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Psychotic disorder, hypertension and seizures associated with vitamin B_{12} deficiency: a case report

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Abstract

This report highlights a rare presentation of vitamin B_{12} deficiency (concurrent psychotic disorder, seizures and hypertension). A 16-year-old girl presented with nervousness that had been persisting for 2 weeks. She had stopped eating and there was decreased self-care and she could not walk and sleep. Two days prior to admission, generalized tonic–clonic convulsions were noted. On physical examination, vital signs were normal, except for hypertension (150/100 mm Hg). She did not respond to conversation; she could not answer the questions. Mood was depressive and hallucinations were noted. Laboratory analyses were normal, except for a low vitamin B_{12} level (<150 pg mL^{-1}). The patient was not given any treatment of hypertension, psychosis or seizures, except vitamin B_{12} injections. After that, she showed improvement within 1 week. In the 7 days of hospitalization, the arterial blood pressure returned to normal, psychotic symptoms were resolved, the visual hallucinations and the depressive mood subsided, and she could eat and speak clearly. No hypertension or convulsions have been detected on the control examinations, and she has now been followed-up without any symptoms or findings. In conclusion, with this report we emphasized that psychosis, seizures and hypertension can be a rare manifestation of vitamin B_{12} deficiency, which is reversible with therapy and serum vitamin B_{12} level should be checked in patients who do not have an obvious cause for psychosis, seizures or hypertension.

Keywords

vitamin B_{12}; psychotic disorder; hypertension; seizures

Introduction

Vitamin B_{12} deficiency may cause various neuropsychiatric and thrombotic manifestations, including dementia, cerebellar ataxia, psychosis, neuropathy, mood disturbances, portal vein thrombosis and myocardial infarction.[1–4] However, to the best of our knowledge, there are no reported articles on cases of concurrent psychotic disorder, hypertension and convulsion associated with vitamin B_{12} deficiency in children and adolescents. In this report, a 16-year-old girl presented with psychotic disorder, convulsion and hypertension, which had been reported to be very rarely seen.

Case report

A 16-year-old girl presented with nervousness that had been persisting for 2 weeks. All of the complaints had begun after a house sale. Her father had sold their house due to financial difficulty. After that event, the patient became an introvert and began to talk to their house and some individuals that did not exist. She always said that the house and her imaginary friends, who were actually absent, were talking to her about prevention of its sale. At that time, she had stopped eating. Self-care was decreased and she could not walk and sleep. Two days prior to admission,

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generalized tonic–clonic convulsions were noted which were observed 3 times a day and that lasted for 5 min. During seizures, she bit her tongue and urinary incontinence was noted. On physical examination, vital signs were normal, except for hypertension (150/100 mm Hg). She did not respond to conversation; she could not answer to questions. Saccadic eye movements were slow, mood was depressive and visual hallucinations were noted. Tendon reflexes and muscle tones were normal and the plantar response was flexor. Sensory, cerebellar and autonomic systems were normal. There was no preceding history of encephalitis or prior use of antipsychotic or antiemetic medications. In her previous history, it was deduced that she did not like to eat animal products, especially meat and milk products. In the family history, it was learnt that she had an older sister who had vitamin B_{12} deficiency and psychosis and who also did not eat animal products. She and her family had no history of atherosclerosis. There was no history of exposure to carbon monoxide, organophosphate compounds or other toxins. Investigations were as follows: hemoglobin was 15.3 g dl^{-1}, reticulocyte count was 0.1% and the mean corpuscular volume (MCV) was 94 fl. The serum vitamin B_{12} level was <150 pg ml^{-1} (normal: >190 pg ml^{-1}) and folate was 8 ng ml^{-1} (normal: 3–24 ng ml^{-1}). There were no hypersegmented polymorphonuclear leukocytes on the peripheral smear and no megaloblastic changes in the bone marrow examination. Renal and liver function tests, serum electrolytes, serum parathormone, ceruloplasmin and thyroid function tests were normal. HIV (enzyme-linked immunosorbent assay [ELISA]) was negative. Serological tests for brucella, salmonella, lupus anticoagulants, antinuclear antibody, anticardiolipin antibody IgG and IgM and *Helicobacter pylori* were negative. Tandem mass metabolic screening test (except for low methionine), cerebral and vertebral magnetic resonance imaging (MRI) and cerebrospinal fluid analysis were normal. Urinary ultrasonographic and echocardiographic examinations also revealed no pathology. A diagnosis of psychotic disorder, hypertension and convulsion secondary to vitamin B_{12} deficiency was made. The 24-hour urine copper level was in the normal range. There was no Kayser Fleischer ring. The analyses for homocysteine and methylmalonic acid excretion in urine were not performed due to lack of laboratory facilities. Electroencephalogram (EEG) examination was normal. She was started on vitamin B_{12} injections. The patient was not given any treatment of hypertension, psychosis or seizures, except vitamin B_{12} injections. Vitamin B_{12} injections were administered at a dose of 100 μg day^{-1} for 5 days and 500 μg day^{-1} twice a week for 2 weeks. After that, she showed improvement within 1 week. In the 7 days of hospitalization, the arterial blood pressure returned to normal, psychotic symptoms were resolved, the visual hallucinations and the depressive mood subsided, and she could eat and speak clearly. On the third week of follow-up, the vitamin B_{12} level was 987 pg ml^{-1}. She is now in the sixth month of follow-up and arterial blood pressure which has been within normal limits has been monitored regularly. No hypertension or convulsions have been detected on the control examinations, and she has now been followed up without any symptoms or findings.

