



Case report

Hiccups as a specific neurological manifestation in males with COVID-19



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ABSTRACT

Several clinical manifestations of COVID-19 have been reported in the literature since then. In addition to upper respiratory symptoms, dysgeusia and anosmia are relatively common neurological manifestations with COVID-19. We had five cases of hiccups in succession; therefore, we assume that hiccups might be a specific symptom of COVID-19. We retrospectively analyzed 46 patients with COVID-19 diagnosed from February 2021 to May 2021. Among the 46 patients, 5 developed hiccups (11%). All patients were male. The median age of was 56 years. None of the patients were smokers. Further, all patients exhibited pneumonia without dysgeusia or anosmia. The median onset of hiccups was 5 days after diagnosis, with a median duration of 2 days. All patients recovered from hiccups and COVID-19. Hiccups might be a specific neurological symptom in male patients with COVID-19.

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Introduction

Currently, it has been more than a year since the start of the COVID-19 pandemic. Several clinical manifestations of COVID-19 have been reported in the literature since then. In addition to upper respiratory symptoms, dysgeusia and anosmia are relatively common neurological manifestations with COVID-19 [1].

We formed the COVID-19 treatment team in February 2021. We have mainly treated patients with mild and moderate disease without any pulmonary dysfunction. We noticed that there were quite a few patients who developed hiccups. To date, 10 short cases have been reported on this topic [2–11]. We witnessed five cases in succession; therefore, we assume that hiccups might be a specific symptom of COVID-19. We investigated the characteristics and outcomes of the patients and reviewed the literature.

Methods

There were 46 patients admitted to our hospital from February 2021 to May 2021. We retrospectively analyzed the prevalence of hiccups, concomitant symptoms and outcomes. This study was

conducted as per the ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Biwako Ohashi Hospital. Written informed consent was obtained from the patients for the publication of this report.

Results

Five out of the 46 patients had hiccups (11%). Patient characteristics are summarized in Table 1. All patients were male, and their median age was 56 years (range: 34–87 years). None of the patients were smokers. All the patients had pneumonia and three of them had cough. However, none of the patients had dysgeusia or anosmia. Three of the patients were treated with remdesivir and two with favipiravir. The median onset of hiccups was 5 days after diagnosis, and the median duration of the hiccups was 2 days. Two of the five patients were treated with chlorpromazine, two of the five were treated with clonazepam and timepidium bromide, respectively. One patient was not treated with any hiccup specific medication. All the patients recovered from hiccups and COVID-19.

Discussion

Hiccups are defined as an involuntary, spasmodic contraction of the diaphragm and intercostal muscles [11]. This contraction causes an active closure of the glottis and results in a characteristic sound

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Table 1
Patients' characteristics.

Patient	Age (years)	Sex	Smoking habit	Treatment for COVID-19	Pneumonia	Loss of taste	Loss of smell	Cough	Day of hiccup onset (from Dx)	Duration of hiccups (days)	Treatment for hiccup	Outcome of COVID-19
1	65	M	-	Favipiravir	+	-	-	+	Day 5	3	Clonazepam	Recovery
2	34	M	-	Remdesivir	+	-	-	+	Day 5	1	-	Recovery
3	56	M	-	Remdesivir	+	-	-	-	Day 9	2	Chlorpromazine	Recovery
4	87	M	-	Favipiravir	+	-	-	-	Day 4	3	Chlorpromazine	Recovery
5	45	M	-	Remdesivir	+	-	-	+	Day 10	2	Timepidium bromide	Recovery

M: male

[12]. Intractable hiccups lasting for < 48 h are called acute hiccups, whereas those lasting for > 48 h are called persistent hiccups. Whereas hiccups of short duration are often benign in etiology, Prolonged hiccups may be attributed to a severe underlying pathology [13].

Although the precise mechanism of hiccups is not completely understood, hiccups result from the stimulation of the central or peripheral components of the hiccup reflex arc.

Regarding the central nervous system, Giancarlo et al. reported that SARS-CoV-2 shows selective neurotropism to areas of the brain controlling respiration [14]. Such a mechanism may also contribute to hiccups. Irritation of this neural network can be a possible mechanism for the development of hiccups.

With respect to the phrenic nerve, it has been reported that pneumonia has an influence on hiccups. Inflammatory pneumonia induced irritation of the phrenic nerve and its pericardial branch may stimulate the diaphragm and lead to the development of hiccups [15]. All of our patients and those in the literature were afflicted with pneumonia (Table 2). Therefore, we assume that there is a causal relationship between pneumonia and hiccups.

