Seizure (2007) **16**, 69—73

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Seizures during treatment of Vitamin B_{12} deficiency

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Received 3 March 2005; received in revised form 12 September 2005; accepted 31 October 2006

KEYWORDS
Seizures;
Vitamin B_{12} treatment

Summary Epileptic seizures during infancy have a wide variety of clinical presentations and the outcome differs according to the etiology. Among the benign and rare causes of infantile seizures, Vitamin B_{12} deficiency has been encountered. Common symptoms of Vitamin B_{12} deficiency in infants include megaloblastic anemia, feeding difficulties, developmental delay, microcephaly, failure to thrive, hypotonia, lethargy, irritability, involuntary movements, seizures and cerebral atrophy. Involuntary movements and seizures may rarely be the initial symptoms of Vitamin B_{12} deficiency. Involuntary movements have also been reported to appear after initiation of Vitamin B_{12} supplementation in isolated cases, whereas, no such information exits for seizures. In this paper, three infants with Vitamin B_{12} deficiency associated with motor and mental retardation are reported because of long-lasting focal/multifocal epileptic seizures following the initiation of intramuscular Vitamin B_{12} treatment. Antiepileptics were introduced in addition to Vitamin B_{12}. Seizures disappeared within a few days or weeks; electroencephalographic findings were normalized in a few months. No relapses occurred during the follow-up period.

Introduction

Epileptic seizures during infancy are often complicated by diagnostic and therapeutic problems. Although they are less common, the benign and

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1059-1311/$ — see front matter © 2006 Published by Elsevier Ltd on behalf of British Epilepsy Association.
doi:10.1016/j.seizure.2006.10.016

treatable forms possess particular importance, because prompt diagnosis is mandatory in such conditions, to avoid unnecessary investigations and possible long-term sequale. Vitamin deficiencies constitute a major group among those conditions as they are largely preventable, and potentially reversible, but may result with serious neurological problems if not treated properly. Vitamin B_{12} is essential, and supplied by diet. Neurological problems resulting from Vitamin B_{12} deficiency have been recognized for many years.[1] The commonly developing symptoms of Vitamin B_{12} deficiency in infants include megaloblastic anemia, feeding difficulties, developmental delay, microcephaly, failure to thrive, hypotonia, and cerebral atrophy with symptoms of lethargy, cerebral involvement with irritability, and rarely seizures.[2] Involuntary movements have been reported rarely to appear after the initiation of treatment with Vitamin B_{12} injection,[3–5] but no such information exists in relation to epileptic seizures, as to our knowledge.

Here, we describe three cases with Vitamin B_{12} deficiency associated by psycho-motor delay in varying degrees who developed epileptic seizures during Vitamin B_{12} replacement therapy. All seizures and/or the ictal electroencephalographic (EEG) changes were focal or multifocal, long-lasting, or continuous in the form of epileptic status.

Case reports

Case 1

A 13-months-old male infant was diagnosed as having anemia related to Vitamin B_{12} deficiency, as also, motor and mental delay. He was referred to our department when twitchings on his face were started on the fourth day of the treatment with 100 μg intramuscular Vitamin B_{12} daily, as they increased in frequency and became continuous by time. He was the fourth child of non-consanguineous parents, born at term. The pregnancy and delivery were uncomplicated. He was only breast-fed until admission. Neurological examination revealed generalized hypotonia with hyperactive deep-tendon reflexes (DTRs). He was slightly malnourished. He was 73 cm (3rd percentile) and 9300 g (3rd–10th percentile), and his head circumference was 45 cm (3rd–10th percentile). The baby had poor social interaction, insufficient head control and was unable to sit without support. He had erratic myoclonias on his face and all extremities, even during sleep.

His initial blood values revealed hemoglobin (Hb) as 6 g/dL, a mean corpuscular volume (MCV) as 89 fL and Vitamin B_{12} levels as 60 pg/mL (44.28 pmol/L). Peripheral blood smear showed anisocytosis and hypersegmentation of neutrophiles; as the bone marrow aspirate revealed significant megaloblastic features. Cranial magnetic resonance imaging (MRI) showed cerebral atrophy.