Discussion

Vitamin B_{12} deficiency is a common problem in adults, and it can be associated with delirium, dementia, depression and psychosis. Psychiatric symptoms can occur in the absence of characteristic hematological or neurological symptoms suggestive of B_{12} deficiency.[2] Multiple cases with acute and chronic psychosis in the setting of vitamin B_{12} deficiency have been reported. Payinda et al.[3] reported an acute onset of persecutory delusions in a patient with symptoms of lower extremity paralysis without megaloblastic anemia, revealing a B_{12} level of lower than 9 pg ml^{-1}. A case report of a patient with a 2-year history of auditory hallucinations and persecutory delusions with signs of posterior column involvement without anemia showed complete resolution of symptoms following vitamin B_{12} replacement.[4] Although there can be resolution of symptoms with vitamin B_{12} supplementation, the exact mechanism of B_{12} deficiency leading to psychosis remains unknown. It is encouraging to note that in cases of psychosis associated with vitamin B_{12} deficiency, there appears to be good outcomes with replacement of vitamin B_{12}, even after prolonged periods (at least up to 2 years) of psychosis.[5] This suggests that vitamin B_{12} deficiency should be considered in any presentation of psychosis, especially in adults. In our patient, an acute onset psychosis was observed and the symptoms (hallucinations and depressive mood) resolved after vitamin B_{12} replacement. According to our knowledge, psychosis associated with vitamin B_{12} deficiency has been reported mostly in adults, especially in the elderly. In children and adolescents, very limited case

reports have been presented about the association of vitamin B_{12} deficiency and pscychosis. Therefore, our case showed that, in children with psychosis, vitamin B_{12} deficiency could be investigated, since this condition can be easily treated, yielding a good response to treatment.

The most common explanations for poor vitamin B_{12} status are a low dietary intake of the vitamin (i.e. a low intake of animal-sourced foods) and malabsorption. Although it has long been known that strict vegetarians are at risk of vitamin B_{12} deficiency, evidence now indicates that not only strict vegeterians but also low intake of animal-sourced foods causes vitamin B_{12} depletion. Malabsorption of the vitamin is most commonly observed as food-bound cobalamin malabsorption due to gastric atrophy in the elderly and probably as a result of *Helicobacter pylori* infection. Transcobalamin II deficiency also causes vitamin B_{12} deficiency.[6] In our patient's history, we determined that she did not like to eat animal-sourced foods, especially meat and milk products. A dietary low intake may have been the etiologic factor of vitamin B_{12} deficiency in our patient. But we did not rule out transcobalamin II deficiency, which may be considered in the etiology according to the family history, though we could not investigate this due to technical insufficiency.

The potential mechanisms that could explain the relationship between vitamin B_{12} deficiency and blood pressure include homocysteine-induced arteriolar constriction, renal dysfunction, increased sodium reabsorption and increased arterial stiffness.[7] Hyperhomocysteinemia enhances arterial stiffness, leading to an increase in pulse pressure, mainly due to elevated systolic blood pressure, and in cardiac load. High homocysteine concentrations are also associated with endothelial cytotoxicity and impaired endothelial function.[8] In the third National Health and Nutrition Examination Survey, persons in the highest quintile of plasma homocysteine had a two- to threefold increased prevalence of hypertension compared to those in the lowest quintile.[9] In a study that was performed by Karatela and Sainani,[7] the authors observed increased prevalence of hyperhomocysteinemia, dyslipidemia and reduced vitamin levels among hypertensive patients compared to normotensive individuals. Among the hypertensive patients, homocysteine was found to be positively and significantly correlated with obesity and arterial pressure levels and negatively correlated with vitamin levels. In our case, the examinations of homocysteine and methylmalonic acid excretion in urine were not performed due to lack of laboratory facilities. However, TMS: Tandem mass spectrometry was performed. We found it normal, except for the low methionine level. As a matter of fact, vitamin B_{12} deficiency and low methonine level in TMS supported the increased homocysteine level. Therefore, it can be said that our patient could have an increased homocysteine level.

