NEW RESEARCH

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Resolution of Hypersomnia Following Identification and Treatment of Vitamin D Deficiency

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A 28-year-old woman was evaluated for 4 months of excessive daytime sleepiness (EDS), after an overnight polysomnogram (PSG) revealed neither sleep disordered breathing nor a sleep related movement disorder. A full sleep evaluation revealed the presence of heavy daytime napping and pervasive fatigue. Epworth Sleepiness Scale (ESS) Score was 10/24. No features characteristic for depression or narcolepsy were present. Chronic pain in the low back and thighs, as well as chronic daily headaches were identified as potential sleep-disrupting forces. Risk factors for hypovitaminosis D included limited natural sun exposure, dark skin tone, and obesity. A 25-hydroxyvitamin D level was low, at 5.9 ng/mL. Vitamin D supplementation was initiated at a dose of 50,000 IU once weekly, and EDS improved within 2 weeks. One week later, a PSG with next-day multiple sleep latency testing (MSLT) failed to show significant pathology. At follow-up, she reported resolution of thigh pain and headaches, with a significant improvement in her low back pain syndrome. EDS had resolved, and her ESS score was 1/24. Follow-up 25-hydroxyvitamin D level was normal at 39 ng/mL. Mechanisms for her clinical improvement could include enhanced sleep quality due to resolution of hypovitaminisos D-associated noninflammatory myopathy, or a possible immunomodulatory effect of vitamin D decreasing central nervous system (CNS) homeostatic sleep pressure via its effects on tumor necrosis factor-alpha (TNF-α) and/or prostaglandin D2. More research is needed to determine if patients presenting with EDS should be more broadly screened for vitamin D deficiency.

Keywords: Hypersomnia, vitamin D, hypovitaminosis D, osteomalacic myopathy, chronic pain

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CASE REPORTS

REPORT OF CASE

A 28-year-old African American female presented to an academic sleep disorders center for further evaluation of approximately 4 months of EDS symptoms. Her symptoms began gradually, insidiously worsening to the point that she began having functional difficulties staying awake to engage in social responsibilities. She kept a standard bedtime between 21:00 and 22:00 and reported that she fell asleep easily and within minutes. She subjectively felt as though the quality of her sleep was good, stating she did not believe she had frequent nocturnal awakenings. She awakened to start her day at 07:30, would assist her children in getting ready for school, and then would routinely return to bed at 08:00 and would often sleep until noon. She would then rise to perform house-related chores and assist her children with returning home from school, often going back to bed for another nap from 16:00–19:00. In total, the patient stated that she was obtaining ≥ 14 h of sleep per day, as a result of her daytime sleepiness. Her ESS score was 10/24, indicating a pathological degree of daytime sleepiness. Her primary care physician requested a sleep study to evaluate for obstructive sleep apnea (OSA).

An overnight PSG using a digital acquisition system (Alice 5, Philips-Respironics) was performed. The study was scored according to rules described in the American Academy of Sleep Medicine (AASM) scoring manual,[1] and raw PSG data were reviewed by a physician board certified in Sleep Medicine. Hypopnea rule 4(A)—requiring 4% oxygen desaturation, along with a 30% drop in nasal pressure transducer airflow tracing—was used during the scoring of this PSG. Results from this study showed reasonably good sleep efficiency, with no evidence of sleep disordered breathing or sleep related movement disorder (**Figure 1**).

A primary hypersomnia syndrome was clinically suspected, and the patient was scheduled for a complete Sleep Medicine evaluation. This consultation occurred approximately 3 weeks after the original PSG was performed. At this visit, she continued to endorse a functionally limiting, pervasive sense of fatigue and "fighting sleep" whenever she was inactive. She denied cataplexy, sleep related hallucinations, and sleep paralysis. She denied emotional depression or anxiety. She endorsed a significant musculoskeletal pain syndrome involving her low back and thighs, which she rated as 6 out of 10 in severity, and stated she believed that this could be negatively affecting her sleep quality. She also endorsed frequent retro-orbital headaches, which were poorly responsive to medications.

Her medical history was remarkable for sickle cell disease, with occasional transfusion requirements (the most recent of which was 2 years prior to her initial polysomnogram), morbid obesity, and chronic low back pain. She reported taking daily oral hydroxyurea and folate supplements but no other regular medications. She admitted to occasionally using hydrocodone/acetaminophen for her headache syndrome, with only marginal benefit. She reported no association between the use of this medication and her EDS symptoms, stating that she felt per-

Figure 1—Results of original diagnostic polysomnography

Sleep latency	5.5 minutes
Sleep efficiency	90%
Total sleep time	350 minutes
Wake after sleep onset (WASO) episodes	14
WASO (total, in min)	33
Rapid eye movement (REM) sleep latency	140 minutes
Stage N1	3% total sleep time
Stage N2	59% total sleep time
Stage N3	23% total sleep time
Stage R	13.9% total sleep time

No apneas, hypopneas, or respiratory effort related arousals were seen.
No periodic limb movements of sleep.

