

# Involuntary movements after correction of vitamin B12 deficiency: a video-case report

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**ABSTRACT** – Involuntary movements can appear before and after initiation of vitamin B12 treatment. The pathogenesis of involuntary movements in vitamin B12 deficiency and their relationship with cobalamin injection remain unclear due to a lack of video-EEG documentation making the electroclinical correlation difficult to ascertain. Here, we report video-EEG and neuroimaging findings of an 11-month-old girl with vitamin B12 deficiency, who acutely developed involuntary movements a few days after initiation of vitamin B12 treatment with normal vitamin plasmatic levels. Abnormal movements were a combination of tremor and myoclonus involving the face, mouth, and left arm, which disappeared after discontinuation of therapy. [*Published with video sequences*]

**Key words:** vitamin B12 deficiency (vB12 deficiency), encephalopathy, involuntary movements, video-EEG

The clinical manifestations of vitamin B12 deficiency (vB12 deficiency) are well known and include developmental delay or regression, hypotonia, irritability, lethargy, weakness, apathy, involuntary movements, and seizures.

Involuntary movements may be part of the neurological syndrome at onset or may acutely and temporarily occur after the beginning of vB12 treatment. The first cases of involuntary movements during vB12 treatment were reported by Grattan-Smith *et al.* who described shaking movements, myoclonus, tremor, chorea, twitching, protrusion or tremor of the tongue, and wander-

ing eyes (Grattan-Smith *et al.*, 1997). It is still not clear whether the movement disorder appearing after the beginning of treatment with cobalamin is a new event or induced by treatment, or an exacerbation of a pre-existing milder movement disorder (Chalouhi *et al.*, 2008). Moreover, when this movement is a combination of tremors and myoclonus, it can be particularly difficult to differentiate from seizures (Yavuz, 2008). The electroclinical data reported in the literature are not sufficient to clarify the differential diagnosis between involuntary movements and seizures; the EEG recordings reported are often



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inaccurate because of a great deal of artefacts and are considered difficult to interpret; moreover, the EEG evaluation frequently refers to the interictal phase. Thus, the EEG is often described as normal or characterised by different EEG patterns, ranging from focal/multifocal epileptiform activities to hypsarhythmia.

We report the clinical data, video-EEG, neuroimaging findings, and follow-up of an 11-month-old female with vB12 deficiency who acutely developed a severe movement disorder five days after starting vB12 treatment. The video-EEG sequence, in particular, is an important contribution to the clinical documentation of a better description and understanding of the type and nature of such a movement disorder.

## Case report

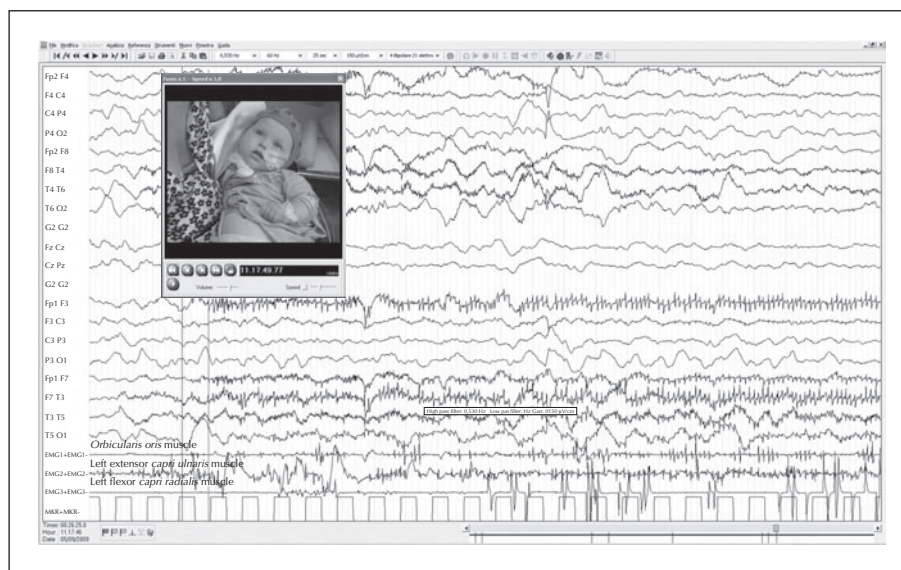
An 11-month-old girl was admitted to our emergency department because she suddenly developed tremors and myoclonic movements five days after initiation of vB12 injections for vB12 deficiency.

