CASE REPORT

Neuroregression as an initial manifestation in a toddler with acquired pernicious anaemia

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SUMMARY

The aetiology spectrum for neuroregression in infants and toddlers is diverse. Vitamin B₁₂ deficiency-mediated neuroregression is less commonly considered as a differential. Prevalence of pernicious anaemia in the general population is 0.1% and is extremely rare in children. We describe a 35-month-old toddler with neuroregression, seizures, coarse tremors, bleating cry and neuropathy. His clinical symptomatology mimicked grey matter degenerative illness and infantile tremor syndrome, a nutritional deficiency-mediated movement disorder. His vitamin B₁₂ level was low and serum homocysteine level was elevated. Haematological manifestations were not overt and anti-intrinsic factor antibody was positive. With parenteral vitamin B₁₂ therapy, there was a dramatic response with clinical and laboratory translation. This report emphasises the need for a high index of suspicion and screening for markers of vitamin B₁₂ deficiency in all children with unexplained acute or subacute neuroregression, seizures and movement disorders as it is potentially reversible.

BACKGROUND

Vitamin B₁₂ is essential for haematopoiesis, normal growth and development in the fetus, infants and children. Neurological presentations in children with vitamin B₁₂ deficiency are seizures, hypotonia, irritability, developmental delay, developmental regression and movement disorders while those in adults usually manifest with dementia, polyneuropathy, autonomic neuropathy, optic neuropathy, cerebellar symptoms and subacute combined degeneration.¹ We describe a well thriving 35-month-old toddler with neuroregression, seizures, coarse tremors, a bleating cry and neuropathy related to vitamin B₁₂ deficiency due to acquired pernicious anaemia. With parenteral vitamin B₁₂ therapy, there was a dramatic response in the clinical and laboratory parameters. This report emphasises the need for a high index of suspicion and screening for markers of vitamin B₁₂ deficiency in all children with unexplained acute or subacute neuroregression, seizures and movement disorders, as it is a potentially reversible syndrome.

CASE PRESENTATION

A 35-month-old boy was born second in birth order to a non-consanguineously married couple from Bangladesh. He was delivered at term by caesarean section with a birth weight of 2800 g. His premorbid development was normal. He developed excessive irritability and poor sleep following recovery from a short febrile illness. Two weeks

later, he developed a 1 h long duration of unresponsiveness associated with frequent episodes of eyelid blinking and multiple brief episodes of left focal motor seizures with generalisation the following day. He was admitted in a local hospital and investigated with cerebrospinal fluid analysis and CT of the brain which were normal. EEG showed diffuse slowing and he was treated with three anticonvulsants following which the seizures were controlled.

A month later, he developed coarse tremors involving all four limbs and the head impairing his gross and fine motor activities. He had a gradual regression of developmental milestones and could only sit with support. His speech deteriorated and he developed reduced fluency with echolalia. He became very irritable and developed a bleating cry and generalised floppiness of all four limbs. From 1 year of age, he had recurrent diarrhoea and was started on a lactose-free diet. However, there was no history of abdominal distension, perianal excoriation, skin rashes, hyperpigmentation or abdominal surgeries. His mother was not a vegetarian and his family history was not contributory. Two months into the illness, he was brought to our hospital for further evaluation and management of neurological syndrome. He had developed lower respiratory tract infection prior to admission to our hospital.

On examination, he was febrile and toxic with tachycardia, but perfusion was normal. He also had tachypnoea with conducted sounds on auscultation. Saturation was maintained with oxygen delivered through nasal prongs. His head circumference was 50.5 cm, weight was 12.5 kg and length was 91.2 cm (normal centiles for age and gender). He had hypopigmented sparse hair with no knuckle or oral hyperpigmentation. There was mild hepatomegaly but no splenomegaly. He was drowsy, arousable, not interacting with his mother, not interested in his surroundings, did not comprehend commands, and there were no meaningful words. Fundus examination was normal. There was hypotonia of all limbs with absent deep tendon reflexes and bilateral extensor plantar responses. He had generalised high amplitude coarse tremors involving all limbs, a mild head tremor (video 1) and intermittent perioral dyskinesias. There were no meningeal signs.

INVESTIGATIONS

Initial possibilities such as autoimmune encephalitis, viral encephalitis, coeliac disease, organic aciduria and neuropsychiatric syndrome secondary to vitamin B₁₂ deficiency were considered. Laboratory

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Video 1 Child in acute phase during admission in ward had sparse hypopigmented hair with coarse tremors involving both upper limbs and mild head tremor.

investigations in this child are listed in [table 1](#). Thyroid antibodies were negative, and initial thyroid-stimulating hormone (TSH) and free thyroxine were low (patient TSH value 0.12 mIU/L; normal range 0.3–4.5 mIU/L and patient free thyroxine level 0.8 ng/dL; normal range 0.8–1.8 ng/dL). Serum cortisol and adrenocorticotrophic hormone were normal. There was no proteinuria excluding the possibility of Imerslund Gräsbeck disease. Anti-*N*-methyl-D-aspartate receptor and anti-basal ganglia antibodies were not significant. MRI of the brain ([figure 1A,B](#)) revealed diffuse cortical atrophy with prominent ventricles and sylvian fissures.

