

In another study in China,⁶ none of the 9 infants from 1 to 11 months of age infected with COVID-19 presented severe symptoms.

Concerning neonatal manifestation, in a study of 33 newborns from mothers with COVID-19,⁷ 2 of them developed mild symptoms, and 1 required respiratory support, but it was certainly due to his prematurity (31 weeks of gestation). We found 2 other case studies in literature: one⁸ referring to a newborn from a COVID-19 laboratory-confirmed mother, diagnosed with SARS-CoV-2 infection in his first day of life, even though he was separated from his mother immediately after birth. His symptoms were mild. Another study reports of a neonate⁹ who developed gastrointestinal symptoms only (refusal to feed and vomiting).

The laboratory results in most cases were normal. In our series of patients, only 2 presented with lymphopenia, which is consistent with laboratory findings in older children.⁵ None of them suffered from liver damage.

In most of our patients, the route of transmission of COVID-19 was close contact with an infected family member or friend in most cases. Four of the 6 children were living in a neighborhood with a high prevalence of the disease. The latter may explain the relatively high number of cases observed in our pediatric unit, compared with other pediatric wards in the same region.

There are no indications of vertical mother-to-child transmission as all mothers were asymptomatic during pregnancy. Two of the mothers developed symptoms of COVID-19 over 2 weeks after giving birth, one of them showed symptoms 7 days after her baby was affected by the virus. None of the children was breast-fed, which rules out transmission of the virus through breast milk in our patients.

CONCLUSION

Our study suggests that infants, and newborns especially, present, as older children do, mostly with mild or moderate form of COVID-19. In our observation, all patients suffered from fever alone or in association with other mild symptoms such as rhinitis, diarrhea and reduced food intake. COVID-19 must be considered as a differential diagnosis in a newborn with fever. Most of them will recover quickly without any other complications, but medical supervision in hospital seems justified in newborns.

REFERENCES

- Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020. doi: 10.1111/apa.15270. Epub ahead of print.
- Lake MA. What we know so far: COVID-19 current clinical knowledge and research. *Clin Med (Lond)*. 2020;20:124–127.
- Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis*. 2020;pii:S1473-3099(20)30198-5.
- Hong H, Wang Y, Chung HT, et al. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatr Neonatol*. 2020;61:131–132.
- Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;pii:20200702.
- Wei M, Yuan J, Liu Y, et al. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. 2020;1313–1314.
- Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020. doi: 10.1001/jamapediatrics.2020.0878. Epub ahead of print.
- Wang S, Guo L, Chen L, et al. A case report of neonatal 2019 coronavirus disease in China. *Clin Infect Dis*. 2020;pii:ciaa225.
- Wang J. SARS-CoV-2 infection with gastrointestinal symptoms as the first manifestation in a neonate. *Chin J Contemp Pediatr*. 2020;22:211–214.

Pediatric Life-Threatening Coronavirus Disease 2019 With Myocarditis

Marie-Laure Oberweis, MD,*† Andrei Codreanu, MD,*
Wolfgang Boehm, MD,* Damien Olivier, MD,*
Charlotte Pierron, MD,* Chantal Tsobo, MD,*
Michel Kohnen, MD,* Tamir T. Abdelrahman, MD, PhD,‡
Nguyen T. Nguyen, MD,‡ Kerstin Wagner, MD,*
and Isabel de la Fuente Garcia, MD, MSc*

Abstract: We report the case of a pediatric life-threatening coronavirus disease 2019 who presented as myocarditis with heart failure. Clinicians should be aware of this severe presentation of the disease in children, possibly linked to an exaggerated inflammatory host immune response to severe acute respiratory syndrome coronavirus 2.

Key Words: severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, myocarditis, Tocilizumab, children
Accepted for publication April 28, 2020.

From the *Centre Hospitalier du Luxembourg, Luxembourg, Grand-Duché du Luxembourg; †Université Catholique de Louvain, Brussels, Belgium; and ‡Department of Microbiology, Laboratoire National de la Santé, Luxembourg, Grand-Duché du Luxembourg.

The authors have no funding or conflicts of interest to disclose.

Kerstin Wagner and Isabel de la Fuente Garcia contributed equally to the work as last authors of the manuscript.

