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What is the frequency of singultus as unique symptom in patients with Covid-19?

Dear editor: In the first days of 2020, a new coronavirus identified as SARS-CoV-2 was declared to cause atypical pneumonia in some Latin American countries. Common symptoms are highlighted in this disease such as: cough, dyspnea, fever, odynophagia, and it can manifest as a common cold or develop severe pneumonia with potentially fatal acute respiratory distress syndrome, multiple organ failure, septic shock, and venous thromboembolism, among others. Additionally, atypical symptoms have been identified in the elderly and immunocompromised patients, such as delirium / confusion, decreased function, reduced mobility, syncope, persistent hiccups, and absence of fever.

Singultus is usually a self-limited disorder caused by the sudden onset of erratic diaphragmatic and intercostal muscles contraction and immediately followed by laryngeal closure. However, when it is prolonged beyond 48 hours, it is considered persistent whereas episodes longer than two months are called intractable. A reflex arc involving peripheral phrenic, vagal, and sympathetic pathways and central midbrain modulation is likely responsible for hiccup. SARS-CoV-2 has a neurogenic tropism recognized, the main mechanism known states that after binding to the receptors of the angiotensin converting enzyme II (ACE2) in the nasal epithelium, it invades the olfactory nerve and the bulb, progressing, to later invade the respiratory centers of the brainstem. To date, we have found in the literature six cases of persistent singultus in men positive to SARS-CoV-2 infection of different ethnic origin in the range of 48-62 years (table I),[1-6] three of them Mexican with comorbidity.

It is important to know better the atypical clinical manifestations of Covid-19 to understand its pathophysiology, so it is necessary to carry out retrospective and prospective studies focused in this symptom to be able to answer the question: What is the frequency of singultus as unique symptom in patients with Covid-19?; With the previous information, the following can be mentioned: 1) A greater number of evidence on atypical neurological data is required; 2) The information published on singultus as the only manifestation is scarce, but it is grouped in an age range of male patients of different ethnic origin with comorbidity where Mexicans are majority. An early identification of this isolated symptom associated with Covid-19 could help to avoid dissemination of the emergent virus.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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Table 1

DESCRIPTIVE AND CLINICAL DATA OF SIX PATIENTS REPORTED IN THE LITERATURE WITH SINGULTUS AS THE PREDOMINANT SYMPTOM IN COVID-19 INFECTION

Characteristics	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*
Age	60 years	48 years	54 years	62 years	48 years	52 years
Sex	Male	Male	Male	Male	Male	Male
Country	Mexico	Mexico	Mexico	USA	Egypt	Iran
Pathological personal history	Obesity, sedentary lifestyle, dyslipidemia	Orthopedic surgery at L5 vertebral level	Obesity, hypertension, type 2 Diabetes	Type 2 diabetes, hypertension, coronary artery disease, weight loss in the previous four months	Hypertension	Congenital factor V deficiency, type 2 diabetes
Covid-19 Test Result	Positive	Positive	Positive	Positive	Positive	Positive
Main symptoms	Persistent singultus	Persistent singultus	Persistent singultus	Persistent singultus	Persistent singultus	Persistent singultus
Symptoms associated	Dysgeusia,fever, rhinorrhea, dry cough, asthenia, adynamic state	Increased heart rate, increase in blood pressure, normal temperature	Asthenia, adynamic state, cough with spectoration, dyspnea, hypertension	Fever 38.4 C, tachycardia and increase in blood pressure	Fever 39.3 C, sore throat, increase in blood pressure, and breathing rate	Episodes of epistaxis and increase in blood pressure
Oxygen saturation	87%	93%	90%	97%	98%	Not reported
Laboratory testing results	Dimero D 1.16 pg/mL, cholesterol, 156 U/L, high-density cholesterol, 27.1 mg/dL, sodium, 132 mmol/L, calcium, 7.9 mmol/L	Glucose 182 mg/dl, platelets 81 000/mcl, leukocytes 4 000/mcl, lymphocytes 700/mcl absolute count	Hemoglobin 12.10 g/dL; C-reactive protein 64.9 mg/dL, albumin 3.2 g/dL; erythrocyte sedimentation rate 34 mm/h; procalcitonin 0.059 ng/mL; fibrinogen 593 mg/dL; brain natriuretic peptide 1296 pg/mL	Platelets, 15 000/mcl, leukocytes, 4 200mcl, sodium 131 mmol/L, chloride 98 mmol/L	C-reactive protein 51 mg/L, ferritin 2 600 ng/mL lactate dehydrogenase 856 U/L	Erythrocytes 5.62 x10^9/L, glucose 138 mg/dL, aspartate aminotransferase 51 U/L, alanine aminotransferase 73 U/L, alkaline phosphatase 318 U/L
Image studies	Chest X-ray with decreased radiolucency and probable parabronchial thickening	Chest CT shows multiple areas of diffuse alveolar damage in both lungs	Chest CT with bilateral patchy consolidation in lower zones on chest and report of ground glass areas	Chest CT with report of regional, peripheral ground-glass opacities in both lungs	Chest CT shows subpleural areas in ground glass and "crazy-paving" pattern	Chest CT with report of ground glass areas
Treatment received in diverse phases	Ilaprazol; Metoclopramide; Aluminum-Magnesium-hydroxide; Lidocaine; Haloperidol; Clonazepam; Dexamethasone; Paracetamol	Metoclopramide; Omeprazole; Ondansetron; Oral frappe magaldrate/simethicone	Analgesics, antipyretics and oxygen with not specification	Ceftriaxone; Azithromycin; Hydroxychloroquine	Proton-pump inhibitor; Domperidone; Baclofen; Ceftriaxone; Azithromycin; Hydroxychloroquine; Oseltamivir; Anticoagulant, and antipyretics not specified	Metoclopramide; Chlorpromazine
Place of the study and date of journal submission	State of Mexico, Mexico June 3rd, 2020	Mexico City, Mexico, July 27th, 2020	Nuevo León, Mexico, June 8th, 2020	Illinois, USA, April 8th, 2020	Cairo, Egypt, July 22nd, 2020	Tehran, Iran, August 18th, 2020

Statistics by country (Mexico, USA, Egypt and Iran) as of now March 2, 2021; Total population (millions): 127.5, 322.2, 95.7, 80.3; Total reported cases (millions): 2.09, 29.4, 0.183, 1.65; Cases in last seven days: 37 015, 401 689, 3 603, 49 074; Total Deaths: 186 152, 529 045, 10 778, 60 267.