DIAGNOSIS

In view of the subacute encephalopathy, hypopigmented hair, tremors, seizures, low vitamin B₁₂ and presence of anti-intrinsic factor antibodies, diagnosis of neuropsychiatric syndrome resulting from acquired pernicious anaemia was confirmed.

TREATMENT

He was started on oral propranolol 1 mg/kg/day and clonazepam for control of extrapyramidal symptoms. One mg of vitamin B₁₂ was administered daily as an intramuscular injection for 2 weeks followed by a similar dose administered once a month. Two weeks after vitamin B₁₂ and oral zinc supplementation therapy, he had developmental gains and there was a significant reduction in the tremor. His irritability had improved and he became cheerful. He had good social interaction and was able to speak in sentences. However, mild truncal unsteadiness, gait ataxia and a positive Romberg test were observed. Sodium valproate and phenobarbitone started elsewhere were tapered and stopped. A repeat thyroid profile revealed mild TSH elevation (7.06 mIU/L) with a low free thyroxine (0.65 ng/L) level, and hence he was treated with low-dose thyroxine. He was also treated empirically for *Helicobacter pylori* infection with clarithromycin, metronidazole and a proton-pump inhibitor for 2 weeks as the parents did not consent to upper gastrointestinal endoscopy.

OUTCOME AND FOLLOW-UP

He was discharged on monthly maintenance doses of parenteral vitamin B₁₂ therapy, daily folic acid, iron supplementation, vitamin D supplementation, thyroxine and levetiracetam. During follow-up at 6 months, he had gained age-appropriate milestones and had no residual neurological deficits. Repeat haemoglobin was 12.8 g/dL, mean corpuscular volume (MCV) was 75.5 fL,

Table 1 Summary of laboratory investigations of our patient

Parameters	Patient value (normal range)
Haemoglobin (g/dL)*	10.4
Peripheral smear	Anisocytosis, normocytic and normochromic picture
MCV (fL)†	86.3
Vitamin B ₁₂ (pg/mL)	172.9 (200–950)
Serum folic acid (ng/mL)	18.52 (3.1–17.5)
Serum total protein (g/dL)	5.3 (4.9–8.1)
Serum albumin (g/dL)	3.3 (2.9–5.8)
Serum homocysteine (μmol/L)	>65 (3.7–13.9)
Urine methylmalonic acid excretion	Elevated
Antiparietal cell antibody	Negative
Anti-intrinsic factor antibody	Positive
Serum methionine (μmol/L)	4 (7–47)
Serum iron (μg/dL)	28 (50–120)
Total iron binding capacity (μg/dL)	320 (300–400)
CSF amino acid	Normal
Serum ferritin (ng/mL)	52.7 (10–290)
Serum zinc (μg/dL)	62 (75–120)
Serum copper (μg/dL)	144 (70–170)
Serum magnesium (mEq/L)	2.03 (1.8–2.4)
Blood ammonia (μg/dL)	54 (20–80)
Blood lactate (mmol/L)	1.4 (0.56–2.25)
CSF analysis	
Cell count	Acellular
Protein (mg/dL)	26.5
Glucose (mg/dL)	57
PCR for adenovirus, herpes simplex, Epstein-Barr virus, cytomegalovirus	Negative
Stool examination	Scant fat globules
Serum transglutaminase	Negative
Urinary orotic acid excretion	Negative
Serum biotinidase	Normal
Nerve conduction studies	Sensory motor axonal polyneuropathy
Visual evoked potential	Normal
EEG	Normal
Screening for HIV	Negative
Ultrasound abdomen and pelvis	Normal

Abnormal values are marked as bold.

*Haemoglobin-2 SD cut-off value for age=11 g/dL.

†Mean value of MCV for age=79 fL.

CSF, cerebrospinal fluid; EEG, Electroencephalography; HIV, Human immunodeficiency virus; MCV, mean corpuscular volume; PCR, Polymerase chain reaction.

vitamin B₁₂ level was 707.9 pg/mL, homocysteine was 6.2 μmol/L and there was no increased urinary excretion of methylmalonic acid (MMA). Thyroid profile was normal. Follow-up assessment after 1 year revealed a normal growth and development ([video 2](#)) with an occasional mild tremor in the left hand.

DISCUSSION

Vitamin B₁₂ is essential for DNA synthesis, formation and maintenance of myelin sheaths and neurotransmitter synthesis. Vitamin B₁₂ deficiency can occur in infants born to vegan mothers, in those with decreased dietary intake of animal products, congenital or antibody mediated intrinsic factor deficiency, gastric surgery, inflammatory bowel disease, *Diphyllobothrium latum* infection, Imerslund Gräsbeck syndrome, prolonged exposure to nitrous oxide and absence of transport protein such as transcobalamin II deficiency.

Figure 1 T2 axial (A) and T1 coronal (B) images showing prominence of lateral ventricles (red arrows), anterior subarachnoid spaces and sylvian fissures (blue arrows).

