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Hypersomnia secondary to severe acute respiratory syndrome coronavirus-2 infection

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Excessive daytime sleepiness (EDS), with or without an excessive need for sleep, is a primary reason for patients seeking consultation at the sleep unit. EDS is observed in ~5% of the general population. Common causes of EDS include obstructive sleep apnea, sleep deprivation, effects of medication, psychiatric disease (especially depression), and circadian rhythm disorders. Coronavirus disease 2019 (COVID-19) infection is a rare cause of EDS. We present a case of mild COVID-19 infection as an unusual cause of hypersomnolence.

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Excessive daytime sleepiness (EDS) may be defined as the inability to stay awake during the usual wakefulness time, and is observed in ~5% of the general population. Excessive need for sleep (ENS) is defined by sleep durations exceeding 9 hours, for which Bassetti et al.[1] found a prevalence of 8.4% in the general population. Hypersomnia due to a medical disorder encompasses various clinical scenarios with diverse etiologies characterized by chronic EDS and/or ENS.[1]

The World Health Organization (WHO) defines post-coronavirus disease 2019 (COVID-19) or long COVID as a complex syndrome with typical symptoms such as fatigue, shortness of breath, and cognitive disorders. Sleep disorders, particularly insomnia, have been reported in more than 30% of patients with long COVID.[2]

We present a rare case of a young patient with persistent hypersomnolence unaccompanied by fatigue following a mild COVID-19 infection.

CASE

A 44-year-old Hispanic male presented to the sleep unit with complaints of EDS and ENS. His past medical history included migraine with visual aura. The EDS had first appeared

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2 years previously after a confirmed diagnosis of mild COVID-19 infection via the polymerase chain reaction test. He experienced persistent somnolence and unintended naps at all times of the day, occurring even during activities such as writing, eating, or, on one occasion, a driving lesson. Compared with his previous routine of sleeping less than 8 hours per night and taking 30-minute naps, at the time of presentation he slept for 8-10 hours every night and took a 2-hour nap daily, which he found nonrestorative. He would go to sleep between 23:00 PM and 1:00 PM, and wake up between 7:00 AM and 9:00 AM on weekdays and between 9:00 AM to 11:00 AM on weekends.

He had worked late shifts from 15:00 PM to 22:30 PM since 2006 as an assistant nurse in a geriatric center, where his colleagues mocked him for falling asleep during work hours. He denied sleep paralysis, hypnagogic or hypnopompic hallucinations, difficulties in initiating or maintaining sleep, habitual or disruptive snoring, sleep apnea, restless legs, nightmares, and symptoms suggestive of cataplexy or parasomnia. He scored 16/21 on the Epworth sleepiness scale (ESS).

The findings of physical and neurological examinations as well as vital signs were unremarkable, and his body mass index was 21.7 kg/m^2. A diagnosis of depression or anxiety was ruled out using the Beck Anxiety Inventory and the Beck Depression Inventory. Polysomnography (PSG) was performed (Table 1) followed by the multiple sleep latency test (MSLT). PSG did not reveal either central or obstructive sleep apnea or an increased periodic limb movements index in the legs. A four-nap MSLT was performed. Sleep was achieved in each nap with a short mean sleep latency of 7.25 minutes, but no sleep-onset rapid eyes movements periods (SOREMPs) were recorded (Table 2). A sleep diary was maintained for nearly 1 month, and indicated an average of 10 hours of sleep per day. Urine toxicology screening and HLA DQB10602 testing were negative. Blood tests revealed normal levels of complete blood count, biochemistry, T4, thyroid stimulating hormone, and ferritin. Brain MRI findings were normal. The EDS was significant despite adequate hours of sleep being achieved as confirmed by the sleep diary. His MSLT revealed pathological sleepiness but without SOREMPs to suggest narcolepsy.

Considering hypersomnolence that lasted for more than 3 months following COVID-19 infection, hypersomnia secondary to COVID-19 infection was diagnosed. This diagnosis was supported by the lack of associated cataplexy, sleep paralysis, and sleep-related hallucinations. The MSLT also revealed a mean sleep latency ≤8 minutes without SOREMPs.