In the preceding week, the child was admitted to the hospital of her town because of emerging feeding difficulties, anorexia, and loss of weight. Regression of pre-existing developmental delay, hypotonia and continuous fine tremors, mainly involving trunk muscles, were observed. The girl was exclusively breast-fed and refused to take any other food. Metabolic assessment revealed megaloblastic anaemia with levels of vB12 that could not be accurately measured (<83 pg/mL, reference range: 180-1100). Vitamin B12 deficiency was also present in the mother, due to atrophic gastri-

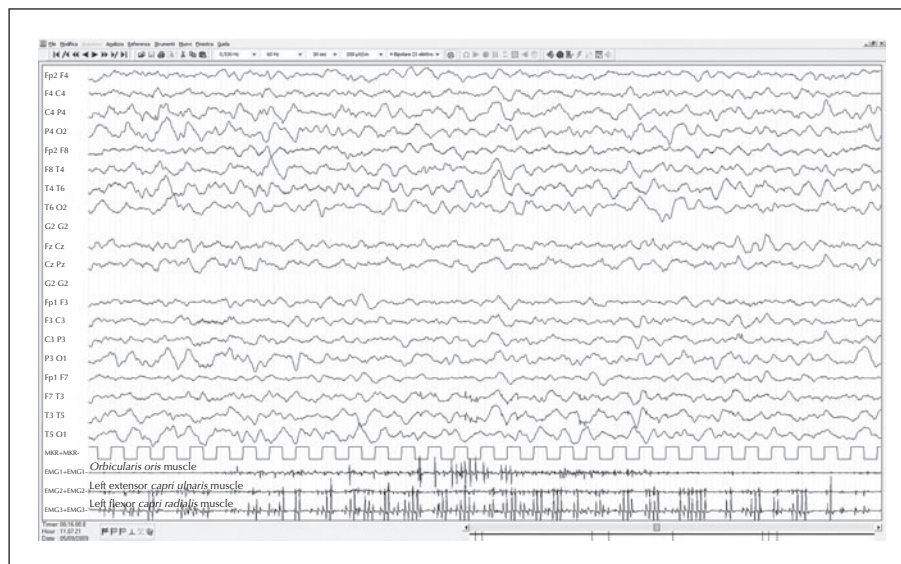
tis undiagnosed up to that point. For the mother's medical history, autoimmune thyroiditis was reported. Vitamin B12 treatment was started with daily vB12 intramuscular injections (cyanocobalamin, 1,000 µg/day). Vitamin B12 plasmatic levels normalised, the girl improved, and she was discharged from the hospital.

The day after, new tremors and myoclonic jerks suddenly appeared, mainly affecting the left arm and persisting during sleep. Myoclonic jerks were observed on the left side of the mouth, with protrusion and twitching movements of her tongue. The child appeared lethargic and hyporeactive without an evident impairment of consciousness.

The same paediatricians who visited and treated the girl before urgently sent her to our hospital with the hypothesis of an epileptic status. At that moment, the child was only receiving vB12 treatment and no previous sedation was performed. On admission, the video-EEG revealed slowing of the basal activity, consistent with diffuse encephalopathy (*figure 1, video sequence 1*). It was possible to observe rhythmic myoclonus on the EMG of flexors and extensor muscles of the left arm. A 6-8-Hz rhythmic activity was present in the anterior and central areas of the left hemisphere, due to muscular artefact. This focal EEG rhythmic activity disappeared during sleep, as well as the myoclonus of the face, and reappeared during a brief arousal, while myoclonic jerks of the arm persisted. This slow activity became more evident and synchronous, and it was possible to observe brief rhythmic sequences of rapid activity and small amplitude on the central-anterior areas, that we interpreted as sleep spindles (*figure 2, video sequence 2*). We



**Figure 1.** EEG recorded on admission, showing a slowing of the basal activity, consistent with diffuse encephalopathy and the presence of a 6-8-Hz rhythmic activity at the anterior and central areas of the left hemisphere, due to muscular artefact. EMG1: orbicularis oris muscle; EMG2: left extensor carpi ulnaris muscle; EMG 3: left flexor carpi radialis muscle.



