

# Narcolepsy Following COVID-19: A Case Report and Review of Potential Mechanisms

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## Abstract

The patient is a 33-year-old Iranian woman without a significant past medical history with the full range of narcolepsy symptoms that started within two weeks after her recovery from COVID-19. Sleep studies revealed increased sleep latency and three sleep-onset rapid eye movement events, compatible with a narcolepsy-cataplexy diagnosis.

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## **Title: Narcolepsy Following COVID-19: A Case Report and Review of Potential Mechanisms**

### **Abstract:**

The patient is a 33-year-old Iranian woman without a significant past medical history with the full range of narcolepsy symptoms that started within two weeks after her recovery from COVID-19. Sleep studies revealed increased sleep latency and three sleep-onset rapid eye movement events, compatible with a narcolepsy-cataplexy diagnosis.

### **Clinical Message**

The immune activation in COVID-19 may trigger narcolepsy in vulnerable patients.

We suggest clinicians carefully evaluate patients with post-COVID fatigue and hypersomnia for primary sleep disorders, specifically narcolepsy.

### **Key Words:**

Narcolepsy, COVID-19, sleep disorders, autoimmune, hypersomnia

### **Introduction:**

Narcolepsy is an uncommon sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. It occurs in about 44.3 per 100,000 people<sup>1</sup>. Sleepiness is the core symptom in these patients and is seen in nearly all patients. Cataplexy is the second most common symptom; hypnagogic hallucinations and sleep paralysis are less common associations. Patients with narcolepsy usually present with a few of these primary symptoms; All symptoms rarely occur in the same patient simultaneously<sup>1</sup>.

The International Classification of Sleep Disorders (ICSD-3) categorizes narcolepsy into two types: Type 1 narcolepsy (NT1), which is associated with cataplexy, and type 2 narcolepsy (NT2), which presents without cataplexy<sup>2,3</sup>. Pathophysiologically, NT1 is differentiated from NT2 in that it is associated with the loss of hypocretin-producing cells in the lateral hypothalamus<sup>4</sup>. Thus, NT1 may be a distinct pathological entity from NT2 and idiopathic hypersomnia<sup>4</sup>. The neuropeptide hypocretin(also called orexin) plays a role in sustaining wakefulness and suppressing rapid-eye-movement sleep<sup>5</sup>. The loss of hypocretin-producing neurons thus results in loss of sleep continuity and breaks the border between sleep and wakefulness.

Narcolepsy may occur secondarily to other conditions (e.g. Parkinson's disease, Niemann-Pick type C, and various vascular, neoplastic, or inflammatory lesions involving the lateral hypothalamic area)<sup>2</sup>. Numerous studies have postulated that narcolepsy may be an autoimmune disorder resulting in a loss of hypothalamic neurons expressing hypocretin<sup>5-8</sup>. Notably, almost all patients with NT-1 have the HLA DQB1\*0602 variant that regulates T-cell immunity in viral and bacterial infections<sup>9</sup>.

On the other hand, COVID-19 has been associated with many neurological sequelae<sup>10</sup>. Since the incidence of narcolepsy has been previously shown to increase during the H1N1 pandemic in China and vaccinations<sup>11,12</sup>,

researchers have called for particular attention to its occurrence in the setting of the current pandemic as a unique opportunity for a better understanding of its clinical and biological features<sup>13</sup>.

We present the case of a woman who presented with classical symptoms of narcolepsy that had started following her recovery from COVID-19. Since there are many immune-mediated presentations after COVID-19 infection<sup>10</sup>, we propose that our patients' narcolepsy had para-infectious pathogenesis.

## Case Presentation:

### Chief Complaints

A 33-year-old woman presented to the outpatient neurology clinic complaining from episodes of falling asleep during the daytime despite about 8.5 hours of sleep per night.

### History of Present Illness

She was a psychologist and she noticed that she could not concentrate on the statements of her clients and that she sometimes saw some dream-like images around them. She also noted increasing lethargy, drowsiness and an irresistible urge to fall asleep many times a day even during conversations, while at work, or driving her car. All of her symptoms had begun immediately after recovery from COVID-19 about nine months before her presentation to neurology clinic. She reported that her symptoms of COVID-19 included fatigue, diarrhea, myalgia, hyposmia and hypogeusia without respiratory symptoms. She had recovered from COVID-19 with supportive and symptom-based treatment.

The patient also complained of frightening visual and auditory hallucinations while falling asleep at night as well as daytime. She had frequently experienced episodes of paralysis in which she was unable to move her body for a few seconds after awakening. She also complained from a sense of muscle weakness associated with drooping of eyelids, brought on by extreme emotions (e.g. laughing, shouting or any severe mental stress).