An EEG recording was done immediately after admission. The EEG of the patient in a status of multifocal erratic myoclonic jerks and a sustained focal clonic seizure involving the left perioral region and the arm revealed high-voltage (200–300 μV), continuous, spike-and-wave activity with a 8–10 Hz frequency, localized in the right fronto-centro-temporal region. Fast activity with medium voltage was present on the left hemisphere, intermixed with some sharp and slow elements on the fronto-temporal region. No discrete discharges associating erratic myoclonias were visible in the EEG.

Oral clonazepam treatment (0.1 mg/kg/day) was initiated. Seizures gradually decreased within the second week and resolved completely at the third week of treatment. A second EEG 10 days after an asymptomatic period, however, showed ictal activity identical to the previous one. No more specific epileptogenic changes were present in the EEG recorded 2 months after the cessation of seizures. Marked improvement in muscle tonus, head control, and social interaction was apparent at that time. The patient is being followed by oral clonazepam and intramuscular Vitamin B_{12} treatment for about a year by now. He is seizure-free and developmental improvement continues.

Case 2

A 13-months-old male infant with mild motor and mental retardation was diagnosed as having Vitamin B_{12} deficiency and a replacement therapy with intramuscular Vitamin B_{12} (1 mg twice, weekly) was started. He was transferred to our unit due to seizures appearing on the 11th day of treatment. Seizures were right-sided, with brachio-facial involvement and of clonic type. They lasted for 5–10 min, and repeated several times a day. The patient was the fifth child of a non-consanguineous couple. He was born at term following an uncomplicated pregnancy and delivery. He had been only breast-fed. On admission, he was pale, and had mild hepatomegaly. He had mild psychomotor delay and growth retardation with a height at 10th percentile and a weight between 3rd and 10th percentiles. Neurological examination revealed mild hypotonia and hypoactive DTRs. In blood tests, Hb level was 5.2 g/dL, MCV was 104 fL, and he had hypersegmentation of neutrophiles and anisocytosis in peripheral blood smear. He was found to have low serum

Vitamin B_{12} levels as 48 pg/mL (35.42 pmol/L), and normal folate levels. His bone marrow aspiration revealed significant megaloblastic features. Cranial MRI showed mild cerebral atrophy. EEG recording during a clinically seizure-free period revealed continuous spike-and-wave activity with high amplitude (100—150 μV) and 7—8 Hz frequency, restricted to the left temporal region. Diffuse, irregular activity with mixed frequency was apparent in all other regions. Immediately after starting clonazepam, seizures disappeared. The patient is seizure-free since then. Second EEG, 2 months later, showed random sharp waves in both fronto-central regions, with left predominance. During his latest examination at 21st month, he had reached age-appropriate psychomotor development. The EEG recording repeated at this time was normal.

Case 3

A 12-months-old female with motor and mental retardation was brought to our unit due to apathy for the last few weeks. Investigations revealed Vitamin B_{12} deficiency and she was put on intramuscular Vitamin B_{12} treatment (100 μg/day). At the eighth day of the treatment, she developed some chewing movements along with clonic jerks on the left perioral muscles, and alternatingly on either, or both arms. She was the ninth child of a non-consanguineous couple. All her siblings were healthy. She was born at term with normal delivery from an uncomplicated pregnancy. The patient had been largely breast-fed. She was previously started on phenobarbitone treatment on one of her earlier hospital visits due to developmental retardation. Her parents deny any previous seizures, but were told that her EEG at that time was 'abnormal'. On admission, she was pale, and had mild hepatomegaly. She was severely malnourished with her height (66 cms) and weight (6180 g) below 3rd percentile. She had generalized hypotonia and diminished DTRs. She could not sit without support.

A complete blood count showed megaloblastic anemia with Hb level of 5.5 g/dL, and MCV of 107 fL. In peripheral blood smear, anisocytosis, poikilocytosis and hypersegmentation of the leukocytes were noted. The serum Vitamin B_{12} level was low as 57.2 pg/mL (42.21 pmol/L), and folate was normal (13.6 ng/mL). Her bone marrow aspiration revealed significant megaloblastic features. MRI of the brain showed delayed myelination and generalized cerebral atrophy. Complete blood count and serum B12 level (583 pg/mL; 430.25 pmol/L) of the mother were normal.

