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Persistent hiccups after treatment of COVID-19 with dexamethasone: A case report

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ABSTRACT

Hiccups are involuntary and spasmodic contractions of the diaphragm, and multiple etiological factors have been suggested to be involved. Medications, such as dexamethasone, as well as some diseases, such as pneumonia, can cause persistent (>48 h) hiccups. Here, we report a 58-years-old male who had a fever, myalgia, cough, and ground-glass view in the chest computed tomography, and his PCR test for Covid-19 was positive. During the treatment course, persistent hiccups were developed after taking dexamethasone and lasted for six days. All cardiac and neurologic examinations were performed, and all of them were normal. After evaluating all of the possible underlying causes, dexamethasone was replaced by prednisolone. Upon a change in his treatment regimen, hiccups began to stop, and his symptoms also disappeared. Hiccups may occur in patients who have pneumonia and other infectious diseases. Dexamethasone can also stimulate hiccups along with infections.

1. Introduction

Hiccups (hiccough or singultus) are involuntary, spasmodic contractions of the diaphragm, intercostal muscles, and early closure of the glottis. During hiccups, 4 to 60 contractions usually occur per minute [1,2]. Acute and persistent hiccups prolong 48 hours and above 48 hours, respectively. Hiccups usually last between 1 and 18 hours to even 1–9 days [3]. The underlying causes of persistent hiccups often result from central nervous system disorders, gastrointestinal diseases, and medication-induced hiccups [4].

Various medications can induce hiccups, such as azithromycin, methotrexate, tramadol, aripiprazole, cisplatin, and dexamethasone [5–10]. Among corticosteroids, hiccups are when dexamethasone is prescribed. A reduction in the threshold of neuronal stimulation is a possible mechanism for the development of dexamethasone-induced hiccups [6]. Hiccups may also be a rare manifestation of other diseases, such as pneumonia, liver abscess, and cancer [11–13].

Although hiccups can be cured by physical therapy and the eradication of underlying causes, a number of medications, such as metoclopramide, baclofen, gabapentin, and chlorpromazine, are empirically used for the treatment of persistent hiccups. Among these medications, oral chlorpromazine (25 mg 4 times a day, up to 50 mg 4 times a day when needed) is reported as a standard treatment [2,14].

As of the emergence of a novel coronavirus (COVID-19) in December 2019 in china, over 100 million individuals have been so far affected [15–17]. Fatigue, fever, and dry cough are the most common symptoms in COVID-19, but under some circumstances, a group of rare symptoms, such as persistent hiccups, might be detected [18,19].

Although comorbidity of Covid-19 with hiccups has been reported so far, there have been no reports of hiccups during the treatment course. Here, we reported a male patient who was afflicted with persistent hiccups during Covid-19 treatment with dexamethasone.

2. Case presentation

A 58-year-old male was admitted to our hospital with pain, myalgia, fever, dry cough. The patient had no chest tightness or shortness of breath. The PCR result for Covid-19 was positive. His vital signs at the time of hospitalization were as follows: blood pressure = 120/80 mm Hg, pulse rate = 100, respiratory rate = 24, Temperature = 36.7 °C, and arterial oxygen saturation = 90%. Chest computed tomography (CT) showed a brief involvement of the lung in the form of ground-glass opacity. The laboratory tests at the time of admission are listed in Table 1. Cell blood count (CBC) was normal except for the platelet count,

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Table 1
The patient's laboratory data on the day of admission.

WBC	3.1 f
RBC	4.43 mill/mm^3
Hb	14.5 g/dl
Hct	41.5%
MCV	93.7 fL
MHC	32 pgm
Platelet	90,000/mm^3
Urea	36 mg/dl
Creatinine	0.9 mg/dl
Serum Na	135 mmol/L
Serum K	3.9 mmol/L
AST	17 U/I
ALT	18 U/I
Alk.p	101 IU/L
Total bilirubin	0.6 mg/dl
Direct bilirubin	0.3 mg/dl
Trononin I	<0.1 ng/ml
CPK	101 U/L
LDH	358 U/ml
Ferritin	433.7 ng/ml

which was low (90,000/mm^3). The vein blood gas (VBG) data are depicted in Table 2. The P.H. of blood was 7.3, which showed acidosis.

