Title page:

Title: Simultaneous acute presentation of generalized chorea and subacute combined degeneration secondary to vitamin b12 deficiency.

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Main text

Subacute combined degeneration (SCD) of the spinal cord is the typical neurological presentation of vitamin B12 deficiency. Acute onset of movement disorders (MD) associated with vitamin B12 deficiency are rare with only five cases reported in the literature and none discarding SCD clinically or with spine MRI [1-5].

We report an exceptional presentation of vitamin B12 deficiency with acute onset of choreic movements and myelopathy, followed by striking improvement after treatment with parenteral cyanocobalamin.

An independent, cognitively normal eighty-year-old woman presented to the emergency room with confusion, involuntary generalized hyperkinetic movements [video 1] and unstable gait. According to relatives, disease onset was 24 hours before arrival to our centre. She had a past medical history of hypertension treated with angiotensin receptor antagonists and mild dyslipidemia without medical treatment.

On examination, the patient was disoriented in space and time and presented generalized severe uncontrolled choreic movements affecting her four limbs without facial or tongue involvement. The abnormal movements did not change with visual fixation. Additionally, marked generalized proprioceptive hypoesthesia with sensory ataxia in the four limbs as well as wide-based gait ataxia with inability to walk unassisted were noted. Muscle strength was normal, reflexes were abolished and Romberg´s sign was present.

Laboratory tests showed severe pancytopenia: hemoglobin 7,4 g/dL with mean corpuscular volume 115 fl, leucocyte count 2,06x10^3/µl, platelets 114x10^3/µl. Serum folate was normal but vitamin B12 level was below detectable reference range (under 83 pg/mL). Methylmalonic acid and homocysteine levels were not requested. Peripheral blood smear showed hypersegmented neutrophils suggestive of megaloblastic anemia. Thyroid function was normal and no other clinical or analytical markers of autoimmune diseases were found. Cerebrospinal fluid was normal. Syphilis, HIV serologies, and ANAs were negative. An upper gastrointestinal endoscopy disclosed atrophic pangastritic and antibodies against gastric parietal cells were positive at 1/160 suggesting a diagnosis of pernicious anemia.

Cervical magnetic resonance imaging (MRI) showed bilateral and symmetric T2 hyperintensities of posterior columns from C2 to C6-C7 highly suggestive of SCD (Figure 1). Cranial MRI did not disclose any acute lesions and body CT scan was normal.

The patient was transfused with two units of red blood cells. Treatment with intramuscular cyanocobalamin was started with 1000 mcg daily during 10 days followed by 1000 mcg weekly during 6 weeks, and monthly thereafter, alongside folic acid 5 mg once daily. Progressive clinical and haematological improvement were noted since the seventh day of treatment. Upon discharge, fifteen days after admission, only mild distal choreic movements affecting her upper limbs were present [video 2] being able to walk with one support. The patient was asymptomatic at five months' follow-up.

Vitamin B12 deficiency can lead to the development of haematological, neurological and psychiatric symptoms; however, SCD with peripheral neuropathy and spinal cord involvement is the classical neurological syndrome[1]. On the other hand, MD such as chorea, dystonia, parkinsonism, blepharospasm, orthostatic tremor or myoclonus have rarely been reported [see table 1] [1-11].

In our patient, the dramatic response to vitamin B12 replacement in the context of pernicious anemia, the presence of lesions typical for SCD and the exclusion of other reasonable causes of acute chorea suggest vitamin B12's causative role in MD appearance.

Since Paccheti C. [2] reported the first case of chorea in the context of vitamin B12 deficiency, another five cases have been described [1-5]. On top of that, cerebellar ataxia [3] has also been reported related to vitamin B12 deficiency but never with acute onset or associating myelopathy.

Pathophysiology of chorea induced by vitamin B12 deficiency is not completely understood. Low levels of vitamin B12 can lead to neurotoxic elevated levels of methylmalonic acid, methyl-tetra-hydrofolate (MTHF) and homocysteine [1]. In addition methylmalonic acid produces abnormal myelination contributing to the emergence of MD in a way similar to what happens in inborn metabolic disorders such as methylmalonic academia [1]. On the other hand, MTHF accumulation can produce neuronal damage similar to the one seen in patients with Huntington´s disease [1]. Finally, hyperhomocysteinemia has a neurotoxic N-methyl-D-aspartate (NMDA) agonist action leading to an excitatory activity in thalamocortical pathway that also results in the development of MD [1, 3].

In our patient, a sensorial deafferentation cannot be definitely ruled out as a possible contributor to the development of abnormal movements. In fact, the term "pseudoathetosis" has been coined for the slow, writhing movements due to loss of proprioception, which might be acute [12]. However, despite absence of craniofacial involvement, the lack of change in patient's movements with eye open and eye closed manoeuvres as well as its velocity support the appearance of real chorea as a primary phenomenon in vitamin B12 deficiency instead of its emergence as secondary to the SCD or exclusively due to the sensory deficit.

