Epilepsi 2017;23(2):77-80 DOI: 10.14744/epilepsi.2016.08760

CASE REPORT / OLGU SUNUMU

Epileptic Spasms and Partial Seizures Associated with Vitamin B12 Deficiency: Case Report and Literature Review

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B12 Vitamini Eksikliğine Eşlik Eden Epileptik Spazm ve Parsiyel Nöbetler: Olgu Sunumu ve Literatür İncelemesi

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Summary

Epileptic spasms associated with vitamin B12 deficiency are rare. Epileptic spasms in addition to partial seizures due to vitamin B12 deficiency have never been reported in the literature. A 3½-month-old girl presented to clinic with partial seizures and epileptic spasms. An extensive workup for metabolic disorders and a 3 Tesla magnetic resonance imaging (MRI) of brain were normal. However, the exclusively breast-fed infant and her mother had low vitamin B12 levels, so both were given intramuscular (IM) vitamin B12 injections. The infant was also treated with oral vigabatrin and IM adrenocorticotrophic hormone (ACTH) injections. Patient's seizures stopped; however, developmental delay and hypotonia remained. Seizures associated with vitamin B12 deficiency in infants are rare, but vitamin B12 level should always be checked as part of routine diagnostic workup.

Keywords: Epileptic spasms; partial seizures; vitamin B12 deficiency.

Özet

B12 vitamini eksikliğine eşlik eden epileptik spazmlar oldukça nadirdir. Epileptik spazm ve birlikte görülen parsiyel nöbetler literatürde daha önce tanımlanmamıştır. Üç buçuk aylık kız çocuğu hastanemize epileptik spazm ve parsiyel nöbetler ile başvurdu. Hastanın 3 Tesla kraniyal manyetik rezonans görüntüleme ve detaylı metabolik taraması tamamen normal bulundu. Ancak sadece anne sütü ile beslenen hastada ve annesinde B12 vitamini düzeyleri düşük idi. Her ikisinde de B12 vitamini replase edildi, ayrıca hastanın nöbetleri için oral vigabatrin ve İM ACTH kullanıldı. Hastanın nöbetleri durmasına rağmen hipotoni ve nöromotor gelişim geriliği halen devam etmekteydi. B12 vitamini eksikliğine eşlik eden nöbetler infantlarda nadir görülmekle birlikte, serum B12 düzeyi mutlaka rutin yapılan testlerin arasında olmalıdır.

Anahtar sözcükler: Epileptik spazm; parsiyel nöbetler; B12 vitamini eksikliği.

Introduction

Vitamin B12 deficiency is associated with neurological symptoms. Common clinical conditions related to B12 deficiency are epileptic seizures, hypotonia and developmental delay.[1,2] B12 deficiency has rarely been associated with infantile spasms in the literature. Presently described is a case of both infantile spasms and partial seizures originating from temporal lobe associated with maternal nutritional vitamin B12 deficiency.

Submitted *(Geliş)*: 22.05.2016
Accepted *(Kabul)* : 09.07.2016
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Case Report