Figure 2—Polysomnography and next-day MSLT results

Polysomnogram

Sleep latency	17 minutes
Sleep efficiency	74%
Total sleep time	394 minutes
Wake after sleep onset (WASO) episodes	27
WASO (total, in min)	118
REM sleep latency	124 minutes
Stage N1	8% total sleep time
Stage N2	65% total sleep time
Stage N3	7% total sleep time
Stage R	18% total sleep time

No apneas or hypopneas were seen.
Apnea Hypopnea Index = 0 per hour of sleep.
29 Respiratory Effort Related Arousals.
Respiratory Disturbance Index = 4.4 per hour of sleep
No periodic limb movements of sleep.

Multiple Sleep Latency Test

	Nap 1	Nap 2	Nap 3	Nap 4	Mean
Sleep latency (min)	4:30	20	20	20	16:52
Sleep duration	22:30	–	–	–	
REM sleep?	–	–	–	–	

vasively sleepy whether she used this medication or not. She denied use of alcohol, recreational drugs, and tobacco products. She slept alone, and denied any problems relating to bed comfort or noise disturbances during the sleeping time frame.

Physical examination revealed a pleasant obese African American woman in no distress. Vital signs were within normal limits. Her body mass index was 40. Examination of the oropharynx revealed a Mallampati I posterior inlet, with 1+ tonsils. A grade 2/6 systolic ejection murmur was present. Her affect was euthymic and showed full range. Her neurologic examination was nonfocal. Aside from marked conjunctival pallor, her skin examination was normal.

Laboratory data obtained earlier that month revealed anemia—consistent with her known history of sickle cell disease—with a hemoglobin of 8.1 g/dL, a value no different from those obtained prior to onset of symptoms. Thyroid stimulating hormone (TSH) was normal at 0.7 μIU/mL. A metabolic panel, including liver function tests and renal indices, was normal.

The patient was tentatively diagnosed with idiopathic CNS hypersomnia with long sleep time, and a repeat PSG with next-day MSLT protocol was planned. The presence of musculoskeletal pain associated with risk factors for vitamin D deficiency prompted further testing (see later). A 25-hydroxyvitamin D level was obtained, returning quite low at 5.9 ng/mL (normal range 32-100 ng/mL). Vitamin D supplementation at a dose of 50,000 international units (IU) once weekly was initiated the following week.

A repeat PSG with next-day MSLT was performed 3 weeks after vitamin D supplementation was initiated. This study showed a few respiratory effort related arousals, but no frank apneas or hypopneas, and fell short of diagnostic criteria for obstructive sleep apnea (**Figure 2**). Compared with her first PSG, the follow-up study showed decreases in sleep continuity, sleep efficiency, and percentage of sleep time spent in stage N3. The MSLT performed the following day revealed sleep in only the first of 4 naps, with a mean sleep latency calculated at 16:52. No sleep-onset REM sleep periods were seen.

At a follow-up clinic visit to discuss results, she admitted that she began feeling better approximately 2 weeks after initiating vitamin D supplementation, and that her EDS symptoms had completely resolved by the time she returned for her repeat PSG and MSLT. She stated that she continued to have mild low back pain, but it no longer seemed to affect the quality of her sleep. The pain in her thighs and daytime headache syndrome had completely resolved. She denied functional limitations due to fatigue, and denied daytime napping. Her ESS score was 1/24. She estimated a total sleep time of approximately 9-10 hours per night. She stated that—aside from initiating vitamin D supplementation—no other circumstances in her life had changed since her initial evaluation: there had been no interval changes in her other medications, diet, social activities, caffeine use, exercise patterns, or work. A 25-hydroxyvitamin D level obtained at her follow-up visit was found to be within normal limits at 39 ng/mL. A hemoglobin level obtained the following day was essentially unchanged from previous levels, at 8.2 g/dL.

DISCUSSION

Vitamin D refers to a group of fat-soluble secosteroid hormones, and is typically ingested in dietary sources (dairy products and fatty fish), or is manufactured in the skin after exposure to UVB light. Vitamin D deficiency/insufficiency is increasingly recognized as a global epidemic, estimated to affect over a billion persons worldwide.[2] Though vitamin D deficiency is commonly understood to be disproportionately represented in underserved populations,[3] patients residing in northern latitudes,[4] individuals with darker skin tones,[2,5,6] the elderly,[7] the obese,[8] and pregnant or lactating women,[9] it is also commonly found in children[10,11] and is surprisingly common in areas with a high degree of year-round sunshine.[12,13] It has been postulated that increasing urbanization of the population as well as an increased awareness of potential dangers of sun exposure with subsequent reliance on sun-blocking skin products are both factors underlying the seeming increase in prevalence.

