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CASE REPORTS

Vitamin B_{12} Deficiency: A Rare Cause of Excessive Daytime Sleepiness

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Excessive daytime sleepiness (EDS) is one of the leading reasons that patients present to sleep clinics. Approximately 10% to 14% of the adults report that excessive sleepiness interferes with their daily lives. Common causes of EDS include obstructive sleep apnea, sleep deprivation, circadian rhythm disorders, medication effects, psychiatric conditions especially depression, and primary hypersomnia such as narcolepsy or central idiopathic hypersomnia. Vitamin B_{12} deficiency is a rare cause of EDS. We are presenting a case of severe vitamin B_{12} deficiency as an unusual and rare cause of hypersomnia.

Keywords: excessive daytime sleepiness, excessive sleepiness, hypersomnia, obstructive sleep apnea, sleep disorders, vitamin B12 deficiency

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INTRODUCTION

The Epworth Sleepiness Scale (ESS) score is the most widely used scale to assess self-reported sleepiness in individuals.[1,2] Obstructive sleep apnea (OSA), as the most common cause of excessive daytime sleepiness (EDS), is thought to affect approximately 5% of the adult US population.[3] The prevalence of OSA can be as high as 20% depending on how OSA is defined. A general population study of randomly chosen, middle aged, state of Wisconsin employees found mild sleep apnea (apnea-hypopnea index [AHI] > 5 events/h) in 17% and moderate to severe apnea (AHI > 20 events/h) in 7%.[4] CPAP is the treatment of choice in management of patients with OSA.[5] CPAP therapy has been reported to significantly improve self-reported and objectively assessed daytime sleepiness in patients with OSA.[6] However, studies have indicated the mean level of sleepiness in some patients does not return to normal levels with CPAP therapy.[7] Wake-promoting agents such as modafinil have been studied as an adjunct therapy for residual excessive sleepiness in patients successfully treated with CPAP.[8]

We describe a rare case of residual sleepiness in a patient with OSA who was treated and was fully adherent to his CPAP therapy. Subsequent evaluation showed severe vitamin B_{12} deficiency. Daytime symptoms of hypersomnolence were reversed after vitamin B_{12} replenishment.

REPORT OF CASE

A 71-year-old man presented to the sleep clinic in 2006 with symptoms suggestive of OSA. He was found to have a baseline ESS score of 6/24 (EDS) and body mass index (BMI) of 32 kg/m^2. An in-facility polysomnogram showed an AHI of 9 events/h. He was treated with an oral appliance because the patient did not want to use a CPAP machine. He did well for about 4 years. In 2010, the patient started experiencing increasing fatigue and tiredness. An overnight pulse oximetry showed oxygen desaturation at nighttime. A thorough pulmonary, cardiac, and neurologic workup was performed and no known etiology of nocturnal oxygen desaturations could be identified. Arterial blood gas was normal with PCO_2 of 35 showing no evidence of hypoventilation. Pulmonary function tests including maximum inspiratory and expiratory pressure (MIP/MEP) were also normal.

The patient had an extensive neurological examination by a neurologist. It included nerve conduction studies. It only showed an isolated mild, chronic, right S1 radiculopathy with no active denervation. There was no electrophysiological evidence of motor neuron disease, cervical radiculopathy, brachial plexopathy, lumbosacral plexopathy, peripheral polyneuropathy, or other lumbosacral radiculopathy. There were no electrodiagnostic findings suggestive of myopathy. MRI scan of the brain was normal.

The patient had mild type 2 diabetes mellitus; however, hemoglobin A1c (HbA1c) levels over many years ranged from 6.5 to 7.0 range. The patient was on metformin for treatment of diabetes; however, EDS predated the initiation of metformin.

Other pertinent medications over the past few years have included Finasteride, Gemfibrozil, Detemir insulin, lisinopril, Pregabalin, Metoprolol, RaNITIdine, and Pantoprazole. None of them was likely to cause any decrease of vitamin B_{12} levels.

The patient was brought to the sleep laboratory for another overnight diagnostic sleep study. It showed an overall AHI of 12.5 events/h. He also had significant nocturnal oxygen desaturation and spent about 51% of the time with oxygen saturation between 80% to 89%. The pattern of oxygen desaturation was gradual decline and did not exhibit a seesaw pattern that is commonly seen in apneic events caused by OSA. The patient underwent a CPAP/bilateral positive airway pressure (BPAP)

titration study and required BPAP of 12/8 cmH_2O along with 2 L of oxygen to correct both OSA and nocturnal oxygen desaturation. However, the patient did not want to use the oxygen and BPAP was increased to 17/13 cmH_2O on a subsequent sleep study to correct both OSA and nocturnal hypoxia. The patient continued to use BPAP with 100% adherence, with an average use of 7 h/night and residual AHI of only 0.4 events/h on adherence data. This was followed up with an overnight pulse oximetry on the BPAP at home and had only 2 minutes of oxygen desaturation < 90% and 0 minutes < 88%.

The patient continued to complain of daytime fatigue and tiredness despite full correction of OSA. Modafinil was tried; however, a severe hemorrhagic rash developed on the patient's back that was attributed to the modafinil and it was discontinued. Modafinil did not improve daytime symptoms either.

