Vitamin B12 Deficiency Related Syncope in a Young Military Pilot

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BACKGROUND: Syncope and near-syncope are commonly encountered symptoms. Many cases are situationally specific or otherwise benign, with no adverse aeromedical implications. Autonomic dysfunction can produce orthostatic intolerance with resultant symptoms and is aeromedically concerning for potential occurrence in flight. Vitamin B12 deficiency is an insidious condition with protean manifestations, which can present with autonomic dysfunction. Neurological abnormalities are often reversible following adequate replacement.

CASE REPORT: We describe a case of vitamin B12 deficiency in a pilot with atypical syncope and abnormal tilt-table testing who had progressively abnormal hematologic findings on review. He was also discovered to have intrinsic factor antibodies. After B12 replacement, he had normal cardiovascular response to exercise stress testing and an unremarkable centrifuge assessment.

DISCUSSION: This case highlights the importance of recognizing subtle laboratory findings and serial laboratory data review in cases of atypical syncope to identify potential reversible etiologies.

KEYWORDS: syncope, B12 deficiency, autonomic dysfunction.

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Syncope (fainting) and near-syncope are commonly encountered symptoms with significant aeromedical implication from resulting subacute to sudden incapacitation. These symptoms have a wide range of etiologies, from benign, preventable, situationally specific provoking factors such as venipuncture, to more ominous causes such as cardiac arrhythmias. Orthostatic hypotension is often a contributing factor to near-syncopal or syncopal episodes. Hypovolemia is a common cause of orthostasis in such cases, but conditions that interfere with autonomic function can also produce orthostatic intolerance.

Vitamin B12 deficiency is an insidious condition with protean manifestations that can affect both the central and peripheral nervous systems.[5,9,10] Autonomic involvement is one potential peripheral nervous system manifestation of vitamin B12 deficiency.[2] Below, we present a case of a young military pilot with somewhat atypical, incompletely explained syncope who was discovered to have vitamin B12 deficiency with intrinsic factor antibodies, and who had normal $+G_z$ tolerance and heart rate variability after replacement therapy. This case illustrates the importance of searching for uncommon, treatable etiologies.

CASE REPORT

This 25-yr-old male Air Force pilot had three brief typical situationally specific provoked vasovagal syncopal episodes in childhood, without any associated injury. He had another episode of situationally specific provoked syncope while attending university, in the context of acute upper respiratory illness with fever and dehydration. These episodes were not felt to require aeromedical waiver. The member successfully completed military flight training, which included a centrifuge assessment, and was assigned to bombers. He then successfully completed land and water survival training. At his next posting, he was attending a long morning briefing seated in a very cold classroom when he noted his hearing sounded distant and he had

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some peripheral vision loss. He was observed to be slow to follow commands and appeared slightly confused. Vital signs and examination findings were unremarkable, and he was assessed as having had a presyncopal episode. Supportive preventive measures were advised and again an aeromedical waiver was felt unnecessary. About 4 mo later, the pilot was delivering a briefing to a morning meeting group and was feeling stressed, as his presentation had not gone well. He was observed to have shifting stance and pallor and had to be assisted to a seated position. Shortly afterwards he lost consciousness and was assisted to the floor, without injury. He had eaten about 1 h before the briefing and denied any concurrent illnesses.

On medical assessment, examination findings were normal. Hemogram was notable for an elevated mean corpuscular volume (MCV) of 95.2. Routine electrocardiogram was unremarkable. He was referred to Cardiology and had normal examination findings. Minimal ethanol use, no tobacco use, and no caffeine intake were reported. One asymptomatic episode of rapid sinus tachycardia was noted with 24-h cardiac rhythm monitoring. Transthoracic echocardiography was unremarkable. Tilt-table testing showed a 7.4-s asystolic period and the member was assessed as having neurocardiogenic syncope, and was advised to take midodrine for symptom management. He took the medication for about 2 wk, without any perceived benefit, and then self-discontinued it. On further comprehensive medical record review, his MCV was in the 86–87 range in 2003 and was in the 95 range in 2013. Serum thyroid stimulating hormone level was normal in 2013. The longitudinal increase in MCV prompted additional testing, which revealed slightly diminished erythrocyte count, a low serum B12 level of 198, normal serum folate level of 9.4, low serum vitamin D level of 24.1, and elevated intrinsic factor antibodies.