Over the past decade, scientific understanding of the role of vitamin D has expanded greatly, beyond its classically described effects on gut and bone,[2] with an explosion of new associations tied to its deficiency. Vitamin D and its analogues appear to have potent immunomodulatory activities, and deficiency of vitamin D has been linked to multiple pulmonary

disorders, including worsening lung function in patients with chronic obstructive pulmonary disease,[14] reactivation of tuberculosis,[15] and increased incidence of childhood asthma and wheezing.[16-18] Vitamin D appears to be necessary for optimum functioning of skeletal muscle as well, with deficiency associated with increased risk for falls[19] and disability[20] among elderly patients, as well as chronic pain,[21] low back pain,[22] and cases of overt painful myopathy.[23-25] In one study of patients admitted to a Minneapolis hospital, 93% of those complaining of nonspecific musculoskeletal pain were found to have significant vitamin D deficiency.[26] Recent publications point to a potential link between vitamin D deficiency and the metabolic syndrome,[27] type 2 diabetes,[28] incident hypertension,[29] as well as a possible association with cancers of the breast, colon, and prostate.[30] Vitamin D deficiency may lead to problems with higher cognitive functioning as well, with associations found with poor stress resilience,[31] depression,[32] and cognitive decline.[33] Finally, some evidence supports a link between vitamin D deficiency and all-cause mortality.[34]

The mechanism for the improvement in this patient's hypersomnia syndrome after identification and remediation of vitamin D deficiency is not known. A simple explanation is that she experienced a significant improvement in her musculoskeletal pain syndrome—which was identified as a sleep-disrupting force on her initial interview—thus leading to improved quality of sleep and decreased daytime consequences. Corroborating this theory is the patient's own description of an improvement in her subjective pain syndrome, along with subjectively more restorative sleep. If this were the sole explanation, however, one would expect that her post-replacement PSG would show an improvement in sleep continuity, as reflected by a decrease in episodes and duration of wake after sleep onset. In reality, the opposite was seen.

Another possible explanation is the notion that vitamin D may play some yet unidentified role in the regulation of homeostatic sleep drive via CNS inflammatory signaling. Slow wave sleep is widely considered to be a marker for homeostatic sleep drive. In this patient, stage N3 sleep showed an interval decrease following vitamin D replacement, suggesting a reduction in homeostatic sleep pressure following this intervention. Recent research on vitamin D lends support to this theory. Petersen and Heffernan found an inverse correlation between serum 25-hydroxyvitamin D and TNF-α levels, suggesting a mechanism by which vitamin D may influence the presentation of inflammatory diseases.[35] Though data are mixed, some research has demonstrated that TNF-α is mechanistically implicated in the sleepiness associated with OSA. In a study of sleepy adults with OSA, Vgontzas and colleagues found that administration of the TNF-α antagonist etanercept markedly decreased daytime sleepiness symptoms.[36] Recently, Barcelo and colleagues showed that patients with so-called "non-sleepy apnea" had significantly lower levels of lipocalin-type D2 synthase compared with their sleepy counterparts.[37] Lipocalin-type D2 synthase is the rate-limiting enzyme responsible for the production of prostaglandin D2, the major prostanoid in the brain, and is a physiologic regulator of sleep. Dovetailing with this is the recent work by Feldman and colleagues showing that vitamin D is a potent biologic regulator of prostaglandin synthesis via inhibition of cyclooxygenase-2.[38] Taken together, these data suggest the possibility that vitamin D deficiency could represent a condition which predisposes a patient to the development of pathologic degrees of CNS-induced sleepiness, mediated by components of the inflammatory cascade.

CONCLUSIONS

Excessive daytime sleepiness is a symptom which may result from a number of different sources, and a comprehensive approach to each patient is needed.[39] To our knowledge, this is the first reported case of clinical excessive daytime sleepiness resolving upon identification and remediation of severe vitamin D deficiency. Further study is needed to elucidate the possible mechanism for this phenomenon, and, importantly, whether more widespread screening for vitamin D deficiency among patients complaining of excessive daytime sleepiness is warranted.

ABBREVIATIONS

CNS, central nervous system
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
MSLT, multiple sleep latency test
PSG, polysomnogram
TNF-α, tumor necrosis factor-alpha
WASO, wake after sleep onset

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