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## Case Report

# Restless Leg Syndrome Is A Rare Presenting Feature Of COVID-19

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## Abstract

There have been several known neurologic manifestations of COVID-19, such as headache, anosmia, etc. Rare cases of restless legs syndrome (RLS) associated with the disease have been reported. Here, the authors describe a patient with six-day nighttime discomfort in both legs that improved with moving them, with dry cough and myalgia added to her symptoms and she was hospitalized due to low oxygen saturation and suspicion of COVID-19. During hospitalization, antiviral and anti-inflammatory drugs were used and after a short time of discharge, RLS was eliminated without any specific drug. We hypothesize that since angiotensin-converting enzyme (ACE2) is highly expressed in Substantia Nigra, SARS-Cov-2 may disturb iron metabolism and homeostasis of dopaminergic neurons which leads to the development of RLS and inflammation exacerbates the condition.

**Keywords:** SARS-CoV-2, COVID-19, Restless legs syndrome, SubstantiaNigra, Sleep disorder

## Case Report

The coronavirus Disease-2019 (COVID-19), caused by SARS-Corona 2 virus (SARS-CoV-2), could involve pulmonary, gastrointestinal, or even neurological systems. Neurological manifestations of COVID-19 are headache, anosmia, seizures, stroke, encephalopathy, neuropathy, and myopathy.

In addition to idiopathic cases, restless legs syndrome (RLS) has several secondary causes such as iron deficiency anemia, diabetes, hypothyroidism, vitamin deficiencies, and excessive consumption of caffeine compounds (1).

Infections are generally not associated with RLS except in some cases like hepatitis C virus, Helicobacter pylori, etc. It has been demonstrated that in these infections there is the relation between the release of inflammatory agents, iron deficiency, and RLS (2).

There were RLS cases associated with COVID-19 (3). Interestingly, we also describe another case of COVID-19-associated restlessness leg as one of presenting features. A 64-year-old woman presented to the emergency department of Dr. Masih Daneshvari hospital at the middle of autumn 2020 with an initial complaint of nighttime discomfort in both legs, from six days ago. Also, she mentioned the urge to move her legs that almost improved by moving them. Worsening symptoms with the onset of dry cough,

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nocturnal sweating, and malaise happened over the next three days. There were no complaints of shortness of breath, chest pain, and fever.

She suffered from hypothyroidism 10 years ago which was controlled by levothyroxine 0.1 mg five days per week. She had no record of RLS or other neuropsychiatric disorders in her family history.

Upon admission, her vital signs were in normal range except peripheral oxygen saturation (SpO2) was 90% and coarse breath sounds were heard in both lower lobes of the lungs. Neurological examinations were normal.

According to the patient's clinical condition and suspicion of COVID-19, a lung Computed Tomography (CT) scan was performed (Fig. 1) and ground-glass opacification in the lower lobes of the lungs was in favor of COVID-19, so she was hospitalized due to decreased oxygen saturation. The polymerase chain reaction (RT-PCR) of the patient's nasopharyngeal swap sample was positive for COVID-19.

Her complete laboratory information during her admission day, hospitalization, and follow-up are given in table 1.

During the hospitalization, she received tab favipiravir (1600 mg 2 times on the first day of admission and 600 mg twice daily for the second to fifth days), amp dexamethasone (4mg subcutaneous two doses a day in between), amp Interferon beta-1a (12mv subcutaneous three doses a day in between), amp ceftriaxone (1g infusion in 100 ml normal saline twice daily), tab azithromycin (500 mg in the first day of admission and 250 mg daily for second to fifth days) were prescribed to the patient as empiric treatment.

She sometimes received nasal oxygen therapy in the hospital anytime that the SpO2 was under 93%. During discharge, the patient breathed ambient air and SpO2 was 98-99%. Significant objective improvements were seen in her symptoms .

At the patient's next visit to the clinic about one month later, discontinue of cough and diminishing malaise were distinct. Restlessness and discomfort in her legs gradually decreased during the follow-up and completely recovered after two months from the onset of the disease.