The treatment regimen chosen for the patient included remdesivir (200 mg on day 1 and then 100 mg daily for 5 days), dexamethasone (4 mg every 4 hours), famotidine (400 mg daily), zinc, vitamin C, and diphenhydramine syrup. The patient's hiccups started after receiving dexamethasone. The echocardiographic results were normal. Neurological examinations were also performed for the patient and showed no obvious abnormality. The patient's hiccups lasted for 6 days and stopped when dexamethasone was replaced with prednisolone. The patient was discharged from the hospital after his symptoms disappeared.

3. Discussion

The neural pathways of the hiccups reflex consist of afferent and efferent nerves as well as the CNS regions. The afferent composition includes the phrenic nerve, vagus nerve, and a T6-T12 sympathetic chain. A group of neurotransmitters also participate in the hiccups reflex, such as GABA, dopamine, and serotonin, in the CNS, along with epinephrine, norepinephrine, acetylcholine, and histamine in the peripheral nervous system (PNS). The central regions are connected to afferent and efferent nerves and compose C3–C5 spinal cord nerves, which are linked to the respiratory center, hypothalamus, nuclei of the phrenic nerve, and medullary reticular formation [3,20].

The etiology of persistent hiccups is important as hiccups can influence the quality of life of patients.

Some etiological factors have been ascribed to persistent hiccups, such as [2,4]:

- Infections (meningitis, encephalitis)
- Brain injury and tumors, ischemic and hemorrhagic brain insults, and some neurological diseases (Parkinson's disease, epilepsy, multiple sclerosis)
- Toxic or metabolic conditions (diabetes mellitus, alcohol consumption, hyponatremia, hypokalemia, hypocalcemia, hypocapnia)
- Thoracic causes (pericarditis, myocardial ischemia, thoracic aneurysm)
- Pulmonary disease (bronchitis, pneumonia, tuberculosis, asthma)
- Gastrointestinal disease (hiatus hernia, gastro-oesophageal reflux disease, peptic ulceration, abdominal abscess, and tumors)
- Psychosomatic causes (anxiety, stress, fear)
- Surgical procedures (central venous catheter, intubation, anesthesia agents, endoscopy)
- Ear, nose, and throat diseases (herpes zoster, rhinitis, pharyngitis)

Table 2
VBG Analysis of the patient.

PH	7.320
PCO2	40.6 mmHg
PO2	47.4 mmHg
HCO3	20.5 mmol/l
O2 saturation	78.4%

The first-line therapy for the treatment of hiccups is physical therapy, including respiratory maneuvers, holding of breath, putting a cold compress on the face, carotid massage, Valsalva maneuvers, induced vomiting, digital rectal massage [2,21,22].

Pharmacological agents affect dopaminergic and GABAergic receptors and lead to the termination of hiccups. Metoclopramide, baclofen, gabapentin, and chlorpromazine are used as the most common medications for the cure of persistent hiccups. Among these medications, oral chlorpromazine (25 mg 4 times a day, up to 50 mg 4 times a day when needed) has been reported as a standard treatment [2].

To date, several cases have been reported to be concurrently afflicted with pneumonia and persistent hiccups [11,23,24]. According to the literature, inflammation of the phrenic nerve and its pericardial branch may be an etiological factor for the development of hiccups in a pneumonia case [25]. Azithromycin, methotrexate, tramadol, aripiprazole, benzodiazepines, and cisplatin also can be potentially considered causative agents for drug-induced hiccups [5,7,10,26–28].

The induction of hiccups as a result of using dexamethasone has been addressed in some case reports. High-dose dexamethasone (40 mg orally) administration was reported to cause hiccups; rather, this phenomenon can happen at a low dose as well [29,30].

In a case-report study published by Peacock and colleagues, they reported dexamethasone-induced hiccups in a 40-old-man with no medical history of systemic disorders who had taken a single prophylactic dose of 8 mg dexamethasone orally approximately 1 hour before implant surgery. Hiccups were initiated at a 5–7 per minute rate after he received 8 mg dexamethasone but resolved after 42 hours [30].

In another report, five patients who received chemotherapy (with a dosage of 15 mg intravenous dexamethasone on the day of chemotherapy and 8 mg oral dexamethasone once a day for a further three days) developed hiccups few days after the initiation of chemotherapy [31].