### History of Past Illness

Her medical history was unremarkable. There was no history of chronic sleep disorders, restless leg syndrome, sleep apnea, and head trauma or medication abuse.

### Personal and Family History

She did not use any substance or drugs. There was no history of sleep disorders in her family history.

### Physical Examination

Upon physical examination, she was a young woman with average body habitus (60 kg, 160 cm and BMI 23.4 kg/m<sup>2</sup>). She did not appear ill or drowsy during the history taking and physical examination. The pharyngeal lumen was patent. There were no craniofacial risk factors for sleep apnea such as retrognathia. She had neither ptosis, nor weakness of facial or limb muscles. The remainder of general physical and neurological examinations were unremarkable.

### Laboratory and Imaging Studies

In addition, routine blood tests and brain magnetic resonance imaging (MRI) revealed no significant pathology. The patient was referred for a polysomnographic study at a sleep clinic the results of which are presented in table 1.

*Table 1 The patient's polysomnographic findings*

Her sleep architecture was unusual in that sleep latency was slightly shorter than normal (2 min), with an 11-minute REM latency and sleep fragmentation. The multiple sleep latency test (MSLT), which consisted of four naps (20-minute sessions, 2 hours apart), showed sleep on all naps with an average sleep onset latency of 1.5 min (normal ~10 min). She had sleep-onset REM periods (SOREMP) in three of four naps.

## Diagnosis

Based on these findings and her typical symptoms for narcolepsy and cataplexy, she was diagnosed with type 1 narcolepsy.

## Treatment, Outcome, and Follow-up

She initially received modafinil and venlafaxine, to which she partially responded.

Since her symptoms did not resolve completely, we prescribed methylphenidate as an add-on with which she experienced moderate improvement but not complete resolution of her symptoms.

## Discussion :

Our patient, a woman in her mid-thirties, presented with excessive daytime sleepiness, episodes of cataplexy, sleep paralysis, and increased REM-associated features throughout the day. All her symptoms had started immediately after recovery from COVID-19. The results of polysomnography (PSG), including MSLT, confirm the diagnosis of narcolepsy syndrome. Our patient developed the symptoms at an older age compared to most patients who are diagnosed in their early twenties<sup>14</sup>. Also, she experienced the full range of possible symptoms in narcolepsy, which is another uncommon finding<sup>15</sup>.

The Academy of Sleep Medicine suggests a diagnosis of NT1 in patients with cerebrospinal fluid hypocretin deficiency; alternatively, the academy recommends the diagnosis of NT1 in patients with clear-cut cataplexy in line with PSG and MSLT findings that show mean sleep latency shorter than 8 minutes and at least two SOREMPs<sup>16</sup>. Our patient was diagnosed with NT1 based on her characteristic symptoms and a shortened mean sleep latency (MSL=1.5 minute) on MSLT, and SOREMPs in 3 of 4 recordings. These findings predict CSF hypocretin deficiency and may be used a surrogate for CSF hypocretin deficiency<sup>14,17</sup>.

The European guidelines on the management of narcolepsy recommend either sodium oxybate or a combination of antidepressants and stimulants as the first line of treatment for patients with narcolepsy-cataplexy<sup>18</sup>. Our patient showed only a partial response to the initial treatment with venlafaxine and modafinil. In such cases, the guideline recommends switching to sodium oxybate. However, since sodium oxybate is not available in Iran, we added methylphenidate, which enhanced the preexisting response to medications.

The pathophysiology of type 1 narcolepsy involves the autoimmune destruction of hypocretin-producing neurons in the lateral hypothalamus. This mechanism is supported by the strong association of HLA DQB1\*0602 phenotypes with the development of narcolepsy<sup>9</sup>. Numerous articles have reported the development of narcolepsy in patients with the HLA DQB1\*0602 phenotype following infections, especially streptococcal infections and flu<sup>11,12,19-21</sup>. Of note, an increase in the incidence of narcolepsy was reported during the 2009 H1N1 influenza pandemic and after massive flu vaccination in some countries<sup>12,22-24</sup>, especially among people younger than 18 years and in France, Denmark, Finland, and Sweden<sup>22</sup>. However, studies from South Korea, Canada, England, Netherlands, and Spain did not show a significantly increased risk associated with H1N1 vaccines<sup>25,26</sup>. The discrepancy in the effects of vaccination across different populations may be caused by the interplay between genetic predisposition and environmental factors in the development of narcolepsy.