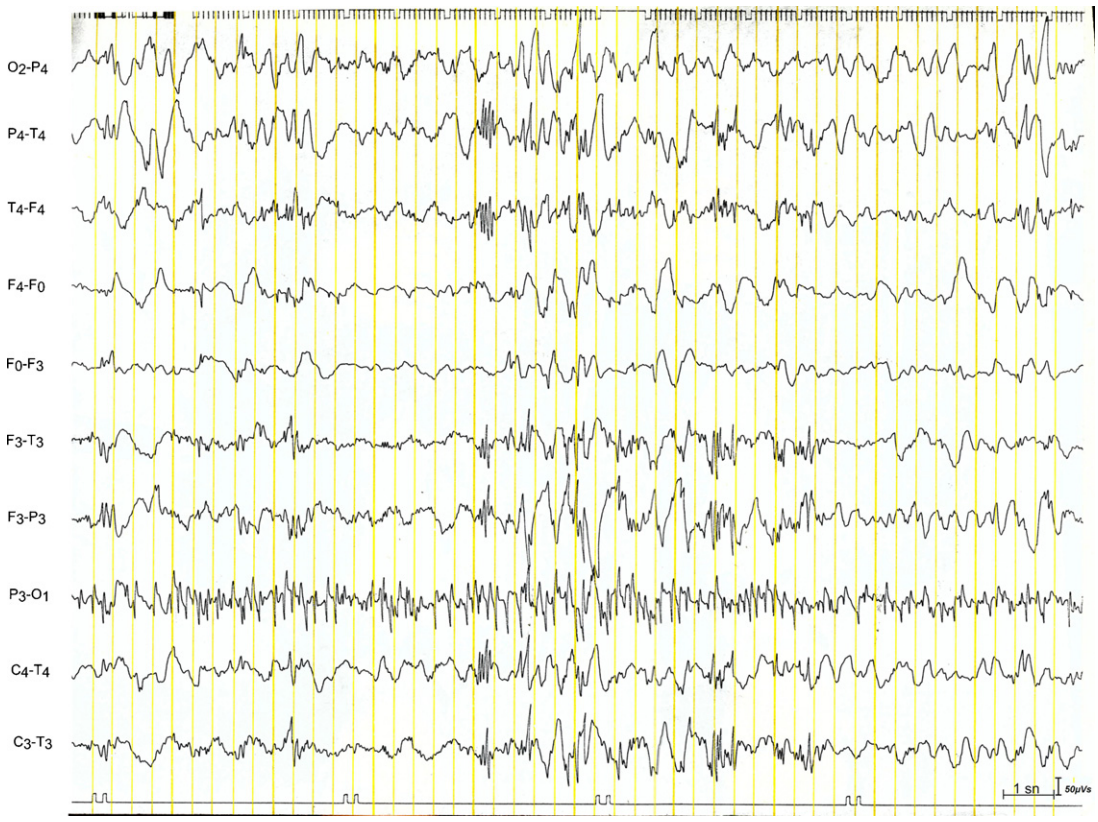

Figure 1 Ictal and interictal EEG findings of Case 3. Note the ictal discharge on left occipital region.

Repeated EEGs during the patient's stay in hospital revealed bilateral, diffuse, polyspike-and-wave discharges with high amplitude (200—300 μV) with or without interhemispheric symmetry. Ictal spiking (Fig. 1) localized to the left occipital region was accompanied by clonic contractions of right arm and chewing movements. Because of epileptic status, oral clonazepam (0.6 mg/day) was added to phenobarbitone (30 mg/day), but no improvement was seen. A steady decrease in the seizure frequency took place after valproic acid (80 mg/day) was added to the treatment. By this combination, epileptic seizures disappeared within a few days. The EEG repeated 2 months later showed a definite improvement.

In her latest control examination, the patient was 2 (4/12) years old, she had no more seizures after her discharge from the hospital. Her cognitive and neurological development was normal for her age; except, there was a mild tremor on both hands. The control EEG was normal, and cranial MRI showed improvement in both myelination and atrophic changes. She is on valproic acid and Vitamin B_{12} treatment, up to present.

A detailed work-up including serum electrolyte levels, thyroid function tests, serum folate, iron, ferritin, biotinidase activity, serum amino acid chromatography, acyl carnitine and amino acid profile with tandem mass chromatography, protein in 24 h urine, and electrocardiography revealed normal results in all patients. Unfortunately, Vitamin B_{12} levels in breast milk nor the tests for intestinal absorption were not available in our patients and the etiology of Vitamin B_{12} deficiency remained unexplained. However, since nutrition in all three patients was restricted mainly to mothers' milk with no additional support, a dietary deficiency was suspected as a possible cause for the condition.

