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What is essential is invisible to the eye

Abstract

In children, COVID-19 is characterized by generally less severe symptoms and a lower case fatality than in adults. 'Silent hypoxia' is characterized by significant hypoxia without important signs of respiratory distress and has been described in adults but not in pediatric patients. We report the case of an obese 17-year-old female evaluated for mild symptoms, without hypoxia or signs of respiratory distress, and diagnosed with SARS-CoV-2 pneumonia. After admission, she developed anosmia and worsening hypoxia without proportional signs of respiratory distress. After clinical deterioration, she started CPAP and completed 5 days of remdesivir, 8 days of dexamethasone and a course of antibiotics, with clinical improvement and discharge from hospital on day 9. This case demonstrates that acute severe infection with SARS-CoV-2 occurs in pediatric age, and that certain risk factors may play an important role. We also highlight 'silent hypoxia' as a possible presentation of COVID-19 in children, which displays the importance of careful clinical examination and surveillance.

Keywords: COVID-19; SARS-CoV-2; Silent hypoxia; Pneumonia.

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Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is spreading rapidly and internationally since its first outbreak in December 2019, in Wuhan, China. COVID-19 has been considered a public health emergency of international concern by World Health Organization since January 30, 2020 and a pandemic disease since March of the same year. It is characterized by fever, cough, dyspnea, and progression to Acute Respiratory Distress Syndrome (ARDS). Some adults with COVID-19 may also have significantly reduced pulse oximetry readings without significant signs of respiratory distress, an entity that has been described as 'silent' hypoxia [1]. Although symptoms are similar in children and adults, their frequency and disease severity varies. It has been described consistently in literature less severe disease and lower case fatality in children than in adults, although severe cases have also been reported [2]. Risk factors for severe disease include prematurity, obesity, immunodeficiency's, chronic lung disease, renal and cardiovascular disease, hematologic or metabolic conditions and age <1 year [3-6]. No cases of 'silent' hypoxia have been described in pediatric age. We describe the first case in pediatric age, in an obese adolescent with few initial symptoms, with progression to severe hypoxemia and severe disease requiring mechanical ventilation.

Case presentation

We describe the case of a 17-year-old girl, with obesity (Body Mass Index 30 kg/m^2, >95th percentile), without any other comorbidities or previous diseases, observed in the emergency department with a history of fever, dry cough, rhinorrhea and chest pain. She reported contact with a COVID-19 patient 4 weeks earlier and had fulfilled prophylactic isolation for 10 days. Her parents had mild symptoms and were positive for SARS-CoV-2. Blood pressure on admission was 111/63 mmHg, heart rate 123 beats/minute, she had a body temperature of 37.3°C and oxygen saturation (SpO_2) 97% on room air. Pulmonary auscultation was normal and she had no signs of respiratory distress. Chest radiograph showed a well-defined hypo