Our patient was a 35-month-old toddler at the time of diagnosis and this is one of the few reports with early age at onset of neurological presentation in acquired pernicious anaemia. Infantile onset symptoms usually result from infants of vegan mothers, infants of the mother with pernicious anaemia, congenital pernicious anaemia or a variant of juvenile pernicious anaemia.^{2,3} Prevalence of pernicious anaemia in the general population is 0.1% and it accounts as an aetiology for vitamin B₁₂ deficiency in up to 50% of adults.⁴ Pernicious anaemia is extremely rare in children and adolescents. Prevalence of vitamin B₁₂ deficiency in children and adolescents varies from 1% to 3%.⁵ Up to three-fourth of the patients with vitamin B₁₂

deficiency manifest neurological symptoms and nearly one-fourth have only neurological manifestations without haematological changes.⁶ Although our patient's haemoglobin was 2 SD below the mean for age, his corresponding MCV was above the mean for his age. A peripheral smear study had shown anisocytosis and there was a concomitant iron deficiency state in our patient. A study in infants with vitamin B₁₂ deficiency had observed anaemia in 80%, elevated MCV in 30%, accompanying iron deficiency in 20%, neutropenia in 35%, hyperhomocysteinemia and low maternal vitamin B₁₂ levels in 100% cases.⁷ An inverse correlation between the severity of haematological and neurological disorders has been reported in patients with hypovitaminosis B₁₂, although the reasons are not well established.⁸ The predilection of central nervous system involvement in our case might be explained by the vulnerability of the developing brain to vitamin B₁₂ deficiency.⁹

Clinical findings observed in our patient during the acute phase were listlessness, irritability, fragmented sleep, loss of developmental milestones, seizures, coarse tremors, hypotonia and absent muscle stretch reflexes, and after 2 weeks of definitive treatment, unmasking of other neurological findings such as truncal unsteadiness, proprioceptive dysfunction and gait ataxia were evident. Other non-neurological symptoms reported in infants such as anorexia, stomatitis, failure to thrive and hyperpigmentation were not present in our case, although diarrhoea and respiratory infection were present as reported in the literature.⁷

A vitamin B₁₂ cut-off value of >210 nmol/L has been proposed by the National Health and Nutrition Examination Survey in the USA.¹⁰ The earliest markers for a vitamin B₁₂ deficient state are low holotranscobalamin II (storage marker) and elevated MMA (functional marker).¹¹ MMA excretion was elevated in our case, but the storage marker was not estimated due to the lack of availability in our centre. Intrinsic factor antibodies were detected, but antibodies against parietal cell mass tested were negative in our case. Anti-intrinsic factor antibodies have 100% specificity and a low sensitivity of 35–50% while antiparietal cell antibodies have 50–80% sensitivity and a specificity of 90–98%.^{4,12,13} Although hypothyroidism was detected, we did not find any associated thyroid antibodies or an underlying Addison disease, coeliac disease, Sjögren syndrome, vitiligo or type I diabetes mellitus. Hypothyroidism could possibly be explained by dietary iodine deficiency or was valproate related.

Video 2 Child during follow-up after definitive treatment with vitamin B₁₂ had normal growth and neurodevelopment.

MRI of the brain findings reported in vitamin B₁₂ deficiency are ventricular dilation, thinning of the corpus callosum, external hydrocephalus, delayed myelination, myelopathy affecting the anterior, posterior and lateral columns in the cervical and thoracic spinal cord, hyperintensities involving the periventricular white matter, centrum semiovale, internal capsule and middle cerebellar peduncle and Morel laminar sclerosis.^{7 14 15} MRI of the brain in our patient had shown diffuse cortical atrophy with prominent ventricles and sylvian fissures.

Treatment protocols for management of vitamin B₁₂ deficiency are diverse and a widely used protocol is the daily 1 mg intramuscular administration of vitamin B₁₂ for 10–14 days followed by 1 mg once weekly for 4 weeks and thereafter once monthly. Vitamin B12 therapy has to be continued for life in patients with pernicious anaemia. A systematic review concluded that a high dose of oral vitamin B₁₂ was as effective as the intramuscular therapy in observing short-term neurological and haematological responses. The effectiveness of the oral dose of vitamin B₁₂ in the above studies can be explained by the fact that 1% of vitamin B₁₂ absorption occurs by passive diffusion irrespective of intrinsic factor (IF).^{16 17} Early recognition and treatment is essential for a better outcome. Our patient had shown good recovery while conflicting responses have been reported in the literature following therapy with vitamin B₁₂.^{18–23}

Learning points

- Prevalence of pernicious anaemia in the general population is 0.1% and it is extremely rare in children and adolescents.
- Neuroregression may be the only initial manifestation in acquired pernicious anaemia without overt haematological manifestations.
- Screening for markers of vitamin B₁₂ deficiency must be done in all children with unexplained acute or subacute neuroregression, seizures and movement disorders.
- An inverse correlation between the severity of haematological and neurological disorders may be observed.
- Early recognition and treatment are essential for better outcome.

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