This case report illustrates the importance of taking into consideration vitamin B12 deficiency in the differential diagnosis of acute-onset chorea, especially when other typical signs as vibratory and positional sensation impairment, anemia and macrocytosis are present. The striking reversibility of neurological

symptoms with replacement therapy supports a causative role for vitamin B12 deficiency in the genesis of the movement disorder in our patient and advocates the need for early diagnosis and supplementation, which may be essential to avoid permanent sequelae.

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Legends

Figure 1. Sagittal T2 cervical magnetic resonance imaging showing bilateral and symmetric hyperintensities of posterior columns from C2 to C6-C7.

Video 1. Severe generalized choreoathetoid movements with greater involvement of upper limbs on patient admission.

Video 2. Mild distal choreothetoid movements 14 days after initiation of replacement therapy.

Table 1 Case reports of movement disorders associated with vitamin B12 deficiency in adults.

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Table 1.
Reports of movement disorders associated with vitamin B12 deficiency in adults

Author and year	Age	Gender	B12 vitamin levels (reference range)	Homocysteine levels (reference range)	MMA acid levels (reference range)	Folic acid levels (reference range)	Haematological disturbances	Movement disorder	Subacute combined degeneration*	Treatments administered (apart from IM cyanocobalamin)	Improvement time after vitamin B12	Others
Natera E 2018 (present case)	70	F	< 82 pg/mL (180-914)	N/A	N/A	17,50 ng/mL (3,90-20)	+	Generalized chorea	+	Folic acid	2 weeks	Propioceptive dysfunction, Romberg´s sign present Positive anti-parietal cells antibodies Atrophic gastritis
Gascón-Giménez F 2017	47	M	148 pg/mL (200-900)	N/A	N/A	N/A	+	Choreoatetoid movements	N/A	Immunoglobulins IV Tiapride	1 week	Migraine, moderate enolism
Santos AF 2015	71	M	83 pg/mL (> 250)	N/A	N/A	N/A	-	Parkinsonism	N/A	Levodopa	9 months	Chronic gastritis
De Souza A 2013	31	M	195 pg/mL (211-911)	16,75 µmol/L (9-14)	N/A	N/A	-	Generalized chorea	N/A	Folic acid Haloperidol	3 months	Marfabiud habitus
Sharieff AZ 2012	43	M	254 pg/mL (200-900)	89,1 µmol/L (4-15,2)	36000 nmol/L (87-318)	Normal (N/A)	+	Delayed saccades, Parkinsonism	+	-	1 week	Globus pallidus hyperintensities. Cognitive, piramidal and proprioceptive sensory alterations Romberg´s sign present
Edvardsson B 2011	62	M	104 pmol/L (150-650)	25 µmol/L (<15)	24 nmol/L (7-40)	0,54 µmol/L (<42)	-	Chorea	N/A	-	3 months	Positive anti-intrinsic factor antibodies
Edvardsson B 2010	51	M	16 pmol/L (150-650)	43 µmol/L (<15)	N/A	24 nmol/L (7-40)	+	Blepharospasm	N/A	-	9 months	Positive anti-intrinsic factor antibodies. Decreased vibratory sensation.
Shyambabu C 2008	40	M	62,96 pg/mL (243-894)	50 µmol/L (5-15)	N/A	N/A	+	Chorea and cerebelar ataxia	N/A	-	2 months	Limb ataxia Hyperpigmentation Parietal acute infarct
Kumar S 2004	55	M	5 pg/mL	N/A	N/A	98 ng/mL (normal)	+	Parkinsonism	N/A	-	1 week	Positive anti-intrinsic factor antibodies Atrophic gastritis
Çelik M 2003	55	M	< 30 pg/mL (reference range N/A)	N/A	N/A	N/A	+	Myoclonus	N/A	-	1 week	Cognitive disturbances Sensory-motor demyelinating polyneuropathy
Pacchetti C 2002	71	M	124 pg/mL (243-894)	40,1 µmol/L (<15)	N/A	Normal (N/A)	+	Right hemichorea, blepharospam, postural tremor	-	Amantadine Tiapride Folic acid	1 year	Sensory neuropathy
Benito-León J 2000	68	M	132 ng/L (222-753)	N/A	N/A	N/A	-	Orthostatic tremor	N/A	Clonazepam	1 year	Positive Schilling test Sensory axonal polyneuropathy

M: male; F: female; MMA = methylmalonic acid; IM: intramuscular; IV intravenous; +: present; - : absent; N/A: not available. Subacute combined degeneration was considered when spinal MRI showed hyperintense lesions within the dorsal columns and discarded if spinal MRI did not have this findings.

Figure 1


C
RM DE CRANEO SIN/CON CONTRASTE

LOC:23,10
THK:3 SP:3,30
HFS
A
P
SENSE-NV-16
NEX:8
EC:1
SE
FA:90
TR:3279,71
TE:120
AQM:244\0\0\175
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Z:1,14
C:235
W:408
DFOV:21,8x21,8cm
Compressed 13:1
IM:8 SE:301
P
cm