All the laboratory workups to evaluate a secondary reason for RLS were negative.

In this case report, we describe a patient diagnosed with COVID-19 who was presented with RLS as a first feature. The diagnosis of RLS is based on typical history, physical examination, and its criteria (1).

Research is ongoing for treatments of COVID-19 and some benefits of antiviral and anti-inflammatory drugs were shown. Besides the improvement of COVID-19, the restlessness of the legs was treated without any specific drugs-dopaminergic agents, benzodiazepines, opioids, and anticonvulsants (4).

Hypothyroidism is one of the secondary causes of RLS, but could not be considered the main cause in our patient since thyroid function has been normal in her annual follow-up, and there is no history of RLS or other sleep disorders before admission .

Although, the role of central and peripheral mechanisms in the pathophysiology of RLS is not fully understood; it is known that iron has a critical role in mitochondria and oxidative metabolism in the brain. Increased mitochondrial numbers and their ferritin content are due to insufficient iron levels and its availability in substantia nigra (SN) neurons in this syndrome. Also, iron homeostasis within cells is regulated by key proteins located on these organelles (5).

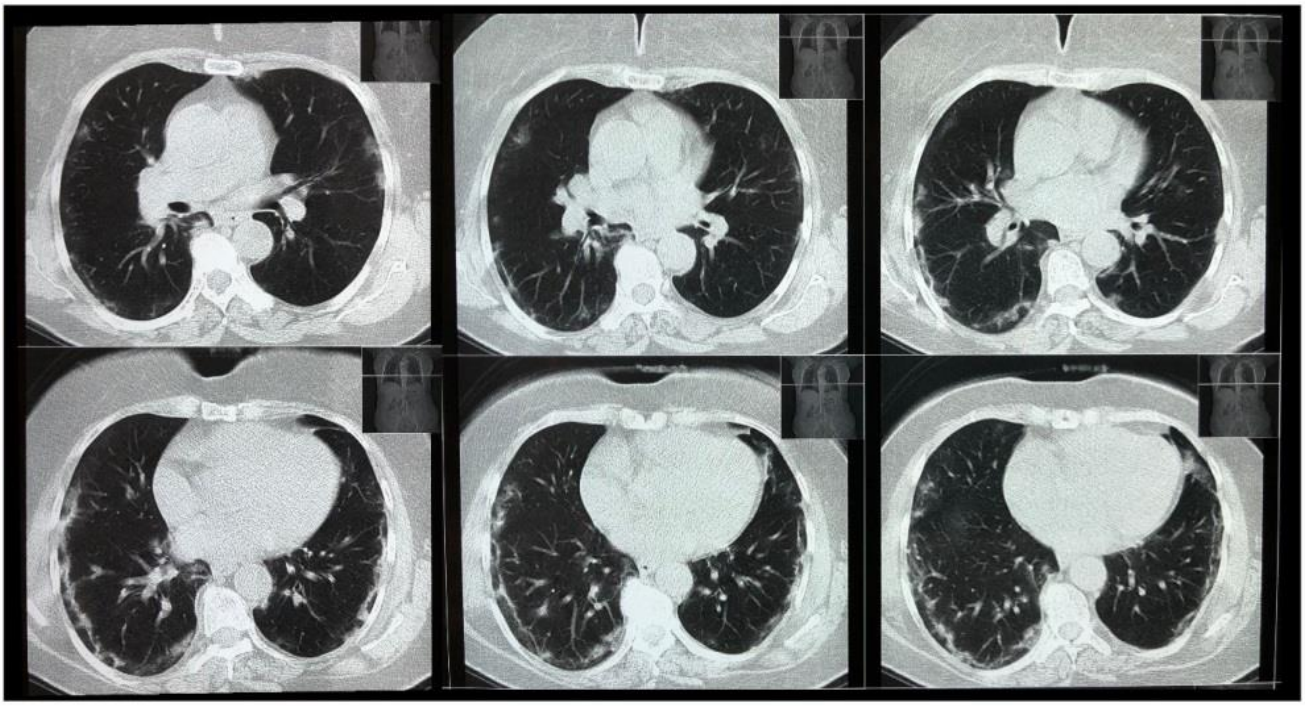
It is shown that the angiotensin-converting enzyme (ACE2) is highly expressed in SN andSARS-CoV-2 invades the host’s cells by binding to the enzyme via its spike proteins (6) SARS-COv-2 targets mitochondria and leads to mitochondria dysfunction, therefore, depletion of iron content in the cytosol (7). On the other hand, an elevated level of Hepcidin in inflammatory cases causes anemia by decreasing iron absorption from the intestine and worsens the condition (8).

