Pearls & Oy-sters: Rapidly Reversible Dementia

Vitamin B₁₂ Deficiency in a 29-Year-Old Woman

Akshata Huddar, DM, Doniparthi Venkata Seshagiri, DM, Subasree Ramakrishnan, DM, and Raghavendra Kenchaiah, DM

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Correspondence

Dr. Kenchaiah
raghoo2k@gmail.com

Pearls

- Vitamin B₁₂ deficiency affects multiple systems, including hematologic, neurologic, dermatologic, and gastrointestinal.
- Vitamin B₁₂ deficiency can present with rapidly progressive dementia, which is reversible.

Oy-ster

- Active search for oral, skin, laboratory, and imaging markers of vitamin B₁₂ deficiency is warranted in patients with rapidly progressive dementia, especially with frontotemporal pattern of cognitive presentation.

A 29-year-old woman presented to us with progressive cognitive impairment over a period of 9 months. She was premorbidly well-adjusted, taking care of her child and all household chores. Initial signs of the condition included decreased interaction, withdrawn behavior, apathy, and executive dysfunction. The woman also experienced impaired judgment while cooking, loss of attention during conversations or while speaking, and perseverating behavior like repeatedly folding clothes, followed by episodic memory impairment. As symptoms progressed over the next 6 months, the woman required increased assistance and encouragement to complete daily activities. For example, when asked to take a shower, she simply sat in the restroom.

Loss of insight into the illness was, and speech. Speech output gradually reduced to single words. There was no history of other errors in language function. The woman did not have prior history of language difficulty, nor any history suggestive of getting lost in familiar or unfamiliar places, hallucinations, delusions, hemineglect, apraxia, or urine and bowel incontinence. Alternatively, she did have a history of veganism, and amenorrhea for 5 months.

Upon examination she had a reddish, smooth tongue and hyperpigmentation of knuckles (Figure, A and B). Neurologic examination revealed a Mini-Mental State Examination (MMSE) score of 19/30 with impairment of attention, calculation, recent memory, and orientation components. Assessment of mental status revealed impaired verbal fluency, recall, 3D construction, clock drawing test (CDT), and calculation (Figure, E–R). Additionally, there was evidence of motor perseveration, as shown in Figures E, F, and I. The overall cognitive profile suggested predominant frontal and temporal lobe dysfunction. Fundi and cranial nerves were normal. Involuntary movements were present in the form of upward twitching of eyebrows and cervical dystonia with anterior and lateral flexion associated with choreoathetoid movements of upper limbs—primarily on the left side. The woman also had hypotonia of limbs with brisk deep tendon reflexes and extensor plantars bilaterally.

Laboratory results included hemoglobin 11.9 g/dL, white blood cell count 5.1 K/ μ L, mean corpuscular volume 114.6 fL, peripheral smear macrocytic hypochromic blood picture, and erythrocyte sedimentation rate 36 mm/h. Serum vitamin B₁₂ of 140 pg/mL (211–911 pg/mL) was low with high serum homocysteine (173.5; <15 μ mol/L) and serum folate level was >25.80

From the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.

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(A–D) Clinical and imaging findings at time of presentation. (A) Smooth and reddish tongue. (B) Knuckle hyperpigmentation (arrows). (C) T2-weighted and (D) fluid-attenuated inversion recovery axial images of brain show periventricular hyperintensities. (E–H) Clock-drawing test: the patient was asked to draw a clock and set the hands at 2:30 (E) at presentation, (F) on the 4th day of treatment, (G) at 2 months follow-up, and (H) at 2 years follow-up. (I, J, N, O) Copying of image given on left side (I, J) before treatment and (N, O) 2 years after treatment. Drawing to command is shown before treatment (K [daisy in flowerpot], L [house in perspective]) and (P, Q) after 2 years showing normal state. (M) Impaired calculation at presentation and (R) normal calculation at 2 years is shown.