However, factors associated with dexamethasone-induced hiccups remained unclear, but reducing the threshold of neuronal stimulation in the CNS is a possible mechanism for the induction of hiccups. It has been demonstrated that the replacement of dexamethasone with methylprednisolone can cure hiccups in patients with cancer. After taking methylprednisolone, the disappearance of hiccups may stem from less permeability of methylprednisolone into the blood-brain barrier (BBB) [6].

In a Japanese study, a 74-years old man with gastric cancer developed hiccups after 10 days from chemotherapy and 2 days from taking dexamethasone (8 mg daily- Day 8 intravenously and on Days 9–11 orally). Hiccups resolved after 1 day of taking dexamethasone in that patient, which was less than our case in terms of dosage. The replacement of dexamethasone with prednisolone (30 mg/d) could resolve hiccups [32].

Overall, different studies confirm the effectiveness of prednisolone replacement with dexamethasone in the treatment course of various diseases [6,32].

Hiccups may be one of the rare presentations of COVID-19. Prince and colleagues reported a 62-year-old man with four-day persistent hiccups and unremarkable physical examinations who had peripheral ground-glass opacities in his lungs according to the C.T. scan results. His hiccups resolved after treatment with hydroxychloroquine [33].

In a similar report, a 48-year-old man with seven-day persistent

hiccups, fever, and sore throat was reported. The results of the C.T. scan of his lung exhibited bilateral peripheral areas of ground-glass opacities as well as the positive covid-19 test. Treatment was initiated with hydroxychloroquine, oseltamivir, baclofen, and his hiccups were terminated [18].

In another report, a 65-year-old man with diabetes mellitus and hypertension developed seven-day hiccups. His PCR test for COVID-19 was positive, and C.T. scan findings showed a peripheral ground-glass view. His hiccups resolved after few days [34].

Although most patients who develop hiccups after COVID-19 or following the treatment course can recover spontaneously over time, resistant cases have also been reported. In two cases afflicted with COVID-19, one had hiccups at the initial time of clinical manifestations, while the other patient had hiccups after 10 days from the COVID-19 diagnosis. The latter patient responded only to chlorpromazine [35]. Chlorpromazine was also used in another study for persistent COVID-19 in a 56-year-old man. In another study, three-day hiccups were resolved in a 61-year-old man with hypertension and low O_2 saturation in response to metoclopramide [36].

As mentioned earlier, there are several reasons for persistent hiccups. Unlike studies mentioned above, which had no definite cause for the development of hiccups other than Covid-19 and dexamethasone, in some cases, other conditions may lead to hiccups in Covid-19 patients. For instance, hyponatremia is known to be a potential cause for the development of hiccups. Since hyponatremia is frequently reported in COVID-19 patients, this medical condition might also be responsible for the development of hiccups in these patients [37].

Persistent hiccups have multiple causes. In a patient who suddenly develops hiccups during any treatments, other significant causes should be considered first. Our patient was evaluated in terms of neurological, gastrointestinal, infections, and medications. The duration of hiccups in this patient was longer than those reported in other studies. Covid-19 disease alone can cause hiccups, and dexamethasone also increases the risk of this comorbidity. Therefore, these two conditions can synergistically increase the risk of hiccups. Hiccups are usually resolved spontaneously in Covid-19 patients, but in dexamethasone-treated patients, the replacement of prednisolone with other anti-inflammatory agents would be effective. In the case of the persistence of hiccups, chlorpromazine could be a choice.

4. Conclusion

Hiccups may occur in patients who are affected by pneumonia and other infectious diseases. Dexamethasone can also stimulate hiccups along with infections. Empirically, the use of prednisolone instead of dexamethasone might be helpful to resolve hiccups. Also, chlorpromazine is capable of resolving hiccups in patients with persistent conditions. Notably, neurological, cardiac, and gastrointestinal examinations must be initially performed on patients with persistent hiccups to rule out other causes of hiccups.

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Ethical approval

Informed consent was obtained from the patient, and it is available upon request.

Author contribution

S.K. drafted the manuscript, F.A. conducted the medical examinations and collected the required data, and A.L. designed the study and drafted the manuscript. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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