**Figure 2.** EEG recorded during sleep; focal EEG rhythmic activity observed during wakefulness disappears, while slow activity becomes more evident and synchronous.

EMG1: *orbicularis oris* muscle; EMG2: left *extensor carpi ulnaris* muscle; EMG 3: left *flexor carpi radialis* muscle.

hypothesized a correlation between the corrective treatment and involuntary movements, and after discontinuation of the supplementation the involuntary movements rapidly disappeared. The video-EEG during wakefulness and sleep, performed a few weeks later, revealed a progressive reduction of the slow activity and the absence of pathological movements.

In the following months, the girl showed a gradual improvement of both psychomotor development and relational skills. A normalisation of the electroencephalographic pattern was observed.

During the acute manifestations, MRI revealed severe and diffuse cerebral atrophy with delayed myelination (figure 3). MRI performed at six months of follow-up showed obvious recovery with a significant reduction of the cerebral atrophy and an improvement of myelination (figure 3).

## Discussion

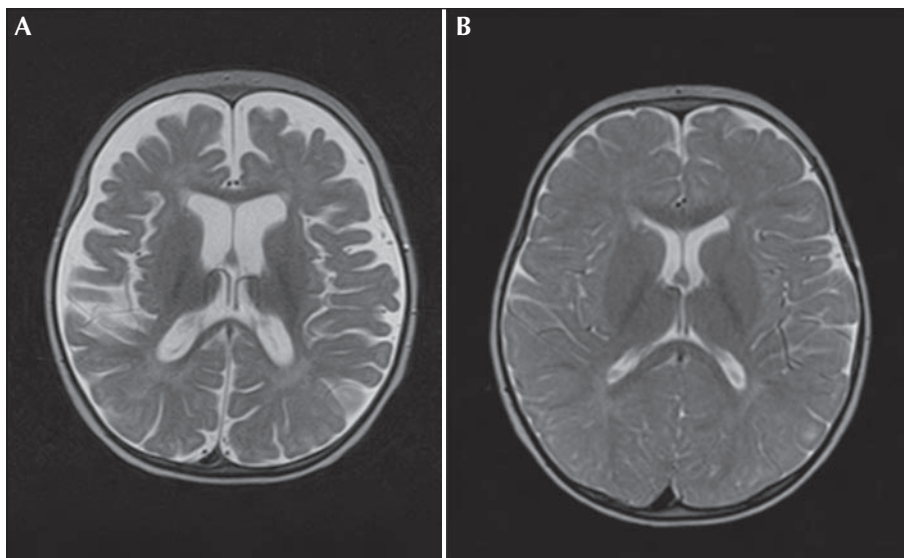
Involuntary movements are a chief component of the neurological syndrome of vB12 deficiency, together with developmental regression. They usually disappear one or two days after treatment, while the long-term prognosis of vB12 deficiency in terms of psychomotor development is thought to depend on the overall duration of the deficiency and severity of symptoms. Infants diagnosed and treated before the age of 1 year have a better neurological outcome (Chalouhi et al., 2008).

The appearance of involuntary movements in vB12 deficiency after some days of corrective treatment

with cobalamin is a rare and less well-known condition. In this case, involuntary movements are usually more severe, become more intense with tactile stimulation and on arousal, and persist, less evidently, during sleep. These movements have a “hyperkinetic” character; shaking movements, myoclonus, tremor, chorea, twitching, protrusion or tremor of the tongue, and wandering eyes are described in literature.

There is no agreement (nor sufficient clinical, humoral, and neurophysiological data) on the nature of the movement disorder. Moreover, it is not clear whether the rare movement disorder appearing after treatment with vB12 is something new, induced by treatment, or an exacerbation of a pre-existing movement disorder. In our case, clinical symptoms of low plasmatic levels of vB12 were: psychomotor regression with feeding difficulties, hypotonia, and a mild tremor mainly involving trunk muscles. This tremor gradually improved and nearly disappeared with the normalisation of vB12 plasmatic levels.