A 3½-month-old girl was brought to pediatric neurology clinic with typical infantile spasms as well as episodes of stiffening, staring, and mouth-smacking starting 2 weeks before presentation. Pregnancy and birth history of infant were unremarkable. She was the only child of non-consanguineous parents. Physical examination revealed no dysmorphic features, hepatosplenomegaly or neurocutaneous findings. Head circumference was 41 cm (75-90 p). The infant had hypotonia and developmental delay; she did not have a good eye contact, smiled very rarely, and did not reach for objects. She was not able to lift chest off the table in prone position. Laboratory workup revealed low vitamin B12 level: 95 pg/mL (normal: 180–914). Patient did not have megaloblastic anemia, hemoglobin level was 11.3 g/dL with mean corpuscular volume (MCV) value of 79.8 fl. Magnetic resonance imaging (MRI) of brain (3 Tesla) and metabolic screening (ammonia, lactate, tandem mass and urine organic acids, liver and kidney function tests, glucose, uric acid, thyroid function tests and folate) were normal. Her electroencephalogram (EEG) revealed hypsarrhythmia (Figure 1a). Right temporal seizure lasting 2 minutes was recorded during which staring, motionlessness, and turning blue were observed (Figure 1b). Mother's vitamin B12 level was checked and was also found to be low: 143 pg/ml (normal:180–914). Mother had no complaints related to hematological or nervous systems; however, she indicated she preferred not to consume animal products. Patient received vigabatrin treatment, starting with 50 mg/kg/day and increasing to 100 mg/kg/day. B12 deficiency was also corrected with intramuscular (IM) injections (500 µg cyanocobalamine) every other day for 5 doses, followed by 3 times weekly for 1 week, 2 times weekly for 1 week, and once weekly injections for a total duration of 2 months. Vitamin B12 level was increased to 600 pg/mL at the end of 2 months. Patient continued to receive monthly vitamin B12 injections (500 µg) afterwards. Although vigabatrin initially totally controlled seizures, they returned and she needed a larger dose of the medication (150 mg/kg/day). She was given 25 units synthetic ACTH IM injections which finally controlled her seizures. At 8½ months old she still had developmental delay and hypotonia despite cessation of seizures.

Discussion

West syndrome is characterized by hysparrhythmia on EEG, developmental delay and epileptic encephalopathy.[3–5] Presently described patient had all 3 features of West syndrome.

She also had partial seizures originating from temporal lobe. Both seizure types in the same patient due to vitamin B12 deficiency has not been reported in the literature. Although there may be a cause-effect relationship between low vitamin B12 status and seizures in our patient, co-occurrence is always a possibility. As metabolic and structural causes of epilepsy were ruled out by normal metabolic screening and normal brain MRI, it is believed that most likely cause of seizures was vitamin B12 deficiency.

Patient did not have macrocytic anemia on complete blood count (CBC) and no methylmalonic acid was found in urine

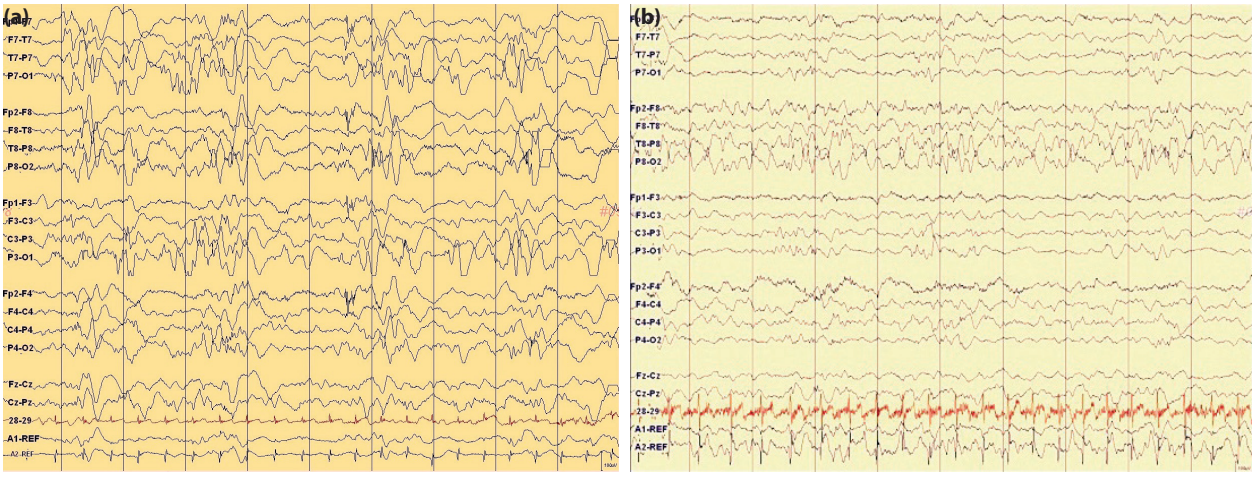

Fig. 1. **(a)** Typical hypsarrhythmia findings in EEG (interictal). **(b)** Seizure originating from right temporal lobe.