transparency of the left inferior lobe and a mild infiltrate on the right inferior lobe but with no pleural effusion on thoracic ultrasonography. Laboratory evaluation displayed leukopenia (3400/mcL), with a normal neutrophile count (1999/mcL), mild lymphopenia (1081/mcL), thrombocytopenia (121.000/mcL) and elevated C-reactive protein (94.3 mg/L). Real-time RT-PCR testing was positive for SARS-CoV-2. Due to a suspected SARS-CoV-2 pneumonia with bacterial superinfection, a blood culture was performed and treatment with antibiotics was initiated. She was then admitted to the Pediatric Department for clinical surveillance. On the first day she developed anosmia but fever improved. However, on day 2 she developed progressive worsening hypoxia (minimum SpO_2 82%), tachypnea (respiratory rate 60 cpm) with shallow breathing and a mild sensation of dyspnea, without proportional signs of respiratory distress. Arterial blood gas revealed pH 7.45, PaO_2 66 mmHg, $PaCO_2$ 41 mmHg and PF 235 (FiO_2 0,28). CT-scan findings included bilateral ground-glass opacification associated with multifocal and confluent parenchymal densification (left superior and inferior lobes) and air bronchogram, compatible with superinfection (Figure 1). Ferritin was increased (462 ng/mL), as well as procalcitonin (0.09 ng/mL), C-reactive protein (94.1 mg/L), fibrinogen (597 mg/dL) and D-dimer levels (961 ng/mL). CK-MB and troponin levels were normal. In the following days, supplemental oxygen requirements increased, associated with dyspnea and orthopnea, which prompted treatment with dexamethasone (6 mg/day), enoxaparin (40 mg/day) and remdesivir (loading dose of 200 mg) and transfer to a Pediatric Intensive Care Unit. On admission blood pressure was 110/54 mmHg, heart rate 110 beats/minute, SpO_2 82% (FiO_2 0.35), SpO_2/FiO_2 ratio (S/F) 234 and respiratory rate 70 cpm, with a shallow breathing pattern. She had then developed signs of respiratory effort with bibasilar crackles on auscultation and pH was 7.49, PaO_2 191 mmHg, $PaCO_2$ 34.6 mmHg, PF 191. These clinical findings were compatible with ARDS associated with severe hypoxia and a low S/F, which prompted the beginning of non-invasive ventilation with Continuous Positive Airway Pressure (CPAP), with a specific ventilator for non-invasive ventilation, initial PEEP 12 and initial FiO_2 1. There was a good response, with improvement of signs of respiratory effort and of the oxygenation index (decrease to 10 on the first two hours), and decrease of ventilatory settings after 24h. Ventilatory support was suspended after three days and oxygen supplementation two days after that. She completed 5 days of remdesivir (200 mg on day 1, followed by 100 mg/day), 8 days of dexamethasone and a course of antibiotics. She remained hemodynamically stable, with no inotropic support, with a normal neurological exam and without fever since day 1. She also maintained a normal renal and hepatic function. She was discharged from the Pediatric Intensive Care Unit after 6 days and from hospital after three days, maintaining a regular follow-up.

Discussion

In children, most reported cases of COVID 19 appear to be asymptomatic or mild, with lower incidence, lower hospitalization rate and better prognosis as compared to adults [7,8]. Despite the trend of increasing hospitalization, children with COVID-19 who require hospitalization are still a minority [4,9]. The symptoms of COVID-19 are similar in children and adults but the frequency varies [9]. According to a systematic review and meta-analysis that analyzed 47 studies reporting the symptoms of COVID-19 in children [10], which were defined as asymptomatic infection, mild, moderate, severe, or critical on the basis of the clinical features, laboratory testing, and radiographic chest imaging, they were mild in 43%, moderate in 52%, severe in 6% and only 4% were critical cases. The most common symptoms reported were fever, cough and nasal symptoms [10]. Our case presented with fever, cough and rhinorrhea, which is compatible with these studies. On initial presentation on the emergency department, despite having a normal oxygen saturation on room air, no signs of respiratory distress and no findings on pulmonary auscultation, the chest radiograph had findings that were compatible with the epidemiological context and the results of the RT-PCR testing. Laboratory results demonstrated a mild lymphopenia, one of the most frequent findings in children with COVID-19 [10]. Inflammatory markers are commonly elevated in COVID-19, as described in our case, which had and elevated C-reactive protein, procalcitonin, ferritin and D-dimer. Some studies have associated it with severe disease in children [11,12]. Despite frequent similar symptoms at presentation, COVID-19 may present with a wide spectrum of symptoms. In adults, an entity termed 'silent' hypoxia has been described, characterized by reduced pulse oximetry readings without proportional signs of respiratory distress [1,13]. No cases of 'silent' hypoxia have been described in pediatric age. The mechanism behind this entity is not entirely understood, but some studies suggest a possible relationship with a blunted response of the respiratory regulatory system to hypoxia. SARS-CoV-2 infection leads to lung edema, with loss of surfactant and superimposed pressure, which in turn leads to alveolar collapse. This results in perfusion of non-aerated lung tissue, intrapulmonary shunting (ventilation/perfusion mismatch) and hypoxemia. The physiologic response to hypoxemia is the hypoxic pulmonary vasoconstriction mechanism, which causes constriction of small intrapulmonary arteries in response to alveolar hypoxia. However, the relative failure of this mechanism has been reported during SARS-CoV-2 infection, which then leads to persistence of high pulmonary blood flow to nonaerated lung alveoli and persistent hypoxia [14,15]. Another important pathway in the pathophysiology of COVID-19 is the renin-angiotensin system. In SARS-CoV-2 infection, the Angiotensin Converting Enzyme 2 (ACE2) serves as the functional receptor for the SARS-CoV-2 to enter the cell. The formation of the ACE2/virus complex results in functional loss of ACE2 activity and leads to a dysregulation in the renin-angiotensin system [16,17]. ACE2 has been found to be highly expressed in multiple tissues, including respiratory epithelial cells, myocardial cells and the proximal tubule cells of the kidney and the gut epithelium [18]. Some studies also state its expression in nasal mucosa and in the carotid body [19], although this fact is controversial [20]. The carotid body is the main peripheral chemoreceptor that senses the arterial PO_2, PCO_2 and ph. The presence of hypoxia is sensed by the carotid body and triggers a reflex that stimulates pulmonary and vascular responses to increase oxygen update and delivery. Direct viral entry into respiratory control centers has been proposed as a potential mechanism underlying respiratory failure in some COVID-19 patients [21]. Infection of the carotid body may impair hypoxic chemo reflexes, as proposed in another study [20]. Additionally, early reports suggest Central Nervous System infection by SARS-CoV-2, although the precise structures infected remain uncertain [22]. Thus, SARS-CoV-2 infection may target regions that are part of the peripheral and/or central nervous system and that control critical mechanisms such as breathing and respiratory sensation, which may explain the "silent" hypoxia. Most importantly, a rapid respiratory rate may be the sole clinical presentation in these patients. In our case, despite absence of information regarding respiratory rate at admission and a normal oxygen saturation, her heart rate was already el-