Involuntary movements that acutely developed after initiation of corrective treatment were quite different in severity and localisation. The video-EEG sequence shows a combination of myoclonus and tremor, more evident on the left arm and on the face (mouth, tongue), while the EEG is characterised by a slowing of the background activity, consistent with the lethargic and hyporeactive state of the child, without any epileptiform activity (video sequence 1). The disappearance of the muscular artefact related to the disappearance of the myoclonus of the face during sleep, with arm myoclonus persisting, remains difficult to interpret. The lethargic and hyporeactive state could not be



**Figure 3.** A) MRI performed at admission shows severe and diffuse cerebral atrophy with delayed myelination. B) MRI performed at six months of follow-up showing an important recovery with a significant reduction of the cerebral atrophy and improvement of myelination.

attributed to sedation or anaesthesia; in particular, we did not use nitrous oxide, according to the recommendation in the literature which contraindicates its use in the investigation of vB12 deficiency (Manson, 2002).

There are few descriptions of involuntary movements appearing after vB12 deficiency correction in infancy (Stollhoff and Schulte, 1987; Avci *et al.*, 2003; Casella *et al.*, 2005; Incecik *et al.*, 2010) and only one case in adult age (Celik *et al.*, 2003). The EEGs reported are usually normal (Emery *et al.*, 1997; Ozer *et al.*, 2001; Mathey *et al.*, 2007; Ozdemir *et al.*, 2010) (*table 1*), but polygraphic video-EEG documentation supporting a more precise electroclinical correlation is lacking.

Grattan-Smith *et al.* who first described the condition, raised the question of whether the involuntary movements could be a manifestation of *epilepsia partialis continua*; however a definite interpretation was not given (Grattan-Smith *et al.*, 1997). More recently, Benbir *et al.* interpreted the involuntary movements as long-lasting or continuous epileptic status (Benbir *et al.*, 2007). Several theories have been developed regarding the mechanisms underlying the neurological manifestations of vB12 deficiency. Involuntary movements appearing after the correction of deficiency are particularly difficult to explain; these could be due to an imbalance of excitatory *versus* inhibitory activity or to a dysfunction along fibre tracts, during recovery from myelin degradation (Stollhoff and Schulte, 1987).

The sudden availability of vB12 after a period of severe shortage results in intense stimulation of cobalamin and folate pathways, causing local deficiencies and excess of metabolic intermediates (Grattan-Smith

*et al.*, 1997). Another explanation thought to play a role in the mechanism of involuntary movements related to vB12 treatment is hyperglycaemia. Urinary concentrations of methylmalonic acid and homocystine are characteristically elevated in vB12 deficiency and in some cases hyperglycinuria can also be an associated finding. Two previous reports demonstrated that methylmalonic aciduria and homocystinuria resolved rapidly after the beginning of vB12 treatment before the onset of involuntary movements, but hyperglycinuria persisted and was present at the start of the movements. On the contrary, Emery *et al.* (1997) did not find elevated levels of glycine in blood or urine before treatment and at a time when the children were symptomatic (Ozdemir *et al.*, 2010).

In our case, we suggest the presence of some metabolic neurotransmitter modification rather than structural changes in the central nervous system, considering the clinical features of the involuntary movements appeared after treatment and the brief duration and timing of involuntary movements relative to vitamin administration.

The severe, diffuse cerebral atrophy with delay of myelination, evident at initial MRI, in our opinion, should be considered as expression of an encephalopathy due to the chronic deficit which gradually recovered in the following six months with the general improvement of the girl.

For the definitive interpretation regarding the origin of movement disorder (cortical, subcortical or epileptic), further information is needed including *ictal* video-EEG with polygraphy, but also plasmatic levels of vitamin B12, amino acids, and neurotransmitters. □



**Table 1.** Onset (time between initiation of B12 treatment and development of involuntary movements/seizures), clinical and EEG features, and therapy of vB12 deficiency cases reported in the literature.