There is a connection between SN and the somatosensory system that abnormality in spinal sensorimotor responses or excitability of the peripheral sensory nerves might be a factor in the development of secondary RLS in our patient (9). Autoimmune damage to basal ganglia due to microglial cell activation can be a physiological explanation for the correlation

| | Admission day | During hospitalization | One month later |
|---|---|---|---|
| **WBC ($10^3$/µL)** | 4.9 | 4.3 | 6 |
| Neutrophil | 71.8% | 82% | 59% |
| Lymphocyte | 22.8% | 16% | 37% |
| Other | 5.4% | 2% | 4% |
| **RBC ($10^6$/µL)** | 4.9 | 4.5 | 3.8 |
| **HB (g/dl)** | 12 | 11.3 | 11.8 |
| **HCT (%)** | 35 | 34.1 | 35.2 |
| **PLT ($10^3$/µL)** | 193 | 174 | 165 |
| **CRP (mg/L)** | 115 | 27 | 4+ |
| **ESR (mm/hrs)** | 95 | 43 | |
| **CPK (IU/L)** | 107 | | |
| **LDH (U/L)** | | 596 | |
| **Urea (mg/dl)** | | 25 | 23 |
| **Cr (mg/dl)** | | 1.1 | 0.8 |
| **TSH (mIU/L)** | | 0.04 | 2.3 |
| **T3 (ng/ml)** | | 0.62 | 94.5 |
| **T4 (µg/dl)** | | 0.07 | 6.85 |
| **IL-6 (pg/ml)** | | 7.1 | |
| **Ferritin (ng/ml)** | 765 | | 282.6 |
| **Iron (µg/dl)** | | | 74 |
| **TIBC (µg/dl)** | | | 230 |
| **HB A** | | | 97.4% |
| **HB A2** | | | 2.6% |
| **HB F** | | | <0.1% |

**Table 1**. Laboratory data parameters; WBC: white blood cell, RBC: red blood cell, HB: hemoglobin, HCT: hematocrit, PLT: platelets, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, Cr. creatinine, TSH: thyroidstimulating hormone, T3: triiodothyronine, T4: thyroxine, IL: interleukin, TIBC: Total iron-binding capacity, HB A, A2 & F: different types of hemoglobin for thalassemia workup

**Fig 1.** Axial images of non-contrast enhanced computed tomography of lung show bilateral multifocal areas of ground glass opacities especially in subpleural location which is compatible with COVID-19 bronchopneumonia



between RLS and COVID-19 (10).

Thus, we make a hypothesis that SARS-CoV2 disturbs iron homeostasis and metabolism in dopaminergic neurons of SN by attacking mitochondria and results in the development of RLS. Also, inflammatory responses of the immune system aggravate RLS symptoms due to both anemias caused by raising the level of Hepcidin and damages to some parts of the brain and ultimately impairment of the somatosensory system as we could see in our patient. However, the association between RLS and COVID-19 should be evaluated by further clinical and laboratory trials.

Further research is needed to prioritize the extent of involvement in biological systems and/or anatomical location in secondary RLS. In this study, we report a woman with transient RLS probably associated with SARS-CoV2 infection that treated without any specific medication for RLS with no reoccurrence.

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## Conflict of Interest

The authors declare that they have no competing interests.

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