organic acids test. B12 deficiency without megaloblastic anemia has been reported previously in the literature.[3,4,6]

There are very few case reports related to B12 deficiency associated with West syndrome in the literature. Erol et al. reported an infant with vitamin B12 deficiency in the absence of macrocytic anemia.[3] Serin et al. described a 6-month-old boy with West syndrome related to severe vitamin B12 deficiency.[4] Malbora et al. described 2 unrelated infants having infantile spasms associated with vitamin B12 deficiency related to maternal nutritional deficiency.[7] A child with infantile spasms and developmental delay was also described.[8] Other types of seizures have been described more frequently in the literature.[1,9–11] İncecik et al. reported 7 infants with vitamin B12 deficiency, 4 of whom had generalized tonic-clonic seizures, 1 had generalized tonic and 2 had focal seizures.[1] None of the infants in their case series had infantile spasms. Taşkesen et al. reported 12 children with seizures of 42 with nutritional vitamin B12 deficiency. Ten patients had generalized tonic-clonic seizures, 1 had focal seizures and 1 had absence seizures. None of their patients had infantile spasms.[11] No patient with both infantile spasms and partial seizures has been described in the literature.

Pathophysiology of epileptic seizures associated with vitamin B12 deficiency is still unclear. Vitamin B12 acts as a coenzyme in an important reaction that is needed for myelin synthesis and stabilization: the conversion of methylmalonyl-CoA into succinyl CoA by the enzyme methylmalonyl-CoA mutase.[12,13] Methylmalonic acid is a myelin destabilizer, excess causes the synthesis of abnormal fatty acids instead of myelin.[6] These abnormal fatty acids are incorporated into neuronal lipids, leading to formation of a fragile myelin sheath, resulting in central nervous system (CNS) dysfunction.[14] It has been suggested that increased levels of homocysteine and methylmalonic acid with altered methionine synthesis contribute to demyelination, leading to axonal degeneration.[1] Another cause is related to excitatory glutamate and homocysteic acid pathways. Homocysteic acid, a metabolic product of sulfur-containing amino acids, is thought to be possible cause of epileptic attacks.[15] Homocysteine acts like an excitatory neurotransmitter, competing against gamma-aminobutyric acid (GABA).[16] Exaggerated effect of glutamate has been revealed in animal studies.[15] The main cause of neural damage has been attributed to elevated homocysteine levels. Homocystinuria-induced endothelial dysfunction results in neuronal damage by promoting mitochondrial dysfunction and apoptotic cell death.[2] It has been suggested that cerebral neurons with destroyed myelin sheaths secondary to vitamin B12 deficiency are more susceptible to the excitatory effects of glutamate.[16]

Insufficient synthesis of succinyl-coA cannot fully compensate for sufficient synthesis of glycine and can lead to insufficient heme synthesis. Glycine may be deposited in tissues. Glycine is an important excitatory neurotransmitter released from inhibitory interneurons in the spinal cord and brainstem, and is an agonist of glycine receptors. Glycine is co-agonist of glutamate in glutamergic N-methyl-D-aspartate (NMDA) receptors in the brain, and may be cause of abnormal movements and convulsions.[17] In a recent study it was mentioned that pro-inflammatory cytokines IFN-γ, IL-1β, IL-2, IL-6, IL-8, TNF-α; granulocyte-macrophage colony stimulating factor (GM-CSF); and anti-inflammatory cytokine IL-10 are all involved in the pathogenesis of epilepsy by exacerbating tissue injury.[18,19] Decreased cytokine activity is observed after initiation of vitamin B12 treatment, preventing further seizures.[13]

Conclusion

Vitamin B12 deficiency is rarely associated with infantile spasms. This is the first case report of a child with both infantile spasms and partial seizures associated with vitamin B12 deficiency. Vitamin B12 status should always be checked as part of routine diagnostic workup in these patients.

Conflict of interest

None declared.

Authorship contributions

Concept: U.I.; Design: U.I.; Data collection &/or processing: S.B.; Analysis and/or interpretation: U.I.; Literature search: S.B.; Writing: U.I., S.B.; Critical review: U.I.

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