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Vitamin B_{12} deficiency needs to be adequately diagnosed and treated

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To the Editor—A 79-year-old Chinese male presented in January 2023 with a 2-week history of depressed mood and a 2-year history of forgetfulness. He had no recollection of his COVID-19 illness in December 2022, after which his memory further worsened. He had been experiencing intermittent dyspepsia since May 2012, with a finding of *Helicobacter pylori*–negative inactive mild chronic antral gastritis in September 2015, for which he took antacids, famotidine, and pantoprazole as required. Review of his history revealed a diagnosis of vitamin B_{12} deficiency anaemia 10 years earlier in September 2013 when he presented with depression, tiredness, dizziness, weight loss, hand numbness, and laboratory findings of macrocytic anaemia (haemoglobin level: 8.2 g/dL, mean cell volume [MCV]: 130.9 fL) along with a low serum vitamin B_{12} level (<37 pmol/L). He was treated with intramuscular cyanocobalamin for 1 year followed by oral cyanocobalamin 100 mcg twice a day for 2.5 years. His symptoms improved and haemoglobin level, MCV (13.7 g/dL and 93.2fL, respectively, June 2014; 15.1g/dL and 93.7 fL, respectively, December 2016) and serum vitamin B_{12} level (513 pmol/L, September 2014) normalised. Examination in January 2023 revealed mildly impaired cognition, depressed mood and positive Romberg test, but no pallor or glossitis. A clinical diagnosis of relapsed pernicious anaemia with neuropsychiatric presentation was made and confirmed by a low serum vitamin B_{12} level (<109 pmol/L, January 2023) and a positive intrinsic factor antibody, although his haemoglobin level and MCV were normal (14.0 g/dL and 97.3 fL, respectively). His mood improved but cognition remained unchanged after high-dose oral vitamin B_{12} (mecobalamin 500 mcg 3 times a day), with normalisation of serum vitamin B_{12} level (318 pmol/L, April 2023). The patient was treated in accordance with the Declaration of Helsinki. Informed consent was obtained for publication of this case.

This case illustrates the importance of determining the aetiology of vitamin B_{12} deficiency, failure to do so may lead to under-treatment and disease relapse or progression. Pernicious anaemia requires lifelong treatment with either parenteral or high-dose (≥1 g daily) oral vitamin B_{12}. Clinicians and pathologists should be familiar with both classic and non-classic presentations, causes, and laboratory diagnosis of vitamin B_{12} deficiency, a common treatable disorder (Table).[1-15] Neuropsychiatric presentations can occur in the absence of anaemia or macrocytosis and may be non-classic (eg, depression, long COVID-19, hallucinations).[1-6] Underlying causes, often multiple in an individual, need to be diagnosed, and persistent cause(s) require lifelong treatment.[1] Although acid-suppressive drugs may have contributed to this patient's vitamin B_{12} deficiency (food-cobalamin malabsorption),[7] intrinsic factor antibody positivity and dyspepsia history point to an additional cause in autoimmune atrophic gastritis. The classic histopathology of this condition should be confirmed by gastric biopsy, including both corpus and antrum.[8] Periodic screening for metformin-induced vitamin B_{12} deficiency in diabetes, though proposed over 50 years ago,[9] has only recently been incorporated into guidelines,[1,10] but is not widely practised.

Vitamin B_{12} deficiency can occur in individuals with apparently normal or supernormal serum vitamin B_{12} or active vitamin B_{12} levels, and clinicians should be aware of factors that affect test results (Table).[1,2,4,11,12] The 2024 National Institute for Health and Care Excellence guideline[1] introduced an indeterminate range for low-normal serum vitamin B_{12} or active vitamin B_{12} levels that necessitates further tests for raised serum homocysteine or methylmalonic acid (Table) to confirm the diagnosis in those with risk factors and compatible manifestations of vitamin B_{12} deficiency. Because of the limitations of vitamin B_{12} levels, the diagnosis and monitoring of treatment adequacy should not depend solely on its level, but should instead be guided by clinical judgement and response.[1] Although a low vitamin B_{12} level in patients on replacement therapy suggests poor adherence or inadequate dosing, a normal or high level does not necessarily indicate adequate treatment and should not prompt reduction discontinuation.[1] The clinical response should be assessed at follow-up instead of merely repeating vitamin B_{12} levels.[1] Individual variability in vitamin B_{12} treatment response and dose requirement has been observed, possibly due to genetic variants of transcobalamin and its receptor. These variants may reduce vitamin B_{12} availability and reduce energy metabolism, ultimately contributing to frailty.[1,2,13]

Author contributions

The author solely contributed to the concept or design of the paper, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. The author had full access to the data, contributed to the paper, approved the

TABLE. Classic and non-classic presentations, causes, and laboratory diagnosis of vitamin B_{12} deficiency[1-15]

	Classic	Non-classic
Presentations		
Haematological	Macrocytic anaemia	Normocytic/microcytic anaemia (concomitant iron deficiency, thalassaemia)
Neuropsychiatric	Peripheral neuropathy; myelopathy (SACD); sensory/gait ataxia; optic atrophy; dementia	Depression; hallucinations (visual, auditory); Alzheimer's disease and related dementias; vascular dementia, Parkinsonism; COVID-19 and post–COVID-19 symptoms
Gastrointestinal	Glossitis	Upper gastrointestinal symptoms
Geriatric		Impaired cognition (dementia/ delirium); impaired mood; impaired vision; falls; immobility; frailty
Causes/risk factors		
Dietary	Vegetarian	Eating disorder; dentition problem; poverty; isolation; impaired cognition; frailty
Drug-induced	Alcohol	Metformin; PPI; H2RA; colchicine; pregabablin; primidone; nitrous oxide
Autoimmune	Autoimmune atrophic gastritis (pernicious anaemia)	
Food-cobalamin malabsorption		Hypochlorhydria of atrophic gastritis: *H pylori*, acid suppressant drugs (PPI, H2RA)
Post-gastrectomy	Total gastrectomy	Partial gastrectomy
Terminal ileal disease	Resection, TB infection	
Genetic	Inborn errors of vitamin B_{12} metabolism	Polymorphisms (genetic variants) of transcobalamin and its receptor protein
High-folate–low-vitamin B_{12} interaction	Vitamin B_{12} deficiency masked and exacerbated by high-dose folic acid	High folic acid intake causing vitamin B_{12} depletion
Laboratory diagnosis		
Serum vitamin B_{12} level/active vitamin B_{12}	Confirmed vitamin B_{12} deficiency: low serum vitamin B_{12} level (<133 pmol/L) or low active vitamin B_{12} (<25 pmol/L)	- Metabolic vitamin B_{12} deficiency: low-normal serum vitamin B_{12} level (133-258 pmol/L) or low normal active vitamin B_{12} (25-70 pmol/L) but raised serum homocysteine or MMA - False normal/supernormal serum vitamin B_{12} level or active vitamin B_{12} from use of vitamin B_{12}–containing vitamins (OTC or prescribed); antibody interfering assay (including IFA); impaired renal excretion; coexisting liver disease; haematological malignancies
Autoimmunity	Schilling test; autoimmune atrophic gastritis of corpus sparing antrum	IFA; GPCA

Abbreviations: COVID-19 = coronavirus disease 2019; GPC = gastric parietal cell antibody; H2RA = H2 receptor antagonist; *H pylori* = *Helicobacter pylori*; IFA = intrinsic factor antibody; MMA = methylmalonic acid; OTC = over-the-counter; PPI = proton pump inhibitor; SACD = subacute combined cord degeneration; TB = tuberculosis

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