised in treating such patients.

Competing interests None.

Patient consent Obtained.

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