	<b>Onset</b>	<b>Movements</b>	<b>EEG</b>	<b>Therapy</b>
Grattan-Smith <i>et al.</i> , 1997	2 days	shaking movements, progressively more severe (limbs, face, tongue, pharynx)	slowing of basic rhythms but no epileptiform activity despite a number of staring episodes during the recording; movement artefacts; no epileptiform activity	ns
	2 days	rapid twitching movements around the mouth and tongue and of the orbicularis oculi	ns	ns
		continuous flexion-extension movements of right hand	slowing of basic rhythms for age, with lower amplitudes over the frontal regions; no epileptiform activity was present; <i>epilepsia partialis continua?</i>	PB
Lundgren <i>et al.</i> , 1999	ns	after treatment with vigabatrin, TC convulsions disappeared and child developed episodes of non-convulsive loss of muscular tonus	normal interictal EEG; ictal registration showing a 2-min long period of electrographic seizure activity over the left frontal region without clinical symptoms	VGB
Emery <i>et al.</i> , 1997	3 days	tremor of the right arm (progressed to the leg and then the entire body)	EEG on admission: slightly slow background activity; during therapy: normal	ns
	3 days	more prominent protrusion of the tongue, generalised tremor, and chorea of the arms	three weeks after, EEG was normal	ns
Ozer <i>et al.</i> , 2001	3 days	shaking movements, combination of tremor and myoclonus, progressively involving tongue, face, pharynx and limbs	EEG did not reveal epileptiform activity from the central regions	CZP
	2 days	shaking movements, involving hands and then tongue and face	EEG did not demonstrate any abnormality	ns
Avci <i>et al.</i> , 2003	3 days	smacking and twitching movements of the lips and marked tremor of the tongue	normal EEG	ns
Casella <i>et al.</i> , 2005	2 days	intense and generalised tremors and myoclonic jerks	no concurrent EEG abnormality	ns
Chalouhi <i>et al.</i> , 2008	3 days	shaking movements, combination of tremor and myoclonus, initially affecting the left hand and forearm, then the left leg	EEG did not reveal epileptiform activity from central regions, although was contaminated by a great deal of movement artefact	DZP, CZP

Table 1. (Continued)

	<i>Onset</i>	<i>Movements</i>	<i>EEG</i>	<i>Therapy</i>
Mathey <i>et al.</i> , 2007	1 month	abnormal paroxystic movements	normal	ns
	ns	tremors, starting at the left arm and then diffusing to the forearms	ns	ns
Korenke <i>et al.</i> 2004		at 4 months, drowsiness and therapy-resistant seizures (GTC), tremor observed at 3 months	generalised slow activity on admission, epileptic discharges at 8 months, normal at 1 year	B6, PB
Benbir <i>et al.</i> , 2007	4 days	twitching on face, multifocal erratic myoclonic jerks, focal clonic seizure (left perioral region and arm)	continuous SW activity (8-10 Hz) in the right fronto-central temporal region, fast activity (medium voltage) on the left hemisphere, intermixed with some sharp and slow elements on the fronto-temporal region, no discrete discharges associated with erratic myoclonias	CZP
		seizures on the 11th day of treatment (clonic, right-sided, with brachio-facial involvement)	continuous SE activity (high amplitude, 7-8 Hz) on the left temporal region. Diffuse, irregular activity with mixed frequency in all other regions	CZP
	8 days	chewing movements along with clonic jerks of the left perioral muscles, and alternating on either, or both arms	diffuse poly SW discharges (high amplitude), ictal spiking localised to the left occipital region accompanied by clonic contractions of right arm and chewing movements	PB, CZP, VPA
Ozdemir, 2010	2 days	severe tremor affecting both hands and chin	normal	CZP
	5 days	shaking movements affecting both hands and limbs, progressively increasing and involving the tongue and face	normal	CZP, piracetam
	4 days	irregular movements involving hands and tongue	normal	CZP

ns: not specified; PB: phenobarbital; VGB: vigabatrin; CZP: clonazepam; DZP: diazepam; VPA: valproic acid.