evated. The following day, the tachypnea became evident, associated with low oxygen saturation and low PaO_2 on blood gas, and only a mild dyspnea. No other signs of respiratory distress were present and she was comfortable, despite the rapid clinical deterioration. This sudden and rapid deterioration in cases of 'silent' hypoxia is also described in literature. Additionally, fever, cough and rhinorrhea are symptoms frequently reported in the context of infection with influenza or other viruses in children. Despites the real epidemiological burden this fact may represent, since they are less likely to be tested, it also may put children at higher risk, due to underestimation of the severity of the disease. Another interesting fact is the presence of obesity as a risk factor. Multiple studies of hospitalized children with COVID-19 describe obesity as the most prevalent underlying medical condition [4,11,12] and it has been described as an independent factor associated with increased risk of ARDS development, which highlights the importance of understanding the underlying pathophysiologic association between obesity and SARS-CoV-2 infection. CT-scan findings at this stage were compatible with most frequent findings described in children with COVID-19. On the following days, clinical deterioration prompted treatment with remdesivir, which is an antiviral that binds to viral RNA, blocking replication and it is recommended in children with more than 12 years old with confirmed SARS-CoV-2 infection, moderate to severe disease with hypoxemia, chest x-ray alterations and/or hemodynamic failure [23,24]. ARDS is characterized by hypoxemic respiratory failure with bilateral lung infiltrates often necessitating invasive respiratory support (after exclusion of cardiac pathology). In adults with COVID-19, this clinical manifestation is frequent and widely described. However, it is less frequent in pediatric patients. Additionally, phenotypic heterogeneity in patients with COVID-19-associated ARDS has been reported. In this context, 3 phenotypes have been described: "L phenotype", associated with low lung elastance, high compliance, lower lung weight and low response to PEEP; pulmonary compliance is preserved and there is an adequate alveolar recruitment; "H phenotype", characterized by high lung elastance, low compliance, higher lung weight and high PEEP response; pulmonary compliance is decreased and alveolar recruitment is required; "H/L phenotype", an intermediate pattern between the two previously described [3,25]. In our case, the clinical presentation was compatible with the H phenotype, associated with further decrease in ventilation/perfusion and worsening intrapulmonary shunt. Thus, a good response to high PEEP and alveolar recruitment was expected. Despite the severe presentation of our case, she significantly improved after beginning CPAP with a high PEEP, which is compatible with the previously described. Non-invasive ventilation was suspended after 3 days and she was discharged after a total of 9 days. Children appear to have a better prognosis than adults, and although there are some theories that may explain why, the reason is still unknown.

What this report shows

Acute SARS-CoV-2 infection associated with severe disease is a possibility in pediatric patients.

Certain risk factors may play an important role, namely obesity.

'Silent hypoxia' is a possible presentation of COVID-19 in children.

Progression to severe disease can be fast.

Careful clinical examination and surveillance are crucial, in order to permit early identification of this subset of pediatric patients.

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