In 2016, the patient reported episodes of hypersomnolence. ESS was 10 of 24. The patient had been fully adherent with BPAP. Because of longstanding daytime symptoms despite correction of OSA and prior side effects related to modafinil, it was decided that the patient undergo Multiple Sleep Latency Testing to objectively assess daytime sleepiness against fatigue. Multiple Sleep Latency Testing showed a mean sleep onset latency of only 5.1 minutes (< 8 minutes is considered abnormal). No sleep onset rapid eye movement was noted. BMI at this time was 29.4 kg/m^2 compared to previous BMI of 32 kg/m^2 in 2010. The patient's medication list had been thoroughly reviewed and none of the medications were associated with EDS. No new medical or psychological disorders could be found to explain EDS as well as fatigue. Sleep history failed to reveal any circadian rhythm disorder.

Further hematological workup was performed to look for a secondary cause of excessive sleepiness. Complete blood count showed hemoglobin and hematocrit levels of 13.5 and 40.3, respectively, with mean corpuscular volume (MCV) of 87 (normal value 80–100) and mean corpuscular hemoglobin concentration of 33.5. Iron studies and ferritin level were within normal range. Levels of thyroid-stimulating hormone 2.1 IU/L (0.358–3.740) and free thyroxine 1.02 ng/dL (0.76–1.46) were normal. 25 hydroxy-vitamin D level at 47.3 ng/mL (normal range 30–100 ng/mL) was normal. Vitamin B_{12} was found to be less than 60 pg/mL (normal range > 246 pg/mL). Interestingly, MCV was normal for this patient over more than 15 years and red cell distribution width was elevated for more than 15 years. The patient had normal folate and iron levels.

Antiparietal cell antibody titers were highly positive at 70.1 (normal < 24.9). A diagnosis of severe vitamin B_{12} deficiency caused by pernicious anemia was made. The patient was started on vitamin B_{12} (2,000 mcg orally daily). At 6-month follow-up vitamin B_{12} level was 1,810 pg/mL (246–911). The patient's EDS completely resolved and ESS score improved from 10 of 24 to only 4 of 24 on the follow-up visit. At 1-year follow-up in June 2018, the patient had complete resolution of his daytime sleepiness.

DISCUSSION

EDS can occur secondary to sleep apnea, sleep deprivation, medication effects, illicit substance use, OSA, and other medical and psychiatric conditions, especially depression. Less commonly, it can be caused by primary hypersomnia of central origin (eg, narcolepsy, idiopathic hypersomnia).[9] To our knowledge, hypersomnia caused by vitamin B_{12} deficiency has not been described in the literature except for an isolated case report.

Vitamin B_{12} deficiency is a common but serious disorder. Clinical manifestation may not be obvious, thus leading to complex issues and significant delay around diagnosis. The most common indications to test for vitamin B_{12} deficiency include anemia with macrocytosis with MCV > 100, known gastrointestinal disorders associated with vitamin B_{12} deficiency, or a vegan diet.[10] Interestingly, however, in our patient the complete blood count did not show anemia or macrocytosis. MCV level was normal. In patients with vitamin B_{12} deficiency, the MCV tends to increase before the hemoglobin level decreases significantly. Even when there is biochemical evidence of vitamin B_{12} deficiency, the MCV often remains within reference range. In one study, more than 25% of patients with neurologic disease have either normal hemoglobin or MCV, and sometimes both.[11] There is no correlation found between vitamin B_{12} and MCV in most cases. MCV should not be the only criteria for ordering assessment of vitamin B_{12} in patients suspected of deficiency. One study demonstrates that traditional criteria for vitamin B_{12} deficiency and MCV association was not followed in about half of the cases.[12]

Antiparietal cell antibodies have been noted to play a causative role in autoimmune gastritis of pernicious anemia and are present in approximately 85% of affected patients.[13]

Clinical features of vitamin B_{12} deficiency include neurological dysfunction including myelopathy, paresthesia, ataxia, spasticity, or hyperreflexia. Psychological impairment may lead to impaired cognition, depression, psychosis, delusions, and irritability.[14] Our patient also had idiopathic nocturnal oxygen desaturations despite an extensive workup to determine etiology. Vitamin B_{12} deficiency has been known to cause neuropathy and myopathy.[15] Retrospectively, it is plausible that the cause of the patient's nocturnal oxygen desaturation may be related to neuromuscular weakness.

To our knowledge, there has been only one case report published by Yamada in 1995, in which a patient with recurrent hypersomnia was successfully treated with vitamin B_{12}.[16] In this case the level was 420 pg/mL before treatment, which is within normal range (in our case vitamin B_{12} was < 60 pg/mL). The exact mechanisms by which vitamin B_{12} deficiency causes EDS are unknown. Vitamin B_{12} has been reported to increase the sensitivity to the environmental conditions including light stimulation. It is thought that vitamin B_{12} phase-advances the human circadian rhythm by increasing the light sensitivity of the circadian clock.[17] There was no evidence of a circadian rhythm disorder in our patient.

CONCLUSIONS

Vitamin B_{12} deficiency is relatively common in older patients mostly because of poor absorption. It can lead to various neurological and psychiatric disturbances. A high index of

suspicion and testing for vitamin B_{12} levels may be performed in patients with an unknown cause of hypersomnia despite normal blood count without any evidence of macrocytosis, as was the case in our patient. Further research may be needed to examine vitamin B_{12} deficiency as the cause of idiopathic nocturnal oxygen desaturations because of demyelination of phrenic nerves causing diaphragmatic weakness.

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DISCLOSURE STATEMENT

The report no conflicts of interest.