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LETTER

Down syndrome and COVID-19, a combination with a poor prognosis

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Dear Editor,

Factors such as obesity, cardiovascular disease and co-infections increase the risk of death in patients with COVID-19.[1] Down syndrome (DS) or trisomy 21 is the most common chromosomal abnormality in humans, with an estimated incidence from 1 in 1,000 to 1 in 100 live births worldwide and 1 in 700 births in Brazil.[2,3] In addition, DS is frequently characterised by anatomical differences in the upper respiratory tract, immune dysregulation, cardiovascular disease and obesity, which may favour co-infections, increasing the risk of death from COVID-19.[4,5]

Here, we report on three cases of COVID-19 in patients with DS admitted from May 2020 to November 2020 to the intensive care unit (ICU) of the Eduardo de Menezes Hospital, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil. COVID-19 was diagnosed using reverse transcriptase PCR assay from a nasopharyngeal swab. Data on the patients' progression were collected from medical records. Samples were also collected for microbiological analysis when there were purulent secretions, radiographic alterations or changes in results from laboratory tests, which may suggest co-infection. Secondary microorganisms were identified using biochemical tests, according to the hospital guidelines. This study was approved by the National Ethics Committee (Comissão Nacional de ÉticaemPesquisa, Brasília, DF, Brazil) and by the Hospital Ethics Committee (Eduardo de Menezes Hospital, Belo Horizonte, MG, Brazil; CAAE: 30627320.6.0000.0008) and the informed consent term was applied.

The mean age of patients was 36.3 years, and the mean hospitalisation time was 13 days. All patients had co-infections and died. The Table gives the general characteristics of the patients included in this case series. The first case refers to a female patient, 47 years old, independent for daily activities, without known diseases or complications resulting from DS. She was admitted presenting odynophagia, fever, cough, dyspnoea, and respiratory distress. Laboratory tests revealed lymphopenia (7%) and a high C-reactive protein level (187 mg/L). Bilateral interstitial infiltrate with consolidation across the chest was seen on X-ray. Admitted to the ICU, she underwent orotracheal intubation. *Acinetobacter baumannii* was isolated from the tracheal aspirate. Clarithromycin, ceftriaxone and dexamethasone were started. The patient's condition worsened with a persistent fever (37.9°C–39.7°C), increased urea levels and hypernatremia. Polymyxin B, vancomycin, meropenem and levofloxacin were

administered. Despite this, she developed an extremely severe condition, and fluconazole was empirically administered. However, the patient died the next day.

A second female patient was 33 years old, obese and had hypothyroidism. She presented low oxygen (O_2) saturation, dyspnoea, respiratory distress, fever, cough, diarrhea and odynophagia. She underwent intubation and was admitted to the ICU 4 days later afebrile, dysglycaemic, and with normal O_2 saturation (96%). Ceftriaxone, azithromycin and oseltamivir were administered. Three days later, bleeding was noticed in the oral cavity (tongue bite with small lesions on the upper and lower surfaces). She presented sub-febrile peaks (up to 38.0°C), and *Staphylococcus aureus* and *Acinetobacter* spp. were isolated from tracheal aspirate. The patient developed a severe condition, with persistent fever (38.3°C–39.7°C) and mouth bleeding. Vancomycin, polymyxin B, meropenem and hydrocortisone were administered. She remained hemodynamically unstable with persistent high fever (39.5°C–40.4°C), hyperkalaemia and metabolic acidosis. Vasopressors (noradrenaline at 160 mL/h and vasopressin at 24 mL/h) were administered. However, she developed refractory shock, was anuric and hyperkalaemic, and showed signs of multiple organ dysfunction and therapeutic failure, which led to her death.

The third patient was male, 29 years old, asthmatic, and with rhinitis, and a history of cardiac surgery at 4 months of age. When admitted to the ICU with low O_2 saturation, he underwent mechanical ventilation by tracheostomy. On further examination, he was hydrated, afebrile, flushed, with photoreactive pupils and good oxygen saturation (95%). X-rays showed a congested pattern, and he received ceftriaxone, azithromycin and dexamethasone. Two days later, he was hemodynamically unstable and developed acute kidney injury secondary to sepsis with probable pulmonary focus. The ultrasound (FAST - Focused Assessment with Sonography for Trauma) showed pattern B in the right pulmonary apex, consolidation in the right pulmonary base, absence of pleural effusion and ascites, presence of pericardial effusion, without signs of cardiac tamponade. *S.aureus* was isolated from blood and *Candida albicans* from urine. However, the patient's condition worsened and he died before the results were available.