(3.1–19.9 ng/mL). Methylmalonic acid and other vitamin levels could not be examined at our center. Other metabolic measures, including thyroid, hepatic, and renal function tests, serum electrolytes, ammonia, and lactate, were normal. Antinuclear antibody profile revealed SSA 2+ positive, with the rest negative (nRNP-Sm, Sm, Ro-S2, SS-B, Scl-70, SSs, PM-Scl 100, Jo-1, CENP B, SSs, PBC, PCNA, dsDNA, nucleosomes, histones, ribosomal P protein, AMA M2). Infectious workup (CSF analysis, HIV, venereal disease research laboratory) and autoimmune encephalitis panel (NMDA, voltage-gated potassium channel, LGI1, Caspr2, anti-TPO) did not reveal any abnormalities.

Ultrasound of the abdomen and pelvis was normal. Nerve conduction studies were normal. Upper gastrointestinal

endoscopy showed normal appearance of mucosa and gastric mucosal biopsy showed mild chronic inflammation and focal atrophy. Brain MRI showed bilateral T2-weighted and fluid-attenuated inversion recovery periventricular hyperintensities (Figure, C and D).

The patient received a B-complex multivitamin injection with vitamin B₁₂ 1000 µL/d daily for 1 week, then once a week, and then monthly. On the 4th day of therapy, the patient's speech and CDT were better compared to pretreatment (Figure, F). At 1 month follow up, there was a reported subjective improvement of 70%. She was able to cook with good judgment, take care of her child, and the perseverating behavior and chorea athetoid movements disappeared. Her menstrual cycles resumed, MMSE improved to 29/30 (1 lost in calculation), and

CDT further improved (Figure, G). After 2 months, MMSE was 30/30, vitamin B₁₂ >2000 pg/mL, and homocysteine 17.7 µmol/L. After 2 years, detailed comparison of construction ability showed normal state (Figure, N–R). Normal state might have been achieved much earlier, but some components were only tested at 2 years.

Discussion

Frontotemporal pattern of cognitive involvement, knuckle hyperpigmentation, smooth and reddish tongue, and complete improvement with B₁₂ supplementation were clinical clues for nutritional dementia in our patient. B₁₂ deficiency was confirmed by low serum B₁₂, elevated homocysteine, macrocytic hypochromic blood picture, and periventricular T2-weighted and fluid-attenuated inversion recovery hyperintensities in brain MRI. Chronic gastric inflammation and vegan diet may be the etiologic factors. Other differential diagnoses considered included immune-mediated (CNS vasculitis, autoimmune encephalitis, or cognitive presentation of multiple sclerosis) and infectious causes (HIV encephalitis and neurosyphilis).¹ After instigation, these possibilities were excluded. More differentials were worked out as the patient was in a young age group and had rapid progression of dementia and choreiform movements, which are rare in B₁₂-related dementia.

More differentials were worked out as the patient was young and had rapid progression of dementia with choreiform movements, which are rare in B₁₂-related dementias. Most of the dementias progress slowly over years and are degenerative. However, some of these are rapidly progressive, developing subacutely over weeks to months, and have been termed rapidly progressive dementias (RPDs).¹ A wide range of disorders can present with RPDs including neurodegenerative disorders, prion diseases, neoplastic disorders, or vascular disorders, where there is no definitive treatment to reverse the disease course.^{1,2} However, a subset of RPDs related to infectious, immune-mediated, or metabolic causes can be potentially treatable. B₁₂ deficiency constitutes a minority (1%–4%) of RPDs.²

It is often challenging to identify potentially reversible B₁₂-related dementia from the wide variety of disease conditions presenting as RPDs. The pattern of reversible cognitive impairment reported in B₁₂ deficiency is predominantly of frontotemporal type.^{3,4} Blundo et al.³ reported executive impairment, alteration in verbal fluency, and response inhibition, together with behavioral abnormalities and abnormal CDT in B₁₂-related dementia. CDT was predominantly perseveration type, where the clock numbers continued beyond 12 with overcrowding.³ However, our patient had perseveration in the form of 3 clock hands instead of 2, along with overcrowding of numbers, which improved significantly with treatment (Figure, E–H). Full recovery from dementia related to B₁₂ can be expected within 3 months in most patients.⁴ Our patient also showed clear signs of improvement on the 4th day with B₁₂ therapy and had normal MMSE score at 2 months.

