COVID-19 and Children With Down Syndrome: is There Any Real Reason to Worry? Case Report

Ahmad Kantar (kantar@centropediatricotosse.com)
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy
https://orcid.org/0000-0002-3445-4612

Angelo Mazza
Pediatric Department, Hospital Papa Giovanni XXIII, Bergamo, Italy

Ezio Bonanomi
Pediatric Intensive Care Unit, Hospital Papa Giovanni XXIII, Bergamo, Italy

Marta Odoni
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy

Manuela Seminara
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy

Ilaria Dalla Verde
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy

Camillo Lovati
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy

Stefania Bolognini
Pediatric Unit, Istituti Ospedalieri Bergamaschi, Gruppo Ospedaliero San Donato, Bergamo, Italy

Lorenzo D'Antiga
Pediatric Department, Hospital Papa Giovanni XXIII, Bergamo, Italy

Case Report

Keywords: Down syndrome, trisomy 21, COVID-19, children

Posted Date: July 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-44432/v1

Version of Record: A version of this preprint was published on December 18th, 2020. See the published version at https://doi.org/10.1186/s12887-020-02471-5.

Abstract

Background: Down syndrome (DS) is characterised by a series of immune dysregulations, of which interferon hyperreactivity is a key one as it is responsible for surging antiviral responses and probable initiation of an amplified cytokine storm. This biological condition is attributed to immune regulators encoded in chromosome 21. Moreover, DS is characterised by the coexistence of cardiovascular and respiratory anomalies as well as obesity, which constitutes a risk factor for SARS-CoV-2 respiratory disease (COVID-19).

Case presentation: Of the total number of children 55 admitted to paediatric wards in Bergamo in the period between February to May 2020 for COVID-19 infection, we present 2 children with DS and confirmed COVID-19 diagnosis that had a severe course. In addition, both cases had one or more comorbidities, being cardiovascular anomalies, obesity, and/or OSA.

Conclusions: Our observations indicate the need to consider children with DS a population at a risk of severe COVID-19.

Background

Down syndrome (DS) is associated with several immune dysregulations [1]. Consequently, the risk of recurrent and severe infections, autoimmune diseases, and inflammatory conditions are commonly reported [2-5].

The mechanisms by which trisomy 21 causes the immune dysregulation observed in individuals with DS is under continuous investigation. In DS or trisomy 21, several genes encoded on chromosome 21 play substantial roles in orchestrating immune responses, and their overexpression could contribute to the immune status. Among the major immune regulators encoded on chromosome 21 are 4 interferon (IFN) receptors which serve as a receptor subunit for cytokines IL-10, IL-22, and IL-26 [6]. Moreover, immune and non- immune cell types in DS are hypersensitive to IFN stimulation [1]. Research studies have showed that T cell lineages of adults with DS show clear signs of differentiation and hyperactivation even in the absence of any obvious infections, a phenomenon which may be attributed to chronic IFN hyperactivity [4]. These data indicate that the IFN response, which is crucial for escalating antiviral responses besides driving and amplifying the cytokine storm, is vigorous in people with DS [1].

Recent studies have confirmed that severe morbidity and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are driven by an exacerbated immune response to the virus, leading to a cascade of events involving a cytokine storm, acute respiratory distress syndrome, thromboembolic processes and multi-organ failure [7]. It is unclear how individuals with DS respond to this infection. In a recent review, Espinosa provided scientific evidence for considering individuals with trisomy 21 as being at a relatively high risk of developing more severe symptoms and increased rates of

hospitalisation, intensive care admission, secondary bacterial infections, and mortality from SARS-CoV-2 infection [1]. In addition to immune dysregulation, it is well known that a majority of children with DS are also affected by various types of congenital anomalies that may increase the risk of developing severe symptoms.

Case Presentation

In Italy, the outbreak of SARS-CoV-2 respiratory disease (COVID-19) started in the Lombardy region, probably on the 18th of February. The province of Bergamo registered the highest incidence of COVID-19 in Italy. Here, we report the clinical cases of children with DS that presented with confirmed COVID-19 in the emergency departments of hospitals in Bergamo province during the period from February to May 2020.

