Pearls & Oy-sters: Rapidly Reversible Dementia: Vitamin B12 Deficiency in a Young Lady

Author(s):
Akshata Huddar, DM¹; Doniparthi Venkata Seshagiri, DM¹; Subasree Ramakrishnan, DM¹; Raghavendra Kenchaiah, DM¹

Corresponding Author:
Raghavendra Kenchaiah
raghoo2k@gmail.com

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Affiliation Information for All Authors: 1. Departments of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru - 560029, India.

Contributions:
Akshata Huddar: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Doniparthi Venkata Seshagiri: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Subasree Ramakrishnan: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
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Pearls:
Vitamin B12 deficiency affects multiple systems, which includes hematological, neurological, dermatological, gastrointestinal.
Vitamin B12 deficiency can present with rapidly progressive dementia, which is reversible.

Oysters:
Active search for oral, skin, laboratory, and imaging markers of Vitamin B12
deficiency is warranted in patients with rapidly progressive dementia especially with Fronto-temporal pattern of cognitive presentation.

Case report

A 29-year-old lady completed her Bachelor degree in Science, homemaker, married and having a child, presented to us with progressive cognitive impairment since nine months. She was pre-morbidly well-adjusted, taking care of her child and all household chores. The illness started with decreased interaction, withdrawn behavior, apathy, executive dysfunction, impaired judgment (putting excess salt, under/over cooking), attention deficits (lost in the conversation while speaking), perseverating behavior (folding the cloths and putting in the bag and removing, repeating multiple times) followed by episodic memory impairment. Symptoms progressed over 6 months to the stage of requiring coxing and assistance for activities of daily living (she just simply sat in restroom when asked to take shower). Loss of insight into the illness was present. Speech output gradually reduced to
single word, however there was no history of other errors in language function. There was no history suggestive of getting lost in familiar/unfamiliar places, hallucinations, delusions, hemineglect, apraxia, urine/bowel incontinence. History of amenorrhea for 5 months. She was pure vegetarian and was not even consuming dairy products. On examination she had reddish, smooth tongue and hyperpigmentation of knuckles (Figure 1A, B). Neurological examination: MMSE 19/30 (attention and calculation, recent memory and orientation components were impaired). On mental status examination she had impaired- verbal fluency, recall, three-dimensional construction, clock drawing test (CDT) and calculation (Figure 1 E-R). There was evidence of motor perseveration as evidenced in Figure 1E, F and I. Overall cognitive profile suggests predominant frontal and temporal lobe dysfunction. Fundi and cranial nerves were normal. There were involuntary movements in the form of upward twitching of eyebrows, cervical dystonia with anterior and lateral flexion associated with choreoathetoid movements of upper limbs left more than right. She had hypotonia of limbs with brisk deep tendon reflexes and extensor plantars bilaterally.

Laboratory parameters: Hemoglobin-11.9 gm/dl, WBC count-5.1 K/ul, MCV-114.6 fl, peripheral smear- macrocytic hypochromic blood picture and ESR was 36mm/hr. Serum Vitamin B12-140 (211-911 pg/ml) was low with high serum Homocysteine-173.5 (<15 umol/L) and serum folate >25.80 (3.1 to 19.9 ng/ml). Methyl malonic acid and other vitamin levels could not be done due to unavailability at our center and financial issues. Other metabolic parameters like thyroid, hepatic, and renal function tests, serum electrolytes, ammonia, and lactate were normal. ANA profile revealed SSA 2+ positive, rest all negative (nRNP-Sm, Sm,Ro- 52, SS-B,Scl-70,SSc, PM-Scl 100, Jo-1, CENP B, SSc, PBC, PCNA, dsDNA,
Nucleosomes, Histones, Ribosomal P-protein, AMA M2). Infectious work up (CSF
analysis, HIV, VDRL) and autoimmune encephalitis panel (NMDA, VGKC, LGI1, Casper2, Anti TPO) did not reveal any abnormalities. Ultrasound of abdomen and pelvis was normal. Nerve conduction studies (NCS) were also normal. Upper gastrointestinal endoscopy showed normal appearance of mucosa, gastric mucosal biopsy showed mild chronic inflammation and focal atrophy. MRI Brain showed bilateral T2W and FLAIR periventricular hyperintensities (Figure 1C, D). She received B-complex Multivitamin injection with Vitamin B12 1000ug/day daily for 1 week then, once in a week, then advised monthly. During hospital stay on 4th day of therapy, her speech and CDT were better compared to pre-treatment (Figure 1F). Her first follow up after 1 month, reported subjective improvement of 70%, able to cook without errors, able to take care of child, perseverating behavior and chorea athetoid movements disappeared, her menstrual cycles resumed, MMSE- 29/30 (one lost in calculation), CDT further improved (Figure 1G). After 2 months MMSE was 30/30, Vitamin B12 >2000pg/ml and Homocysteine was 17.7umol/L. Detailed comparison of construction ability was done after 2 years showed normal state (Figure 1 N-R). Normal state might have been achieved much earlier, but some components were tested at 2 years.