Full recovery from dementia related to B₁₂ can be expected within 3 months in most patients.⁴ Our patient also showed clear signs of improvement on the 4th day of B₁₂ therapy and had normal MMSE score at 2 months. The median duration of cognitive symptom onset to presentation is about 7 months; delay in presentation usually occurs because of initial treatment by psychiatrists and ignorance of signs and symptoms of nutritional deficiency in these disorders.^{3,4} Our patient was managed by a psychiatrist with an antipsychotic drug (olanzapine 10 mg/d) for 2 months and stopped 20 days prior to the presentation. Involuntary movement disorders related to B₁₂ deficiency are limited to case reports. Tremor, myoclonus, parkinsonism, and chorea can occur with B₁₂ deficiency, and these symptoms are reversible within few weeks.⁵ Our patient had choreoathetosis and mild dystonia, which resolved within a month of treatment. The proposed mechanisms included increased methyltetrahydrofolate and homocysteine, which act as agonist at NMDA receptors.⁵

Olanzapine is an atypical antipsychotic that can cause facial tardive dyskinesias when taken for a few months to a year.⁶ In our case, it is difficult to conclude whether improvement was related to B₁₂ therapy or withdrawal of olanzapine due to the short duration of olanzapine and inadequate history regarding relation between initiation of antipsychotic treatment and the development of involuntary movements.

Neuropathy with or without nerve conduction abnormalities is reported in around an estimated 50% of patients with vitamin B₁₂ deficiency.⁴ Our patient had normal nerve conduction studies. Oral signs of B₁₂ deficiency include red smooth tongue, angular cheilitis, recurrent aphthous ulcers, and diffuse erythematous mucositis.⁷ Hyperpigmentation in B₁₂ deficiency can be generalized but more common sites are flexural areas and at pressure areas like the elbow, phalanges, and knees.⁷ Oral signs and hyperpigmentation are reversible with B₁₂ supplementation.⁷ Our patient had red smooth tongue and hyperpigmentation over knuckles. B₁₂ is cofactor for methionine synthase and methyl malonyl-CoA mutase enzymes.⁸ Defect in the function of these enzymes results in impaired DNA synthesis and defective formation of fatty acids involved in myelin synthesis. Demyelination is responsible for various neurologic manifestations.⁸ After correction of B₁₂ deficiency, the abnormal metabolites disappear rapidly and remyelination occurs with prompt reversal of B₁₂ deficiency symptoms.

Active search and management of etiologic factors for B₁₂ deficiency is warranted to prevent re-occurrence of symptoms.⁸ Vitamin B₁₂ deficiency is usually treated with hydroxocobalamin/cyanocobalamin 1000 µg/d injection daily for 1 week then weekly until clinical improvement, treatment once in a month can be given.⁸ High oral dose 1000 µg/d is also effective.⁸ However, in acute settings, particularly with neurologic involvement, parenteral route is preferred.⁹ Folic acid supplementation in vitamin B₁₂ dementia can worsen cognitive decline.¹⁰ Our patient might have taken folic acid, inadvertently leading to high serum

folate levels and rapid worsening of cognitive decline. Long-term or even life-long supplementation might be required, especially for those with malabsorption defects. Patients usually respond well to therapy if there are no other attributable causes.^{4,8}

We report a case of rapidly progressive dementia presenting with predominant frontotemporal pattern of cognitive decline and involuntary movements along with clinical signs of nutritional deficiency, which reversed completely with treatment. Neurologists should be vigilant about various systemic manifestations of B₁₂ deficiency so that an early diagnosis can be made, and simple therapy instituted.

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Disclosure

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