Successful Treatment of Megaloblastic Mania with Cobalamin in a Patient with Pernicious Anemia

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Abstract

While secondary mania is relatively uncommon, general medical conditions with potential effects on the central nervous system can lead to a clinical picture indistinguishable from primary mania. Our patient was admitted in a "manic state," with no prior psychiatric history and of relatively advanced age. Despite various etiologies either ruled out or treated (including drug- and alcohol-induced state, hyperthyroidism and direct central nervous system pathology), low vitamin B12 levels and its subsequent replacement ultimately resulted in attenuation of our patient's symptoms of mania with psychosis. Cobalamin (vitamin B12) deficiency is usually associated with the triad of neurologic changes, glossitis and macrocytic anemia. It is also widely accepted as a cause for reversible dementia (1). Even though there is also growing evidence of reversible psychiatric symptoms caused by vitamin B12 deficiency, there are few cases of mania reported in current literature. The mechanism behind the mania is even more of a mystery. Treatment with vitamin B12 has been shown to completely reverse the mania in these cases. This case report discusses a woman with mania whose diagnosis was difficult to establish due to multiple medical problems, but was ultimately determined to have pernicious anemia.

Key Words: Metabolic Side Effects, Paranoia, First Episode

Case Report

Our patient was a fifty-five year old female admitted to our teaching hospital, with a history of untreated hyperthyroidism and no prior diagnosis of psychiatric illness, who initially presented with nausea, vomiting and abdominal pain due to a high-grade bowel obstruction. The patient's medical record indicated no prior psychiatric history. Her family did report that, within the past year, the patient seemed to experience several episodes of depression where she was described as having self-imposed isolation, decreased energy, anhedonia, and change of sleeping and eating pattern. The patient's family also described periods of manic symptoms that included pressured speech and racing thoughts, increased goal-directed behavior such as cleaning the whole house, and decreased need for sleep, which was notably uncharacteristic of her. The patient had no reported history of psychosis. She and her family also denied any history of substance abuse. The patient (and family) denied any history or family history of other autoimmune illnesses. Neurological examination was remarkable for mild bilateral lower extremity weakness, paresthesia and position sense. The patient did have ataxia but Romberg sign was negative. There was no evidence of glossitis on physical examination. On hematological evaluation, her hemoglobin was 10.1 g/dl, and a mean corpuscular volume of 102 f/l.

After an emergency surgical reduction of her bowel obstruction, the patient became febrile, tachycardic, and progressively confused and combative. It was at this point of her hospitalization that our psychiatric team was consulted. Our initial impression was that her symptoms were secondary to delirium due to postsurgical thyroid storm or secondary

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to a urinary tract infection (UTI). However, after treatment with propylthiouracil, resulting in a euthyroid state, and treatment of her UTI, the patient still showed signs of altered mental status. Even after one week of "euthyroidism," our patient continued to be reported as uncooperative and agitated and was noted to have paranoid delusions requiring haloperidol. This intervention was met with minimal success. At this juncture, there was no obvious cause for the patient's continued manic symptomatology. Computed tomography (CT) scan of the head was obtained and showed an old small vessel cortical frontal infarct as well as white matter changes. Electroencephalogram (EEG) showed slowing with some questionable left frontal changes. The patient was treated with quetiapine 100 mg po TID; then ziprasidone 80 mg po BID (with, as needed, lorazepam), and demonstrated little clinical improvement. Upon further investigation, it was found that the patient had a low level of vitamin B12 of 107 pmol/l (normal vitamin B12: 211 to 911 pmol/ml), 757 micro mol/l methylmalonic acid (MMA) (normal: 73 to 379 nmol/l), a mean corpuscular volume (MCV) of 114 femtoliters (normal: 80 to 95 fl), and positive intrinsic factor antibody. The diagnosis of pernicious anemia was made, and the patient was treated with vitamin B12 1,000 micrograms intramuscularly (IM) daily for nine days.

Using the Young Mania Rating Scale (YMRS), the patient's behavior was assessed before being treated with vitamin B12 and after receiving nine days of IM vitamin B12. Before treatment, the patient scored a twenty-two on the YMRS, in comparison to after treatment when her score decreased dramatically to six. It is important to note that the patient was on ziprasidone for two weeks, but did not show significant improvement until after treatment with vitamin B12.

Interestingly, our patient's manic symptomatology significantly attenuated within two days of treatment with vitamin B12, while the ziprasidone was discontinued after the third day of vitamin B12 administration. At discharge, seven days later, our patient's YMRS score was zero and she was on no psychotropic medications, but was continued on monthly IM vitamin B12. As a follow-up, one month after discharge, the patient was contacted by phone and continued to be euthymic. We were unsuccessful in trying to recontact our patient six months after discharge; therefore, longer term remission in symptoms could not be verified.

Discussion

This case illustrates a patient with pernicious anemia who presented with symptoms of mania, including agitation, paranoid delusions, irritable mood, pressured speech and flight of ideas. Verbanck and Le Bon (2) also introduce a patient who developed similar symptoms of mania, was ultimately diagnosed with pernicious anemia, and whose symptoms resolved after vitamin B12 replacement. As in this case, the symptoms disappeared after beginning vitamin B12 replacement therapy. In the Verbanck and Le Bon case, the patient was asymptomatic five years later. The Zucker et al. study (3) reported the following psychiatric symptoms in vitamin B12 deficiency: paranoia 53%, violence 47%, depression 40%, irritability 40%, and disorientation 33%.