The exact autoimmune processes that cultivate narcolepsy remain to be explained. Initial hypotheses were focused on specific antibodies<sup>27-32</sup>; however, recent findings more strongly support a T-cell-mediated cellular damage in patients with specific polymorphisms in alpha locus of the T-cell receptor<sup>33,34</sup>. The damage inflicted by T-cells following infections may be triggered via molecular mimicry or as a side effect of systemic hyper-activation of the immune system and cytokine storms<sup>4,8</sup>. Our patient developed typical symptoms of

narcolepsy-catalepsy after infection with COVID-19; this concurrence may point to an underlying autoimmune or para-infectious process causing sleep disruption in our patient.

A recent review article has emphasized the important potential role of SARS-CoV2 infection as a triggering factor for narcolepsy<sup>35</sup>.

COVID-19 infection has shown several neurologic manifestations such as encephalitis, stroke, headache, Seizures, and Guillain–Barrè syndrome<sup>10</sup>. Although the exact mechanism of the neurologic damage associated with SARS-CoV-2 is unclear, suggested mechanisms include systemic inflammatory response, immune-mediated injury, direct neuroinvasion, and microvascular damage<sup>10</sup>. The same mechanisms, and most probably an immune-mediated injury may have contributed to cell damage in the lateral hypothalamus in our patient.

Coronavirus infection and its resultant cytokine storm can increase the permeability of the blood-brain barrier making the brain more susceptible to the effects of systemic inflammation as well as migration of T-cells<sup>36</sup>. The patient’s HLA phenotype has been shown to affect the type of symptoms and their severity in COVID-19<sup>37</sup>. Unfortunately, we could not perform HLA typing in our patient due to financial limitations. However, it is possible that specific HLA phenotypes may predispose to narcolepsy following COVID-19. Olfactory dysfunction is another interesting concurrence in narcolepsy and COVID-19. COVID-19 has been shown to affect the olfactory bulb probably by viral invasion and inflammation causing anosmia and parosmia<sup>10,35,38</sup>. Narcolepsy is also frequently associated with olfactory dysfunction that responds to intranasal orexin<sup>39</sup>. Still, the role of olfactory dysfunction as a mediating factor in the development of narcolepsy is unknown<sup>35,39</sup>. Our patient experienced olfactory dysfunction during the course of COVID-19; However, her taste and smell had recovered by the time she started experiencing sleep issues. We postulate that primary infection and inflammation of the olfactory bulb with SARS-COV2, by recruiting T-cells, may have played a role in the pathogenesis of narcolepsy via immune sensitization to hypocretin-producing cells.

## Conclusions

The autoimmune mechanisms in narcolepsy on the one hand and profound activation of the immune system during COVID-19 may increase the occurrence of narcolepsy in susceptible individuals after COVID-19. In our patient, the diagnosis of narcolepsy was made relatively late, approximately nine months after symptom onset. Thus, we recommend considering the diagnosis of narcolepsy in patients with excessive fatigue and drowsiness following COVID-19. This consideration should be based on careful history taking, specifically inquiring about symptoms of narcolepsy, followed by specific sleep studies according to the constellation of symptoms. We also recommend measuring inflammatory markers and hypocretin, as well as HLA typing in patients with narcolepsy after COVID19 to guide a better understanding of the pathogenesis of narcolepsy following COVID-19.

## Disclosures

### Informed Consent

Written informed consent was obtained from the patient for publication of this case report.

### Competing interests

The authors declare that they have no financial or personal conflicts of interest associated with this case report.

## Authors' contributions

R.Y. is the neurology resident who participated in the patient's evaluation, diagnosis, and care and gathered the information for this case report.

F.B. is a general practitioner who composed the manuscript and the literature review.

M.A.D. is the attending neurologist who participated in the patient's evaluation, diagnosis, and care.

M.S. is the sleep neurologist who conducted and interpreted the results of the sleep studies and contributed to patient-care.

B.Z. is the attending neurologist who participated in the patient's evaluation, diagnosis, and care.

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## Availability of data and materials

The data supporting the findings of this study are available within the article.

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Table 1 The patient’s polysomnographic findings

The patient’s findings	The patient’s findings	
Duration of Recording	Duration of Recording	445.53 minutes
Sleep Efficiency	Sleep Efficiency	70.5%
Sleep Stages	Stage I	5.7%
	Stage II	55.2%
	Stage III	23.4%
	REM	15.7%
	Respiratory Disturbance Index( RDI)	Respiratory Disturbance Index( RDI)
Mean Arterial Oxygen Saturation	Mean Arterial Oxygen Saturation	95.8%
Mean Heart Rate	Mean Heart Rate	69.3 bpm
Leg Movement Count	Leg Movement Count	174
Periodic Leg Movements Index(PLMI)	Periodic Leg Movements Index(PLMI)	13.8