After these findings were noted, the member was given oral vitamin D and parenteral vitamin B12 replacement, with normalization of serum levels in 1 mo (vitamin B12 $>$ 2000, vitamin D 66.1). The pilot was strongly suspected of having early vitamin B12 deficiency associated autonomic insufficiency as the primary etiology of his recent syncopal episode and abnormal tilt-table test result.

He was then seen at the U.S. Air Force School of Aerospace Medicine for evaluation about 2.5 mo after being started on vitamin replacement. He reported no further episodes of near-syncope or syncope. Cardiac and neurological examination findings were normal; orthostatic vital sign measurements were normal. Transthoracic echocardiography was normal. Normal heart rate variability was shown with 24-h cardiac rhythm monitoring, with measures indicative of normal autonomic function. Exercise stress testing to maximal age-predicted heart rate of 194 bpm with 17.2 METS exertion and double product over 38,000 did not produce any clinical symptoms during or following exercise. No abnormal postexercise pulse or blood pressure changes were seen. The member then underwent a medically monitored centrifuge assessment with one run of +4 G_z for 15 s, two runs of +4 G_z for 30 s, and one run of +5 G_z for 15 s. All runs were accomplished with only anti-G straining maneuvers; no anti-G equipment was worn. These +G_z levels well-exceeded operational +G_z limits of the member's primary assigned aircraft. No clinical symptoms were reported and no cardiac arrhythmias were noted. Repeat tilt-table testing was considered but was ultimately not deemed necessary given these reassuring findings. Based on the evaluation results, the pilot was recommended for an unrestricted return to flying waiver. Continued indefinite vitamin B12 replacement and general supportive measures were also recommended. The pilot was able to maintain normal serum vitamin B12 levels with oral replacement therapy.

DISCUSSION

It has long been known that neurological symptoms in B12 deficiency often precede development of anemia, and the severity of megaloblasitic anemia inversely correlates with the degree of neurological dysfunction.[11] Fortunately, with early diagnosis and treatment, even significant central nervous system signs such as myelopathy from spinal cord involvement can be reversed.[8] Orthostatic hypotension has been reported with vitamin B12 deficiency and is also reversible following adequate treatment.[6,12]

Vitamin B12 deficiency can be caused by inadequate dietary intake as in vegetarian diets.[1] It can also be associated with inadequate absorption. In our case, we postulated there was slow depletion of intrinsic B12 stores from inadequate intestinal absorption, reflected in progressively increased MCV values. In turn, this led to early autonomic dysfunction, manifested by syncope and an abnormal tilt-table test response. Our pilot was found to have antibodies to intrinsic factor. These are seen in pernicious anemia and, in such cases, management with oral vitamin B12 replacement is often inadequate.[3,4] Treatment of the vitamin B12 deficiency in pernicious anemia patients addresses the hematologic and neurological consequences, although it does not reduce the risk of gastric and other cancers.[7]

A limitation to more definitive proof of our pathogenesis hypothesis in this case was not obtaining follow-up tilt-table testing. As normal heart rate variability was seen on 24-h rhythm monitoring, no abnormal blood pressure or pulse responses were noted on maximal exercise stress testing, and no signs or symptoms were observed during centrifuge assessment, these results were felt sufficient to reasonably validate our clinical suspicion.

In conclusion, vitamin B12 deficiency is an uncommon but readily treatable cause of syncope. Recognition of our pilot's condition facilitated appropriate vitamin replacement and undoubtedly prevented development of more serious neurological and hematologic complications. Assessment of serum B12 level should be considered in cases of unexplained syncope and also in any syncope cases where an increased MCV is found.

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