Ten cases of hiccups with COVID-19 have been reported to date (Table 2). All patients were male and were afflicted with pneumonia, which is consistent with our patients. All the patients exhibited hiccups for > 3 days. All patients recovered from COVID-19, although one patient was lost to follow up.

Hiccups were reported as adverse event with favipiravir (< 0.1%) [16]. There is no report of remdesivir as causing hiccups. Some reports suggested that relation between steroids and hiccups [17]. However, we don't think that the treatments would induce hiccups because four in the reported cases were without treatment and others were used various treatments (Table 2). Therefore, it is difficult to prove the involvement of specific treatment.

Table 2
Review of the literature.

Reference	Age (years)	Sex	Smoking habit	Treatment for Covid-19	Pneumonia	Loss of taste	Loss of smell	Cough	Duration of hiccup	Treatment for hiccup	Outcome of COVID-19
2	62	M	-	Hydroxychloroquine	+	-	-	-	>4 days	-	Recovery
3	48	M	NA	-	+	-	-	-	>4 days	Metoclopramide	Lost to follow-up
4	34	M	-	Hydroxychloroquine/ Oseltamivir	+	-	-	-	>7 days	Baclofen	Recovery
5	60	M	-	Favipiravir	+	-	-	-	>3 days	Chlorpromazine	Recovery
5	68	M	-	Favipiravir/ Hydroxychloroquine	+	-	-	-	>3 days	Metoclopramide/ Chlorpromazine	Recovery
6	62	M	NA	-	+	+	-	+	>3 days	Metoclopramide/ Lidocaine/ Clonazepam/ Haloperidol	Recovery
7	61	M	+	Dexamethasone	+	-	-	-	>3 days	Metoclopramide	Recovery
8	72	M	NA	Oseltamivir/Favipiravir	+	-	-	-	>5 days	Baclofen	Recovery
9	65	M	-	-	+	-	-	-	>7 days	Baclofen	
10	64	M	-	-	+	-	-	-	>3 days	-	Recovery

M: male

NA: not available

The most interesting finding of our study is that all the patients were male. In the literature, all reported cases are of males. It is unlikely that this is a mere coincidence. We believe that hiccups might be a specific symptom of COVID-19 in males. Lee et al. reported that hiccups were seen more frequently in males. They assumed that male susceptibility to developing hiccups could potentially be attributed to lower synaptic threshold and easier excitability of afferent or efferent nerves in the hiccup reflex arc among males [18]. This may contribute to the predominance of hiccups in males. Regardless of COVID-19, hiccups are more common in males.

The median day when the patients developed hiccups was 5 days from COVID-19 diagnosis. This indicates that hiccups are not an early symptom. It may occur after the disease condition has progressed to a certain extent. Three patients developed cough that disappeared before the hiccups developed. Other typical neurological symptoms such as dysgeusia and anosmia did not coexist. In the literature, only one patient showed the coexistence of dysgeusia. We assume that these symptoms rarely overlap with hiccups or are simply less common in variant types. The reason for this finding remains unclear.

Fortunately, all patients recovered from COVID-19. In the literature, all but one patient who was lost to follow-up showed good outcomes. Therefore, hiccups might not have a correlation with poor prognosis.

Our study has several limitations. First, this study was conducted in one facility with a small number of patients. Second, we only treated patients with mild and moderate disease; therefore, we do not know whether the findings are applicable to patients with severe disease. Third, we administered anti-hiccup medications immediately after the hiccups developed; therefore, we do not know the natural course of the hiccups. Despite these limitations, we

believe that our findings are worth reporting to demonstrate the practical manifestations of COVID-19.

Our findings showed the characteristics of patients with hiccups: all males, afflicted with Mild or Moderate COVID-19 pneumonia, non-smokers, and with a lack of other symptoms.

Further investigation and accumulation of cases to determine the clinical significance of hiccups in COVID-19 are warranted.

Author statement

Study design: A.N., E.O., data collections: Y.K., M.Y., E.Y., K.H., S.T., Y.T., Y.M., M.H., M.Y., Y.K., Y.A., K.Y., S.S., K.O., K.I., data analysis: A.N., writing: A.N., E.O.

Ethical approval

This study was conducted as per the ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Biwako Ohashi Hospital.

Consent

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

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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