Case 1

A North African, 34-month-old female with DS and secundum atrial septal defect was admitted to the our paediatric ward at the end of January due bilateral interstitial pneumonia that was managed with oxygen delivery using nasal cannula and antibiotics (ceftriaxone and azithromycin), and required a total of 15 days of hospital stay. No swabs were performed at that time (since not yet available before SARS-CoV-2 outbreak in Bergamo). After two weeks of recovery she was readmitted for high fever and cutaneous rash lasting for 3 days, antibiotic treatment with cefotaxime was initiated. On the third day, she started to present typical signs of Kawasaki disease, such as bilateral non-purulent conjunctival injection, red and cracked lips, strawberry tongue, redness of the palms and soles with peeling of the skin, lymph node enlargement at the neck, and irritability. Haematological examination detected normal thrombocyte levels, high sedimentation rate, high leucocyte count with neutrophilia, low haemoglobin level, and raised C-reactive protein. Abdominal ultrasound scanning was normal. Electrocardiogram and echocardiogram evaluations for coronary artery aneurisms were normal. The child was treated with intravenous immunoglobulin, oral steroids and high doses of aspirin. Because of persistent fever, a second dose of immunoglobulin was administered. After this treatment, the fever resolved and aspirin treatment was continued thereafter for a total of 6 weeks. Serology for SARS-CoV-2 (IgM, IgG) were positive. Follow up visits did not reveal cardiac or other organ abnormalities.

Case 2

A 14-year-old Caucasian female child with DS was admitted to our ward because of fever, cough, nasal congestion, sore throat, fatigue, and dyspnoea. She had no cardiac anomalies, but she was overweight with a body mass index (BMI) of 36 and suffered from obstructive sleep apnoea (OSA). Before admission, she was already started on amoxicillin-clavulanate and acetaminophen because of fever. On admission, chest radiography revealed bilateral interstitial pneumonia. Nasopharyngeal and oropharyngeal swab sampling for SARS-CoV- 2 were positive. Due to her worsening respiratory condition,

she was transferred to the intensive care unit (ICU), where she was initially intubated, then weaned to continuous positive airway pressure (CPAP), and later supported by oxygen mask. She underwent treatment with antibiotics (ceftriaxone and azithromycin), antiviral drugs (lopinavir and ritonavir), hydroxychloroquine, and low-molecular-weight heparin. Respiratory symptoms recovered after 14 days the course was complicated by a sacral bedsore needing prolonged curettage. A lung CT performed after recovery revealed diffuse ground glass opacities and bilateral air trapping. No evidence of thromboembolism was found. Spirometry 30 and 60 days after recovery was normal.

Discussion And Conclusions

Experience with previous coronavirus outbreaks indicates that there is a reduced propensity for these viruses to affect children. Among patients infected during the 2003 SARS-CoV-1 outbreak, only 6.9% were children, and there were no fatalities in patients aged <18 years. Additionally, children experienced a milder form of the disease [8]. In the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012, only 2% of the patients were children [9].

At the beginning of this pandemic, children seemed to be relatively spared; however, later reports from various centres described a potentially COVID-19-related severe multisystem inflammatory syndrome in children and young adults [10,11].

A study of 46 paediatric COVID-19 patients admitted to ICUs in Canada and the United States for COVID-19 found that comorbidities were prevalent in this paediatric cohort, with 50% having 1 comorbidity, 17% with 2, and 19% with 3 or more significant comorbidities [12]. Reported comorbidities were: medically complex conditions with dependence on technological support, immune suppression, malignancy, obesity, diabetes, seizures, sickle cell disease, lung disease, congenital heart disease, and other congenital malformations.