Together, this series of patients with DS had unfavourable outcomes resulting from severe COVID-19. To date, COVID-19 has killed almost 5 million people worldwide.[6] DS is frequently associated with immune defects, abnormalities in the airways, heart problems, obesity and diabetes.[4,5] Furthermore, overexpression of the

TMPRSS2 gene, located on chromosome 21, may contribute to the severity of COVID-19 in patients with DS.[7] Conjointly, these factors may contribute to unfavourable outcomes of infections. DS is associated with the increased need for oxygenation, mechanical ventilation, corticosteroids, systemic antibiotics, ICU admission, and is more likely to result in mortality in patients with respiratory infections such as respiratory syncytial virus infection[8] and COVID-19.[7,9] In addition, all reported patients used corticosteroids and broad-spectrum antibacterials, underwent invasive mechanical ventilation, and developed secondary infections, all factors related to increased risk of death.[10–12]

Although our sample size is small, it represents the total number of patients with DS admitted to the hospital's ICU during the study period. The unfavourable outcome in all reported cases contrasts with the overall fatality rate in our ICU, which is around 50%,[12] suggesting that patients with DS and severe COVID-19 might indeed have a worse prognosis. A study in the United Kingdom, which included 8.26 million adults with COVID-19 (4,053 with DS), concluded that patients with DS have a four-fold increased risk of hospitalisation and a 10-fold increased risk of mortality (39.7% among patients with DS and 20.3% among non-DS patients).[13] Furthermore, DS patients are at greater risk of developing severe COVID-19 at a younger age, even considering their reduced life expectancy.[14] For example, in our case series, patients were on average 36.3 years old and spent around 13 days in the ICU, whereas in the study by Hüls and colleagues,[15] the mean age was 29 years and the length of stay in the ICU was around 8.46 days. To note, the ICU admission rate of patients with DS in that study was 50%.

As this was a retrospective study, the data presented were limited to those available in the medical records. Even so, this information corroborates other studies that highlight a significant vulnerability of patients with DS to severe COVID-19.[7,9,13–15] This should be a matter of great concern for health authorities, who have the role of improving prevention measures, monitoring, and treating COVID-19.

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Conflicts of interest: none declared.

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Table General characteristics, signs/symptoms on admission, comorbidities, risk factors, laboratory parameters[†] and clinical evolution of the patients included in this case series.

Characteristic	Patient 1	Patient 2	Patient 3
General characteristics			
Sex	Female	Female	Male
Age, years	47	33	29
Signs and symptoms*			
O_2 saturation <95%	Yes	Yes	Yes
Dyspnoea	Yes	Yes	No
Respiratory discomfort	Yes	Yes	No
Fever	Yes	Yes	No
Cough	Yes	Yes	No
Diarrhoea	Yes	Yes	No
Odynophagia	Yes	Yes	No
Comorbidity/risk factor			
Cardiovascular disease	No	No	Yes
Diabetes	No	No	No
Obesity	No	Yes	No
Asthma	No	No	Yes
Hypothyroidism	No	Yes	No
Laboratory data[†]			
Haemoglobin concentration, g/dL	7.6	11.5	7.7
Platelets count, /mm³	148,000	140,000	151,000
Leukocyte count, /mm³	24,500	17,000	13,700
Bastonetes, %	3	4	2
Segmented, %	87	74	78
Eosinophil, %	1	2	1
Basophils, %	0	0	0
Lymphocyte, %	7	14	17
Monocyte, %	2	4	2
Myelocyte, %	0	2	0
Promyelocyte, %	0	0	0
Metamyelocyte, %	0	0	0
Reactive lymphocytes, %	0	0	0
C-reactive protein, mg/L	187	180	173
Lactate, mmol/L	1.2	1.2	1.7
Urea, mg/dL	117.6	92.6	91.6
Serum creatinine concentration, mg/dL	1.0	0.6	1.3
Hospitalisation, days	18	7	14
Clinical outcome	Death	Death	Death

[†]Laboratory data were obtained at the time of detecting co-infection.