

## Intractable Epilepsy as the Presentation of Vitamin B<sub>12</sub> Deficiency in the Absence of Macrocytic Anemia

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Vitamin B<sub>12</sub> deficiency often produces hematologic and neurologic deficits including macrocytic anemia, myelopathy, neuropathy, or mental abnormalities, which may become irreversible if not promptly treated (1–3). The diagnosis of vitamin B<sub>12</sub> deficiency can be difficult when the typical macrocytic anemia is absent (1). A few cases with seizures as the manifestation of vitamin B<sub>12</sub> deficiency have been reported, and macrocytic anemia also was noted in these patients (4,5). We report a patient with vitamin B<sub>12</sub> deficiency presenting as intractable epilepsy in the absence of macrocytic anemia. The seizure attacks and all other symptoms/signs of vitamin B<sub>12</sub> deficiency resolved after an intramuscular administration of cobalamin.

### CASE REPORT

A 76-year-old man began to experience frequent generalized tonic-clonic seizures 3 years before visiting our hospital. The frequency was ~3–5 times monthly. The initial investigations in a local hospital were normal except for mild normocytic anemia. He was diagnosed with epilepsy of an unknown etiology, and phenytoin (PHT), 300 mg once daily, was given to prevent seizure recurrence. In spite of a plasma drug concentration of 15.4 µg/ml (target concentration, 10–20 µg/ml), the frequency of seizures was still ~3–5 times monthly. Valproate (VPA), 500 mg twice daily, was added, but without an improvement in seizure control. One year later, he felt numbness at the plantar area of both feet. The abnormal sensation ascended to the knees within a few months. Because of these problems, he was admitted to our hospital in March 2003.

The neurologic examination showed an alert consciousness. The Mini-Mental Status Examination (MMSE) re-

vealed a mild cognitive impairment (score, 22 of 30; normal score, >24). The muscle strength was full. Deep tendon reflexes (DTRs) were absent at the knees and the ankles. Plantar responses were flexor bilaterally. Sensation to pinprick was decreased throughout the legs. Sensory ataxia was noted.

The laboratory survey showed a low cobalamin serum level of 55 pg/ml (normal, 160–970 pg/ml). Homocysteine was elevated to 175.5 µM (normal, <12 µM). Normocytic anemia was present, with a hemoglobin of 11.0 g/dl (normal, 13.5–17.5 g/dl), a hematocrit of 33% (normal, 41–53%), a mean corpuscular volume of 96.5 fl (normal, 80–100 fl), and a slightly decreased reticulocyte count of 0.6% (normal, 0.5–1.9%). The anti-gastric-parietal-cell antibody was positive. The gastric biopsy showed atrophic gastritis. The EEG showed generalized continuous slow waves (4–6 Hz) over bilateral hemispheres. The brain MRI was normal. The nerve-conduction study (NCS) showed sensory-predominant polyneuropathy with mixed demyelinating changes and axonal degeneration. This was compatible with polyneuropathy caused by a vitamin B<sub>12</sub> deficiency or PHT toxicity. The cervical and thoracic MRI demonstrated a hyperintensity signal at the bilateral fasciculus gracilis, which was compatible with subacute combined degeneration.

Initial treatment consisted of daily intramuscular injections of 1 mg of hydroxycobalamin in the first week, followed by weekly injections for 1 month. The maintenance schedule was a monthly injection of 1 mg. The cobalamin has been administered for 22 months. The hemoglobin, hematocrit, reticulocyte count, and homocysteine after the cobalamin treatment have all returned to a normal level (13.3 g/dl, 42%, 0.8%, and 8.6 µM, respectively).

The patient had the last seizure attack during the admission before the replacement therapy, and no further seizure was noted after the first dose of hydroxycobalamin. The numbness in the legs improved gradually, and the gait became normal by the end of 6 months of cobalamin treatment. The NCS 3 months later was normal, except for an absence of bilateral H-reflexes. The MMSE 1 year

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later was normal (score, 29/30). The EEG 1 year later was normal, and PHT and VPA were thereafter tapered and stopped 2 months after the EEG study. Since then, he has been seizure free for 8 months.

### DISCUSSION

The patient presented herein displayed intractable seizures, polyneuropathy, myelopathy, and normocytic anemia, all of which resolved gradually after hydroxocobalamin replacement therapy. Although the possibility that the patient has a dual-pathology idiopathic epilepsy and vitamin B<sub>12</sub> deficiency could not be excluded, it is reasonable to assume a cause-effect relation between the documented vitamin B<sub>12</sub> deficiency and the intractable seizures, because the patient remained seizure free after starting cobalamin therapy and even after stopping the AEDs. Although the neurologic complications of vitamin B<sub>12</sub> deficiency are myriad (1–3), seizure is an uncommon manifestation of this deficiency in adult individuals (4,5). Whether the polyneuropathy in this patient was caused by a vitamin B<sub>12</sub> deficiency or the PHT administration could not be confirmed on the initial NCS. After cobalamin therapy, the symptoms of polyneuropathy resolved, and the NCS 3 months later was normal, except for an absence of bilateral H-reflexes. During this period, PHT was still administered; therefore the polyneuropathy was most likely caused by a vitamin B<sub>12</sub> deficiency, rather than the PHT administration.

The crucial metabolic events leading to seizures in cobalamin deficiency are still uncertain, but experimental studies have suggested that homocysteinemia might play a role. Vitamin B<sub>12</sub> is essential for remethylation of homocysteine to methionine (6). As shown in our patient, the homocysteine level increased with the deficiency of vitamin B<sub>12</sub> and returned to a normal level after the cobalamin replacement therapy. Systemic administration of high doses of homocysteine in animals has produced convulsive seizures (7). Homocysteine and its product, homocysteic acid, have been proven to induce seizures in adult as well as immature rats, with some age-dependent differences in the seizure patterns (i.e., seizures are longer and more severe in immature rats than in adult rats) (7,8). These results showed that younger animals are more prone

to homocysteine-induced seizures, which most likely reflects the immaturity of the blood-brain barrier (8). This may explain why epileptic seizures are common manifestations of congenital cobalamin deficiency in infants (9) but are rare in adult patients.

The failure to recognize vitamin B<sub>12</sub> deficiency as the etiology for epileptic seizures is complicated by the absence of macrocytic anemia, which is widely regarded as the cardinal feature of this disease (1). However, among 141 consecutive patients with neuropsychiatric abnormalities due to cobalamin deficiency in one study, 28% had no anemia or macrocytosis (2). Given that 31% of the patients with epilepsy having their first seizure after age 50 years had seizures of unknown origin (10), and an examination of the cobalamin level is seldom part of a routine seizure evaluation, seizures caused by cobalamin deficiency are probably misdiagnosed. Our report highlights the importance of placing vitamin B<sub>12</sub> deficiency in the list of etiologies of epilepsy, when adult patients are first seen with unexplained recurrent seizures, even when macrocytic anemia is absent.

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