Vitamin B12 deficiency causing night sweats

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Abstract
Vitamin B12 deficiency is common. It is known to cause a wide spectrum of neurological syndromes, including autonomic dysfunction. Three cases are discussed here in which drenching night sweats were thought to be caused by vitamin B12 deficiency. All three responded dramatically to vitamin B12 therapy.

Keywords
Vitamin B12, night sweats, autonomic neuropathy

Case 1
A 57-year-old man was referred for assessment of 3–4 years history of drenching night sweats needing replacement of bed sheets almost on a nightly basis. The sweating involved only the upper portion of his body from top of the head to mid-chest around the level of the nipples and seemed to be worse after drinking alcohol. He denied any bowel symptoms, weight loss, fever, cough or skin rash. His past medical history was significant for hypertension treated with hydrochlorothiazide. He had a 27-pack year history of smoking, drank occasionally and did not use illicit drugs.

Prior to his referral, he was found to have normal serum levels of fasting glucose, urea, creatinine and electrolytes, liver enzymes and thyroid stimulating hormone (TSH) and T4. Haemoglobin was 144 g/L (140–180), white blood cells (WBC) 6.8 x 10^9/L (4.0–10) and platelets 290 x 10^12/L (150–400). Red cell count (RCC) was 4.16 x 10^12/L (4.30–5.40) and mean corpuscular volume (MCV) was 99.3 fL (82.0–97.0). Also, 24-hour urine catecholamines were measured in 2009 on two occasions and showed modest elevation of norepinephrine at 653 and 681 nmol/d (0.0–505) and total catecholamines at 739 and 768 nmol/d (0.0–630). Other indices of catecholamine metabolism including 5-hydroxyindolacetic-acid (5-HIAA) were normal. CT scan of the adrenal glands was reported normal. A repeat 24-hour urinary catecholamine measurement in 2011 was normal.

His BMI was 25, pulse rate 68/min and blood pressure 150/90 mmHg without any postural hypotension. Examination of the cardiovascular, respiratory and abdominal systems was unremarkable. Vibration sense was reduced in both feet up to ankles. Other sensations were intact. Rest of the neurological examination was normal.

Further investigations revealed low serum vitamin B12 levels at 152 pmol/L (175–880). Homocysteine levels were 14.9 μmol/L (5.0–12.0). Vitamin B12 injections 1000 mcg daily for 7 days followed by monthly injections were prescribed. Celiac antibodies, antibodies to parietal cells and intrinsic factor were negative. Patient reported a dramatic response of his sweating after the second injection of vitamin B12 and remained asymptomatic at three months follow-up.

Case 2
A 74-year-old man was referred for episodic sweating, intense enough to require change of clothing or bed sheets, of 10 years duration. These episodes occurred 1–3 times a week and lasted for 10–30 min. There was no

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for coronary artery disease, congestive heart failure, weight loss. Her past medical history was significant were mainly nocturnal and would at times require sweats of several years duration. The sweating episodes extreme tiredness, dizziness and drenching night

A 71-year-old woman was referred for assessment of Case 3

Discussion

Night sweats are drenching sweats that require changing bed sheets. Diagnostic considerations include infection, malignancy, medications and endocrine disorders (Table 1). Tuberculosis, histoplasmosis, coccidiodomycosis, infectious mononucleosis, sub-acute infective endocarditis, parasitic diseases and human immunodeficiency virus (HIV) are the common infective causes. Hodgkin’s lymphoma and other solid organ malignancies, thyrotoxicosis, pheochromocytoma, carcinoid syndrome and hypoglycemic disorders account for a fair proportion. Medications like antidepressants, antipyretics, tomixifen, leuprolide, niacin, cholinergic agonists and meperidine may cause profuse night sweating.1,2

An assessment should include history of fever, cough, weight loss, risk factors for tuberculosis and HIV, travel to endemic areas for fungal and parasitic infections, and medication including over the counter medication. History of flushing, diarrhoea and wheezing will point to carcinoid syndrome whilst history of paroxysmal hypertension, tachycardia, anxiety and restlessness are clues to the presence of pheochromocytoma. Tachycardia, tremor, weight loss and diarrhoea
are symptoms suggestive of thyrotoxicosis. Personal and family history of diabetes and use of oral hypoglycemic agents or insulin should specifically be sought. Physical examination should include blood pressure measurement, heart rate, skin examination for rashes, lymphadenopathy, cardiovascular system for central and peripheral signs of endocarditis, chest for fungal, tuberculous and parasitic infections, thyroid examination, lipo-atrophy and hypertrophy as evidence of insulin injections, and abdominal system for hepato- splenomegaly. Investigations should include complete blood count, sedimentation rate, thyroid-stimulating hormone, sputum for acid fast bacilli and chest radiograph. Further testing may include blood cultures, urinary catecholamines and 5-HIAA, sputum cultures, and echocardiogram. Some patients will, however, remain undiagnosed despite a thorough assessment and investigations.