We describe here two paediatric cases of DS who developed severe COVID-19. DS is the most common chromosomal abnormality in people worldwide; the prevalence is ≈1/1,000 live births. It is characterised by a variety of dysmorphic features, congenital malformations, and other disease conditions. During the SARS-CoV-1 outbreak, no cases of children with DS were reported. Whereas throughout the emergence of MERS-CoV, Menish et al. [13] described a case of a 14-year-old girl with DS having repaired ventriculoseptal defect with residual severe mitral regurgitation, history of systolic and diastolic left ventricular impairment, and pulmonary hypertension. Furthermore, she was obese (BMI 42.2) and suffering from hypothyroidism and OSA that was managed with home oxygen. On her admission, chest radiography revealed bilateral infiltrate. Nasopharyngeal swab samples tested positive for MERS-CoV. She was treated symptomatically and received nebulisation treatment, intravenous diuretics, imipenem, and oseltamivir. Her condition gradually improved and supplemental oxygen was discontinued. She was discharged after 7 days and remained in good health.

A confidence study of paediatric COVID-19 cases in 17 paediatric emergency departments in Italy taken between 3 and 27 March reported 27% of comorbidities. However, it did not report any case of children

with DS [14].

Another retrospective cohort study at the Children's National Hospital, Washington DC, included 177 children and young adults with clinical symptoms and laboratory-confirmed SARS-CoV-2 infection treated between 15 March and 30 April 2020 [15]. From 177 infected patients who sought medical attention, 44 were hospitalised, and of these 35 were non- critically ill and 9 critically ill. The study found that cardiac, haematologic, neurologic, and oncologic diagnoses were more common in hospitalised children with COVID-19 compared to non-hospitalised children with the disease. Among the critically ill patients, a 7-week-old female child with DS was reported. She was admitted due to progressive tachypnoea and fever, and chest radiography revealed right-lower-lobe pneumonia. Ventilatory support with RAM cannula was administered.

Literature on COVID-19 in DS patients is unavailable thus far. De Cauwer et al. described the clinical course of 4 adults with DS during an outbreak of COVID-19. In all 4 patients, disease course was severe, warranting hospital care in 3 patients and resulting in a fatal outcome in one [16]. The first case was a 60-year-old female with DS who was treated with oxygen and antibiotics (amoxicillin-clavulanate, initially, and meropenem, subsequently) with a favourable outcome. The second case was a 48-year-old female who was treated with oxygen, amoxicillin-clavulanate, azithromycin, and chloroquine and recovered. The third case was a 55-year-old female who was treated with oxygen, amoxicillin-clavulanate, chloroquine, and azithromycin; however, she did not respond to therapy and died in the hospital. The fourth case was a 62-year-old patient with DS who developed respiratory failure and subsequently received supportive care.

Of the total number of children 55 admitted to paediatric wards in Bergamo (February - May 2020) for COVID-19 infection, 2 children with DS and confirmed COVID-19 diagnosis had a severe course. In addition, both cases had one or more comorbidities, being cardiovascular anomalies, obesity, and/or OSA. Children with DS have a unique profile of cardiovascular disease. In addition, diverse anatomic abnormalities of the airways are considered major risk factors for respiratory infections in DS. OSA is very common in DS and can trigger pulmonary complications [17]. In the context of COVID-19, obesity is a recognised risk factor. In a recent study, it was reported that 30.4% of children admitted for hospitalisation were obese [18] and that obesity is prevalent in DS [19] This currently presents a challenge in distinguishing the role of comorbidities in the development of COVID-19 in DS. Research studies suggest that children with trisomy 21 could be genetically vulnerable to severe infections by the SARS-CoV-2 virus [1].

During the COVID-19 outbreak in Italy, the incidence of paediatric emergency visits declined drastically. This observation is attributed to the closure of schools, intensifying of public hygiene measures, and the wearing of facemasks. These measures of mitigating the spread of the disease seemed to be efficient in protecting not only adults but also children during the peak period. Nevertheless, a few severe infections still occurred in children. As lockdown measures begin to ease and schools reopen in countries still battling SARS-CoV-2, it is strongly recommended that sufficient measures are implemented to protect

children with DS, in particular those with comorbidities, considering the possibility of COVID-19 resurgence.

List Of Abbreviations

DS: Down syndrome

INF: Interferon

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

BMI: Body mass index

OSA: Obstructive sleep apnoea

Declarations

Ethics approval and consent to participate

Not applicable.

