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Clinical Letter

Central Apnea in an Adolescent With COVID-19

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Coronavirus disease 2019 (COVID-19) has been associated with a wide spectrum of symptoms, and neurological complications characterized by anosmia, hypogeusia, seizures, hemorrhagic stroke, neuromuscular problems, and encephalopathy have been reported in over 30% of cases.¹ The pathogenesis is still unclear, although underlying genetic susceptibility, viral invasion, and cytokine storm may play a role.² We describe a girl with COVID-19-associated encephalopathy characterized by focal seizures and central apnea.

This 14-year-old girl with no prior medical history presented with six days of fever, nasal congestion, and myalgia, followed by three generalized tonic-clonic seizures with perioral cyanosis. The patient was initially lethargic, but otherwise had a normal neurological examination. She had ongoing hypoxia and chest x-ray revealed bilateral infiltrates; she subsequently tested positive for COVID-19 polymerase chain reaction via nasopharyngeal sampling. Laboratory evaluation was unremarkable, cerebrospinal fluid profile and culture were normal, and cerebrospinal fluid polymerase chain reaction for COVID-19 was negative. The patient was started on levetiracetam and a 10-day course of remdesivir.

Two days after admission, she experienced two apneic episodes, necessitating intubation. Electroencephalography monitoring

during these apneic periods exhibit an epileptiform correlate. There were only mild elevations in inflammatory markers, and the serum cytokine panel was normal (see Table).

Magnetic resonance imaging of brain and spine was normal. Over the following week, she remained intubated despite minimal sedation; efforts made to decrease ventilatory support resulted in rising serum carbon dioxide without any response in respiratory drive. Her mental status improved over another week and she was able to follow commands, but only rarely had spontaneous respirations on the ventilator. Caffeine was initiated, and two days later her apnea improved to one to four brief, self-resolved episodes daily.

An apneic episode at this point was associated with lip smacking; further electroencephalography monitoring revealed a seizure correlate arising from right posterior temporal region. Lacosamide was added with complete resolution of apneic events and the patient was extubated. On follow-up, the patient was doing well without further seizures.

Discussion

Central apnea occurs because of impairment of a pontomedullary pacemaker resulting in lack of activation of inspiratory thoracic muscles. Both acquired and genetic disorders can result in sleep-related alveolar hypoventilation despite normal neuromuscular and pulmonary function. A congenital cause is rare, and typically attributed to central alveolar hypoventilation syndrome from PHOX2B mutations that result in disordered central and peripheral chemoreception.³ Affected individuals have an abnormal respiratory drive that manifests as shallow breathing with no distress or

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TABLE.
Relevant Laboratory Results and Values of Inflammatory Markers on Initial Presentation

Test	Value	Normal Range
Fibrinogen	274	300–520 mg/dL
D-dimer	234↑	<230 ng/mL
LDH	350↑	135–225 U/L
Ferritin	314↑	15–150 ng/mL
Procalcitonin	0.07	0.02–0.1 ng/mL
CRP	6.6↑	<5 mg/L
ESR	21↑	<20 mm/hr
Serum cytokine panel:		
Interferon- γ	<5	\leq 5 pg/mL
Interleukin 1 β	6	\leq 36 pg/mL
Interleukin 10	<5	\leq 18 pg/mL
Interleukin 12	<5	\leq 6 pg/mL
Interleukin 13	<5	\leq 5 pg/mL
Interleukin 17	<5	\leq 13 pg/mL
Interleukin 2	12	\leq 12 pg/mL
Interleukin 2 receptor	783	\leq 1033 pg/mL
Interleukin 4	<5	\leq 5 pg/mL
Interleukin 5	<5	\leq 5 pg/mL
Interleukin 6	<5	\leq 5 pg/mL
Interleukin 8	<5	\leq 5 pg/mL
Tumor necrosis factor	<5	\leq 22 pg/mL

Abbreviations:

CRP = C-reactive protein

ESR = Erythrocyte sedimentation rate

LDH = Lactate dehydrogenase

arousal in response to hypoxemia and hypercapnia. Acquired causes of central apnea abound because of brainstem, diencephalic, or

spinal cord disorders, and have been reported in cases of viral encephalitis, such as dengue.⁴

In contrast to persistent and continuous central apnea, intermittent apneic events are well known to correlate with seizures. Studies have demonstrated that the hippocampus and amygdala are limbic breathing control regions.⁵ Sudden unexpected death in epilepsy is a severe complication of patients with refractory epilepsy, often thought to be related to ictal or postictal central apnea with hypoventilation.⁶ This patient brings attention to a previously unreported encephalopathy with seizures and central respiratory disturbance associated with COVID-19 in the absence of inflammatory biomarkers and normal magnetic resonance imaging of the brain. It remains to be seen whether COVID-19 may precipitate an increase in sudden unexpected death in epilepsy in patients with epilepsy.

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