Vitamin B12 deficiency is known to cause a wide spectrum of neurological syndromes. These include peripheral neuropathy, myelopathy, cognitive and psychiatric syndromes and autonomic dysfunction. Sensory neuropathy manifesting as paraesthesias in the extremities and ataxia of gait is the commonest of all the neurological manifestations of vitamin B12 deficiency. In advanced cases, corticospinal tract involvement may lead to spastic paraparesis. Dementia and amnesia are the most common cerebral syndromes associated with vitamin B12 deficiency, but psychiatric syndromes such as depression, hypomania, agitation and psychosis have also been described. Urinary incontinence, impotence and orthostatic hypotension are well-recognized autonomic manifestations.3

Although autonomic dysfunction due to vitamin B12 deficiency is well recognized, vitamin B12 deficiency has not been reported as a cause of drenching night sweats previously. Changes in the peripheral autonomic nervous system may be the earliest manifestations of small-fibre neuropathy and hyperhidrosis frequently accompanies small-fibre peripheral neuropathy.4 Episodic hyperhidrosis also occurs commonly in patients with familial dysautonomia, a hereditary sensory and autonomic neuropathy.5 Two studies investigated heart rate variability in patients with vitamin B12 deficiency and found long- and short-term measurements of parameters of heart rate variability to be significantly lower in vitamin B12 deficient subjects compared to controls.6,7 Beitzke et al found major hemodynamic and autonomic impairment in patients with vitamin B12 deficiency.8 Defective sympathetic activation and decreased catecholamine release has been postulated as pathogenic mechanisms. Reduction of sudomotor sympathetic unmyelinated fibres has been described in patients with vitamin B12 deficiency and orthostatic hypotension.9 Similarly, in patients with spinal cord injury at or above the level of T6, spinal preganglionic sympathetic neurons disconnected from supra-spinal regulation have been shown to exhibit episodic unchecked reflexes.10

Vitamin B12 deficiency in two of our patients was diagnosed in the presence of normal serum vitamin B12 levels. One patient had elevated blood homocysteine levels and the other had elevated blood homocysteine and MMA levels. Diagnosis of vitamin B12 is fraught with problems because of unavailability of robust assay.11 Vitamin B12 is a necessary coenzyme in the metabolism of MMA to succinyl choline, and is also a necessary coenzyme with folate in the metabolism of homocysteine to methionine. Therefore, vitamin B12 deficiency leads to elevated levels of unmetabolized MMA and homocysteine.12 MMA is considered a more sensitive indicator of vitamin B12 status, although it has relatively low specificity, particularly in patients with renal impairment.13 Recently, cobalamin-saturated transcobalamin, also called holotranscobalamin (holoTC), has been found to be an early and more
sensitive marker of vitamin B12 deficiency. Patients with vitamin B12 levels in the lower normal to just below normal range should have testing for MMA/homocysteine or holoTC (if available).

The exact mechanism of excessive sweating in vitamin B12 deficiency is a matter of speculation and will require further studies. Spinal sympathetic overactivity is one plausible explanation and involvement of only the upper trunk in the first patient would suggest segmental hyperactivity of sympathetic preganglionic neurons involving T1 to T12 segments. Modest rise in urinary catecholamines would be consistent with sympathetic over-activity. Sparing of proximal nerve segments in the dying-back neuropathy may be argued to cause sweating in our first patient but will not explain the exclusive involvement of upper trunk only and would more likely cause sweating abnormalities in the proximal parts of both upper and lower limbs.

Conclusion

Vitamin B12 deficiency may cause spinal cord abnormalities responsible for segmental or generalized autonomic sympathetic hyperactivity resulting in drenching night sweats. This phenomenon of drenching sweating likely due to sympathetic nervous system overactivity because of vitamin B12 deficiency has not been reported before. Vitamin B12 status should be ascertained in patients with unexplained night sweats.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

None declared.

References