Written informed consent has been obtained from caregivers of each reported case as indicated by ethical committee.

Consent to publish

Informed written consent was obtained from caregivers of each child for publication of these 2 cases. A copy of the written consent is available for review by the Editor-in-Chief of this journal. Caregivers were involved in healthcare decisions.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.Data are available upon request from corresponding author.

Competing interests

All authors declare that they have no competing interests

Funding

The authors declare that they received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Authors' Contributions

AK and LD'A made substantial contributions to the conception and drafted the final work. AM, EB, MO, MS, IDV, CL, and SB followed the patients and ordered the integrity of all part of the work. All authors gave final approval for the Article to be published

Acknowledgements

The authors would like to thank the families for their consent to publish this report.

References

1. Espinosa Down Syndrome and COVID-19: A Perfect Storm? published online Cell Rep Med. 2020; May 19;1(2):100019. doi: 10.1016/j.xcrm.2020.100019
2. Pierce MJ, LaFranchi SH, Pinter Characterization of thyroid abnormalities in a large cohort of children with Down Syndrome. Horm Res Paediatr. 2017;87(3):170-8.
3. Liu E, Wolter-Warmerdam K, Marmolejo J, Daniels D, Prince G, Hickey F. Routine Screening for Celiac Disease in Children with Down Syndrome Improves Case J Pediatr Gastroenterol Nutr. 2020. doi: 10.1097/MPG.0000000000002742.
4. Araya P, Waugh KA, Sullivan KD, Núñez NG, Roselli E, Smith KP et al. Trisomy 21 dysregulates T cell lineages toward an autoimmunity- prone state associated with interferon hyperactivity. Proc Natl Acad Sci USA. 2019;116 (48): 24231–241.
5. Spina CA, Smith D, Korn E, Fahey JL, Grossman Altered cellular immune functions in patients with Down's syndrome. Am J Dis Child. 1981;135(3): 251–5.
6. de Weerd NA, Nguyen T. The interferons and their receptors– distribution and regulation. Immunol Cell Biol. 2012;90(5):483–91.
7. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, Intensive Care Med. 2020;46(5);846-8.
8. Stockman LJ, Massoudi MS, Helfand R, Erdman D, Siwek AM, Anderson LJ, Parashar UD. Severe Acute Respiratory Syndrome in Children. Pediatr Infect Dis J. 2007;26(1):68-74.
9. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013;13(9):752-61.
10. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. et al. Hyperinflammatory shock in children during COVID-19 pandemic. 2020;395(10237):1607-8.
11. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.
12. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and

Canadian pediatric intensive care units. JAMA Pediatr. 2020; published online May 11. doi: 10.1001/jamapediatrics.2020.1948.

13. Memish ZA, Al-Tawfiq JA, Assiri A, AlRabiah FA, Al Hajjar S, Albarrak A, et Middle east respiratory syndrome coronavirus disease in children. Pediatr Infect Dis J. 2014;33(9):904-6.
14. Parri N, Lenge M, Buonsenso D, Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in pediatric emergency departments in Italy. N Engl J Med. 2020; published online May 1:NEJMc2007617. doi: 1056/NEJMc2007617.
15. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, eta al. Severe COVID- 19 in children and young adults in the Washington, DC metropolitan region. J Pediatr. 2020; published online May 13. doi: 1016/j.jpeds.2020.05.007.
16. De Cauwer H, Spaepen A. Are patients with down syndrome vulnerable to life- threatening COVID-19? Acta Neurol Belg. 2020; published online May 22;1-3.doi: 10.1007/s13760-020-01373-8.
17. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with down syndrome. Pediatrics. 1991;88(1):132–9.
18. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York city. J Pediatr. 2020; published online May 11:S0022- 3476(20)30580-1.
19. O' Shea M, O' Shea C, Gibson L, Leo J, Carty The Prevalence of obesity in children and young people with down syndrome. J Appl Res Intellect Disabil 2018;31(6):1225- 9.