In our particular patient, bowel obstruction could potentially have been a cause of vitamin B12 deficiency and have lead to this manic episode. Vitamin B12-intrinsic factor complex is carried to the terminal ileum, where it is ultimately absorbed. Not only could bowel obstruction possibly cause a structural barrier for absorption to occur (4), but it is also conceivable that malabsorption could develop due to blind loop syndrome with bacterial overgrowth. That is, the bypassed portion of the small bowel ("blind loop") caused by obstruction leads to stasis of food and ultimate bacterial overgrowth. The latter could produce toxins that result in the malabsorption of vitamin B12 (5).

A limitation to our diagnostic opinion is that prospective studies of patients with hyperthyroidism suggest that remission of affective symptoms can occur up to six months of patients becoming euthyroid; therefore, it is possible that our patient's resolution of symptoms could have been the result of a delayed affective response after normalization of her thyroid axis (6). In comparing the known reports of megaloblastic mania with our patient, we would like to refer to the Zucker et al. review (3) and the Goggans case report (7). In the Zucker et al. review, as in our patient, the most common psychiatric symptoms were organic brain syndrome, paranoia and violence. Interestingly, several of the Zucker et al. study's patients were not anemic and had no neurologic deficit, differing from the symptoms of our patient.

In the Goggans case report, as in our case, the patient has grandiose and paranoid delusions, pressured speech, irritable mood and decreased need for sleep. Additionally, both patients had no prior psychiatric history. Furthermore, both patients' manic symptoms resolved after a one-week course of vitamin B12 replacement, with sustained remission after discharge from the hospital; however, as Goggans noted in his case and we have acknowledged, as well, "improvement could have been related to factors other than B12 replacement." Two major differences between these two case reports were that Goggans' patient's manic symptoms did improve after antipsychotic administration and that Goggans was able to follow up with his patient up to six months after discharge. Goggans reported that, with monthly B12 injections, his patient's "mental status remained normal."

One crucial problem in detecting and treating vitamin B12 deficiency is that the reference ranges currently used are based on hematological indices. Vitamin B12 deficiency has been proposed to occur at 100 pg/ml or from 100 to 400 pg/

ml if either serum MMA or homocysteine levels are elevated (8).

Traditionally, neuropsychiatric symptoms in vitamin B12 deficiency have been proposed to occur at less than 200 pg/ml; however, some studies indicate that, in the elderly, this value may be somewhat higher (8). Serum vitamin B12 concentrations are not very sensitive or specific in the elderly (9), as vitamin B12 bound to protein in foods cannot be cleaved and released in conditions that interfere with gastric acid production. Atrophic gastritis, with resulting hypochlohydria, is a major cause of this food-bound malabsorption in the elderly (10).

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Another issue is that vitamin B12 deficiency is not often considered as a cause for mania. Only two other case reports of mania secondary to vitamin B12 deficiency have been published (3, 7). The classic triad of vitamin B12 deficiency is widely known to include glossitis, macrocytic anemia and neurologic findings. In a review of fifteen cases of vitamin B12-induced psychosis, only one out of the fifteen cases presented with the classic triad (3). Mental or psychological changes may precede hematological signs by months or years. They can be the initial symptoms or the only symptoms. Durand et al. described the case of a patient with vitamin B12 deficiency in which hypomania, paranoia and depression had been successively present during a period of five years before anemia developed (10). It is thus possible, as in the Verbank et al. review, that psychiatric symptoms may occur in the absence of any neurological abnormalities; however, the pathophysiology behind the psychiatric symptoms is unclear. Several theories have been proposed to explain the psychiatric symptoms alone. One of the theories is that the mania is due to hypoxia as a result of anemia induced by B12 deficiency. There is little evidence to support this theory given the fact that anemia is not always present in patients with B12 deficiency and psychiatric symptoms. The anemia usually occurs after prolonged low levels of vitamin B12. In clinical experience, psychiatric symptoms do not correlate with the degree of anemia, and EEG changes found with pernicious anemia are not a result of the anemia but of a specific defect in cerebral metabolism (3).

There is scarce literature regarding the changes occurring in the brain as a result of pernicious anemia and, more generally, vitamin B12 deficiency. As previously stated, vitamin B12 deficiency is classically associated with neurologic disturbances, specifically subacute combined degeneration. The pathologic changes include spongy degeneration and diffuse demyelination of the posterior and lateral columns of the spinal cord. Pathologic changes in the brains of vitamin B12 deficient individuals are less well studied, and MRI abnormalities in the brain have not received much attention (11). Stojsavljevic et al. (11) report a case of a patient with severe neurological deficits due to vitamin B12 deficiency with a normal magnetic resonance imaging (MRI) of the spinal cord, but whose brain MRI demonstrated nonspecific changes. This area may warrant further investigation in regards to its contribution to the neurological and psychiatric changes present in this condition.

Despite its elusive pathophysiology in the etiology of mania, we feel vitamin B12 deficiency should continue to be considered in the differential diagnoses of atypical presentations of psychiatric symptoms, especially in the context of consultation liaison psychiatry.

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