Discussion

Vitamin B_{12} deficiency has been shown to be a benign and rare cause of epileptic seizures, during infancy.[6] Although, this deficiency can be tolerated by adults for several years through compensation by the endogenous pool, infants may become symptomatic within a few months because of the limited hepatic reserve.[7] Upon administration, increase in blood Vitamin B_{12} levels can be detected; however, the clinical signs need 4—6 months to recover. Moreover, some severe pictures, especially those related to neurological and cognitive involvement may be irreversible.[2]

Infantile Vitamin B_{12} deficiency was first defined by Jadhav et al.,[8] nutritional Vitamin B_{12} deficiency was reported later, most often in infants of vegetarian mothers.[9,10] Lundgren and Blennow also pointed out that Vitamin B_{12} deficiency could facilitate the appearance of familial benign seizures.[11] On the other hand, Vitamin B_{12} therapy was resulted in arrest of convulsions in an infant with severe epileptic encephalopathy.[12] Involuntary movements and epileptic seizures may infrequently be the initial symptoms of Vitamin B_{12} deficiency.

Involuntary movements were observed after the initiation of Vitamin B_{12} treatment [3—5]; but, no such report exists about seizures, to our knowledge. In the present cases, epileptic seizures developed during the course of intramuscular treatment with Vitamin $B_{12.}$ Although, some EEG abnormalities were reported before the substitution of Vitamin B_{12} in the third case, there was no history of seizures until they became apparent following the initiation of treatment. There was no familial history of infantile seizures either, that might have been triggered with Vitamin B_{12} deficiency. An additional feature common for all three cases presented here, was the very long-lasting focal seizures, in the form of focal or multifocal motor epileptic status accompanied by prominent EEG changes. A prompt cessation in seizures took place in one case, and within a few weeks, in the remaining two. Disappearance of the epileptogenic changes in the EEGs and normalization of the background activity were achieved within a few months, in all. It was observed that epileptic seizures did not show any relapses in the follow-up periods, and repeated EEGs revealed normal findings.

The pathogenesis of the neurological complications in Vitamin B_{12} deficiency, including myoclonus and tremor, is not clearly understood. Among different theories proposed, changes in plasma amino acid concentrations and hyperactivation of the metabolic pathways containing Vitamin B_{12} by the initiation of its treatment following a deficiency state were mainly considered in the pathogenesis of involuntary movements.[4] Also, pathophysiology of epileptogenesis due to Vitamin B_{12} deficiency is not clarified yet. Homocysteine, a sulphur-containing amino acid, has been shown to induce seizures in rats.[13—15] A clear anticonvulsant action of glutamate receptor antagonists against seizures induced by homocysteine and by homocysteic acid has been demonstrated.[16,17] 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.[18] These experimental 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 needed for a thorough understanding of all the processes involved. The assumption that a transient disequilibrium in the metabolic pathways caused by initial local deficiency and later produced excessiveness suggested for the development of involuntary movements[4] may also be relevant for the pathogenesis of the epileptic seizures following the initiation of replacement therapy by Vitamin B_{12}.

Cases reported here, suggest that Vitamin B_{12} deficiency should be considered in the etiological diagnosis of neurological symptoms in infants, especially in the presence of megaloblastic anemia and developmental delay. As well as during the deficiency state, epileptic seizures, even focal or multifocal motor epileptic status, may also be seen after the initiation of replacement therapy. Early diagnosis and treatment is important for Vitamin B_{12}-deficient children, since the age of onset and the duration of neurological symptoms may contribute to the development of irreversible deficits. It is not clearly evident from the present data whether or not prophylactic anticonvulsant treatment is needed after the acute episode subsides. Absence of seizure recurrence and normalization of the EEG within a limited time may be considered as factors in favor of eliminating long-term prophylaxis. These data suggest that in conditions where epileptic seizures may take place at the time of replacement therapy with Vitamin $B_{12,}$ antiepileptic treatment may be administered without any interruption in the replacement procedure, and, both the selection of the appropriate antiepileptic drug, as also the duration of the treatment may be decided on an individual patient's basis.

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