Discussion:

Fronto-temporal pattern of cognitive involvement, knuckle hyperpigmentation, smooth and reddish tongue, and complete improvement with B12 supplementation were clinical clues for nutritional dementia in the present study patient. B12 deficiency was confirmed by low serum B12, elevated homocysteine, macrocytic hypochromic blood picture and periventricular T2W and FLAIR hyperintensities in Brain MRI. Chronic gastric inflammation and vegetarian diet may be the etiological factors. Other differential diagnosis considered include immune mediated (CNS...
vasculitis, autoimmune encephalitis, cognitive presentation of multiple sclerosis) and infectious causes (HIV encephalitis, neuro- syphilis). All these were excluded with appropriate investigations. More differentials were worked out as patient was in younger age group, rapid progression of dementia, choreiform movements being rather rare in B12 related dementia.

Most of the dementias progresses slowly over years and are degenerative. However, some of these are rapidly progressive developing sub-acute over weeks to months and have been termed as Rapidly progressive dementias (RPDs). Wide range of disorders can present with RPDs. These can be neurodegenerative disorders, prion diseases, neoplastic disorders, vascular disorders where there is no definitive treatment to reverse the disease course. However, a subset of RPDs related to infectious, immune mediated, metabolic causes can be potentially treatable. B12 deficiency constitute to minority (1-4) of RPDs. It is often challenging to identify potentially reversible B12 related dementia from wide variety of disease conditions presenting as RPDs. The pattern of reversible cognitive impairment reported in B12 deficiency is predominantly of fronto-temporal type. Blundo C et al., reported executive impairment, alteration on verbal fluency, 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 over crowding, however our patient had perseveration in the form of 3 hands of clock instead of 2, along with overcrowding of numbers which improved significantly with treatment (Figure 1 E-H). Full recovery from dementia related to B12 can be expected within 3 months in most of the patients. Our patient also showed clear signs of improvement on 4th day with B12 therapy and had normal MMSE score at 2 months.
Median duration of cognitive symptom onset to presentation is about 7 months, delay in presentation usually occurs in many of these patients as they were treated by psychiatrist initially and ignorance of signs and symptoms of nutritional deficiency in these disorders \(^3\,^4\). Our patient was also managed by psychiatrist with antipsychotic drug (Tab Olanzapine 10 mg/day) 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 completely within a month of treatment. The proposed mechanisms include increased methylenetetrahydrofolate and homocysteine which act as agonist at NMDA receptors\(^5\). Olanzapine being atypical antipsychotic can cause tardive dyskinesias mainly involving face when taken for few months to year\(^6\). However, it is difficult to conclude whether improvement was related to B12 therapy or withdrawal of olanzapine due to short duration of olanzapine, inadequate history regarding relation between initiation of antipsychotic and development of involuntary movements. Neuropathy with/without nerve conduction abnormalities is reported in around 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 areas of pressure like 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 neurological 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 for etiological factors for B12 deficiency is warranted to prevent re-occurrence of symptoms\(^8\). Vitamin B12 deficiency is usually treated with Hydroxycobalamin/cyanocobalamin 1000ug/day injection daily for one week then weekly till clinical improvement. After clinical improvement once in a month can be given\(^8\). High oral dose 1000ug/day is also effective\(^8\). However, in acute settings particularly with neurological 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, involuntary movements along with clinical signs of nutritional deficiency, which reversed completely with treatment. Neurologist should be vigilant about various systemic manifestations of B12 deficiency so that an early diagnosis is made and simple therapy will be rewarding to both the patient and doctor.
References:


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Figure legends:

Figure Title: Clinical, imaging and mental status examination findings in a patient with Vitamin B12 deficiency.

Figure 1: (A-D) Clinical and imaging findings at time of presentation (A) smooth and reddish tongue (B) knuckle hyperpigmentation (arrows) (C) T2W and (D) FLAIR axial images of Brain showing periventricular hyperintensities. (E-H) clock drawing test: asked to draw clock and set at 2:30 (E) at presentation (F) on 4th day of treatment (G) at 2 months follow up (H) at 2 years follow up. (I, J,N,O) Copying image given on left side (I,J) Before treatment (N,O) two years after treatment impaired drawing.

Drawing to the command (K- daisy in flowerpot, L- draw house in perspective before treatment. P and Q are drawn after 2 years showing normal state). (M) impaired calculation at presentation and (Q) normal calculation at 2 years.
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