In vitamin B_{12} deficiency, neurological involvement often occurs along with macrocytic anemia, but this can occur in the absence of anemia or macrocytosis.[10] It is unclear why vitamin B_{12} deficiency leads to neurological disease in some and hematological disease in others. Explanation of this has been attempted with homozygosity for methylenetetrahydrofolate reductase (MTHFR) C677T gene theory. MTHFR polymorphism has been postulated to protect vitamin B_{12}-deficient patients against anemia. Homozygosity for the MTHFR C677T gene could cause dissociation between hematological and neurological disease seen in some patients with vitamin B_{12} deficiency.[11] The pathophysiology of epileptogenesis due to vitamin B_{12} deficiency has not yet been clarified. Homocysteine, a sulfur-containing amino acid, has been shown to induce seizures in rats.[12] A clear anticonvulsant action of glutamate receptor antagonists against seizures induced by homocysteine and by homocysteic acid has been demonstrated.[13] It has also been suggested that cerebral neurons with destroyed myelin sheaths secondary to vitamin B_{12} deficiency are more susceptible to the excitatory effects of glutamate.[14] These studies may indicate an epileptogenic role of both homocysteine and its metabolite in the pathophysiology of central nervous system involvement in vitamin B_{12} deficiency, although the situation may be more complex, and further studies may be required for a thorough understanding of all the processes involved.

Generalized tonic–clonic and focal seizures have been described as vitamin B_{12} deficiency-related seizures.[15] The seizures in these cases began before treatment with vitamin B_{12} and therapy resulted in prompt cessation of seizures.[15] However, therapy-resistant seizures may occur.[15] The EEG of patients with vitamin B_{12} deficiency and seizures may demonstrate various features including hypsarrhythmia, generalized slow activity or EEG consistent with a seizure disorder of multifocal cortical origin, and diffuse cortical dysfunction.[15] On MRI examination of patients with vitamin B_{12} deficiency and neurological

signs, cortical atrophy is found to be a major finding. But, in some reports about seizures due to vitamin B_{12} deficiency, the authors suggested that EEG and MRI could be normal.[16,17] In literature, one such case was reported by Erol et al.[16] The authors reported a 16-month-old girl with West's syndrome who had an EEG that was showing modified hypsarrhythmia and a normal MRI examination despite the refractory seizures. In another study which was published by Incecik et al.,[17] a total of 15 children with neurological finding due to vitamin B_{12} deficiency were presented and only 8 patients had cortical atrophy on cerebral MRI. The remaining seven patients had normal MRI. Additionally, in this report, only three patients had abnormal EEG examination.[17] In our patient, generalized tonic–clonic seizures were noted and EEG and MRI were found to be normal prior to treatment.

In conclusion, psychotic disorder, seizures and hypertension can be rare manifestations of vitamin B_{12} deficiency, which are reversible with therapy. Serum B_{12} level should be checked in patients who do not have an obvious cause for psychosis, seizures or hypertension.

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References

1. Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. *Medicine (Baltimore)* 1991; 70: 229–245.
2. Evans LD, Edelsohn GA, and Golden RN. Organic psychosis without anemia or spinal cord symptoms in patients with vitamin B12 deficiency. *Am J Psychiatry* 1983; 140: 218–221.
3. Payinda G and Hansen T. Vitamin B12 deficiency manifested as psychosis without anemia. *Am J Psychiatry* 2000; 157: 660–661.
4. Rajkumar AP and Jebaraj P. Chronic psychosis associated with vitamin B12 deficiency. *J Assoc Physicians India* 2008; 56: 115–116.
5. Sabeen S and Holroyd S. Vitamin B12 and psychiatric illness. *Ann Long Term Care* 2009; 17: 32–36.
6. Allen LH. Causes of vitamin B12 and folate deficiency. *Food Nutr Bull* 2008; 29: S20–S34.
7. Karatela RA and Sainani GS. Plasma homocysteine in obese, overweight and normal weight hypertensives and normotensives. *Indian Heart J* 2009; 61: 156–159.
8. van Guldener C and Stehouwer CD. Hyperhomocysteinemia, vascular pathology, and endothelial dysfunction. *Semin Thromb Hemost* 2000; 26: 281–289.
9. Lim U and Cassano PA. Homocysteine and blood pressure in the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2002; 156: 1105–1113.
10. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988; 318: 1720–1728.
11. Kvittingen EA, Spangen S, Lindemans J, and Fowler B. Methionine synthase deficiency without megaloblastic anemia. *Eur J Pediatr* 1997; 56: 925–930.
12. Kubová H, Folbergrová J, and Mares P. Seizures induced by homocysteine in rats during ontogenesis. *Epilepsia* 1995; 36: 750–756.
13. Folbergrová J, Haugvicová R, and Mares P. Behavioral and metabolic changes in immature rats during seizures induced by homocysteic acid: the protective effect of NMDA and non-NMDA receptor antagonists. *Exp Neurol* 2000; 161: 336–345.
14. Akaike A, Tamura Y, Sato Y, and Yokota T. Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. *Eur J Pharmacol* 1993; 241: 1–6.
15. Roschitz B, Plecko B, Huemer M, et al. Nutritional infantile vitamin B12 deficiency: pathobiochemical considerations in seven patients. *Arch Dis Child Fetal Neonatal Ed* 2005; 90: 281–282.
16. Erol I, Alehan F, and Gümüs A. West syndrome in an infant with vitamin B12 deficiency in the absence of macrocytic anaemia. *Dev Med Child Neurol* 2007; 49: 774–776.
17. Incecik F, Hergüner MO, Altunbaşak S, and Leblebisatan G. Neurologic findings of nutritional vitamin B12 deficiency in children. *Turk J Pediatr* 2010; 52: 17–21.