The patient was started on 100 mg of modafinil at lunchtime. He developed dizziness, a generalized rash, and des-

Table 1. Diagnostic PSG findings

PSG finding	Value
Recording time	23:24 to 7:16
TRT (minutes)	460
Sleep latency (minutes)	16
SE	93.7
TST (minutes)	431
N1	6.4
N2	53.7
N3	15.0
REM	24.9
REM latency (minutes)	80
AI (number/hour)	10.7
TST supine	38.5
AHI (number/hour)	1
AHI REM (number/hour)	3.9
Oxygen nadir	95
TST <90% O_2 sat	0
PMLI (number/hour)	5.5
Maximum HR (bpm)	77
Minimum HR (bpm)	53

Values are presented as number (%).
PSG, polysomnography; TRT, total recording time; SE, sleep efficiency; TST, total sleep time; N, non-rapid eye movement; REM, rapid eye movement; AI, arousal index; AHI, apnea-hypopnea index; PMLI, periodic leg movements index; HR, heart rate.

Table 2. MSLT findings

Trial (nap time)	SOL (minutes)	SOREMs
Trial I (9 hours)	5	No
Trial II (11 hours)	9	No
Trial III (13 hours)	4	No
Trial IV (15 hours)	11	No
Mean latency	7.25	0/4

MSLT, multiple sleep latency test; SOL, sleep onset latency; SOREMs, sleep onset REM periods; REM, rapid eye movement.

quamation on the soles and palms 3-4 days later. Modafinil was suspended and he completely recovered within 1 week. He was prescribed 10 mg of the fleeting stimulant methylphenidate, to which he responded positively as indicated by improved EDS (ESS score=8/21). This improvement was further confirmed by a maintenance of wakefulness test that revealed an average sleep latency of 29.25 minutes.

DISCUSSION

EDS can occur secondary to sleep apnea, sleep deprivation, medication or substance use, restless legs syndrome, periodic limb movement disorder, and medical or psychiatric disorders. It is less commonly caused by narcolepsy or idiopathic hypersomnia. We are aware of only three cases of hypersomnia due to COVID-19 infection having been described in the literature.[2]

Our patient was young and had no sleep disorders, EDS, or ENS before the COVID-19 infection, suggesting a causal association between hypersomnolence and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

The current WHO definitions of long COVID, postacute sequelae of COVID-19, and post-COVID indicate that the three most common symptoms are fatigue, shortness of breath, and cognitive dysfunction. Neither EDS nor ENS were considered in this definition.[3-6] An international survey study found that fatigue, insomnia, and EDS are amongst the most common symptoms of long COVID.[7]

Mechanisms potentially contributing to post-COVID pathophysiology include 1) direct viral damage; 2) immune system dysregulation and chronic inflammation; 3) expected sequelae of postcritical illness; and 4) persistent brainstem dysfunction.[8,9] The olfactory pathway is the most likely route via which the causative virus can disseminate to the central nervous system (CNS).[10] Angiotensin-converting enzyme 2 is the receptor that SARS-CoV-2 uses to infect cells.[9] Studies have also found this receptor expressed in the CNS, including the striatum, cerebral cortex, substantia nigra, and brainstem.[10] Some of these brainstem nuclei are involved in sleep-wakefulness regulation, such as the dorsal raphe nucleus, locus coeruleus, pedunculopontine tegmental nucleus, periaqueductal gray substance, sublaterodorsal nucleus, and laterodorsal tegmental nucleus.[1,2]

A limitation of this case report was that the ENS of the patient was not formally defined using objective measures such as actigraphy or 24-hour PSG.

Sleep symptoms, especially insomnia, are common in post-COVID. EDS, but not ENS, is a symptom found to present in long COVID. There have been few cases of hypersomnia secondary to COVID-19 reported in the literature. Our patient responded to the wakefulness-promoting agent methylphenidate. This study highlights the importance of sleep pathology in post-COVID. Further studies are needed to understand the pathological mechanism, clinical course, prognosis, and management of hypersomnia related to COVID-19 infection.

Conflicts of Interest

None.

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