**Disclosures.**

The authors have no financial disclosures to report. The authors have declared that no conflict of interest exists.

**Legends for videosequences****1 Video sequence 1**

The video-EEG recorded at admission shows the presence of jerking movements which appeared a few days after the initiation of treatment and the normalisation of vB12 plasmatic levels; movements have a multifocal presentation with tremors and parcellar myoclonic jerks affecting the left arm, fine tremors of the left side of the mouth, and protrusion and twitching movements of her tongue, persisting during sleep. The child appears lethargic and hyporeactive, without obvious impairment of consciousness. The EEG shows a slowing of the basal activity, consistent with diffuse encephalopathy and the presence of a 6-8-Hz rhythmic activity at the anterior and central areas of the left hemisphere, due to muscular artefact.

**2 Video sequence 2**

During sleep, focal EEG rhythmic activity disappeared, even if myoclonic jerks persisted, while slow activity became more evident and synchronous.

**Key words for video research on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)**

*Syndrome:* not applicable

*Etiology:* vitamin B12 deficiency

*Phenomenology:* nonepileptic paroxysmal event

*Localization:* not applicable

**References**

Avci Z, Turul T, Aysun S, Unal I. Involuntary movements and magnetic resonance imaging findings in infantile cobalamin (vitamin B12) deficiency. *Pediatrics* 2003; 112: 684-6.

Benbir G, Usyal S, Saltik S, et al. Seizures during treatment of vitamin B12 deficiency. *Seizure* 2007; 16: 69-73.

Casella EB, Valente M, Medeiros de Navarro J, Kok F. Vitamin B12 deficiency in infancy as a cause of developmental regression. *Brain & Develop* 2005; 27: 592-4.

Celik M, Barkut IK, Oncel C, Forta H. Involuntary movements associated with vitamin B12 deficiency. *Parkinsonism Relat Disord* 2003; 10: 55-7.

Chalouhi C, Faesch S, Anthoine-Milhomme MC, Fulla Y, Dulac O, Chéron G. Neurological consequences of vitamin B12 deficiency and its treatment. *Pediatr Emerg Care* 2008; 24: 538-41.

Emery ES, Homans AC, Colletti RB. Vitamin B12 deficiency: a cause of abnormal movements in infants. *Pediatrics* 1997; 99: 255-6.

Grattan-Smith PJ, Wilcken B, Procopis PG, Wise GA. The neurological syndrome of infantile cobalamin deficiency: developmental regression and involuntary movements. *Mov Disord* 1997; 12: 39-46.

Incecik F, Ozlem Herguner M, Altunbasak S, Leblebisatan G. Neurological findings of nutritional vitamin B12 deficiency in children. *Turk J Pediatr* 2010; 52: 17-21.

Korenke GC, Hunneman DH, Eber S, Hanefeld F. Severe encephalopathy with epilepsy in an infant caused by subclinical maternal pernicious anaemia: case report and review of the literature. *Eur J Pediatr* 2004; 163: 196-201.

Lundgren J, Blennow G. Vitamin B12 deficiency may cause benign familial infantile convulsions: a case report. *Acta Paediatr* 1999; 88: 1158-60.

Manson JI. Involuntary movements in infantile cobalamin deficiency appearing after treatment. *Pediatr Neurol* 2002; 26: 411.

Mathey C, Di Marco JN, Poujol A, et al. Failure to thrive and psychomotor regression revealing vitamin B12 deficiency in 3 infants. *Arch Pediatr* 2007; 14: 467-71.

Ozdemir O, Baytan B, Gunes AM, Okan M. Involuntary movements during vitamin B12 treatment. *J Child Neurol* 2010; 25: 227-30.

Ozer EA, Turker M, Bakiler AR, Yaprak I, Ozturk C. Involuntary movements in infantile cobalamin deficiency appearing after treatment. *Pediatr Neurol* 2001; 25: 81-3.

Stollhoff K, Schulte FJ. Vitamin B12 and brain development. *Eur J Pediatr* 1987; 146: 201-5.

Yavuz H. Vitamin B12 deficiency and seizures. *Dev Med Child Neurol* 2008; 50: 720.