Address for correspondence: Isabel de la Fuente Garcia, MD, MSc, Children's Hospital – Kannerklinik, CHL, 4 Rue Ernest Barblé, L-1257 Luxembourg, Grand-Duché du Luxembourg. E-mail: delafuentegarcia.isabel@chl.lu.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/INF.0000000000002744

With more than 2 million cases worldwide and above 200,000 attributed deaths, the coronavirus disease 2019 (COVID-19) has become an urgent public health matter because it rapidly spread from Wuhan to the rest of the world. It is caused by a single-stranded RNA betacoronavirus of the Coronaviridae family called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Because of the pandemic, a lot of reports are now available on adult patients with severe cases consisting of respiratory distress at the forefront. Until now, severe cardiac involvement without pulmonary disease has only been exceptionally described in adults.¹ The pediatric population seems to be spared by the pathogen as children tend to present with milder symptoms or flu-like states. However, we describe a case of pediatric COVID-19 with life-threatening myocarditis presenting in heart failure.

REPORT OF THE CASE

A previously healthy 8-year-old boy of African origin (height 130 cm and weight 29 kg) presented to our hospital with a 4-day history of fever, coughing, weight loss and severe fatigue. On physical examination, he was febrile (39.6°C) and presented a warm, painful and swollen erythema with adenopathy on the right side of the neck. He was diagnosed with cellulitis, which was confirmed by echography, and initially hospitalized for intravenous antibiotics. Within a few hours of admission, he developed tachycardia (138 bpm), low blood pressure (94/40 mm Hg) resilient to fluid bolus and associated with the appearance of hepatomegaly and oliguria. The blood test showed an increased C-reactive protein (CRP, 73 mg/L), leukopenia (4260/mm³) with lymphopenia (400/mm³), thrombocytopenia (118,000/mm³), renal function impairment (urea: 37 mg/dL, serum creatinine: 0.62 mg/dL), hepatic cytolysis (glutamic oxaloacetic transaminase: 88 U/L, glutamic pyruvic transaminase: 50 U/L), myocardial necrosis (high-sensitivity troponin T levels: 0.044 ng/mL, N-terminal pro-brain natriuretic peptide: 5112 pg/mL) as well as elevated D dimers (>4.40 µg/mL) and interleukin-6 (IL-6, 377.8 pg/mL).

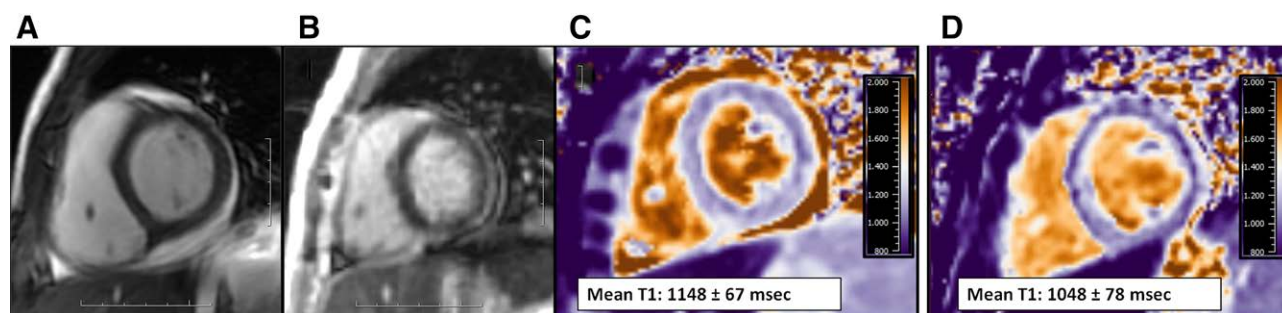


FIGURE 1. 3 Tesla Cardiac magnetic resonance (GE Discovery MR750 and Medis Suite MR) of the patient. A: Gadolinium magnetization-prepared steady-state free-precession cine showing mild pericardial effusion during acute phase. B: Late Gadolinium enhancement imaging illustrating mild subepicardial enhancement of the lateral wall. C: Native T1 mapping revealing global increase in T1 values, suggesting diffuse myocardial edema (T1 normal values: 928 ± 68 msec). D: One-week follow-up native T1 mapping showing slightly decreased T1 values consistent with partial regression of myocardial edema (Please note that the acute and follow-up T1 maps use the same scale).

Two-dimensional echocardiography revealed normal cardiac anatomy with impaired left ventricular function (fractional shortening: 21%) and trace mitral insufficiency as well as a small pericardial effusion with neither evidence of left ventricular dilatation nor myocardial hypertrophy or significant pulmonary hypertension. The electrocardiogram was significant for discrete ST elevation in V3 consistent with pericarditis.

The patient was admitted to the intensive care unit, anticoagulated with Enoxaparin and treated with Dobutamine which quickly normalized his blood pressure and restored diuresis. He also received oxygen to support heart function.

Follow-up blood tests showed a rapid increase of the inflammatory markers (CRP max: 151 mg/L, interleukin-6 max: 1023 pg/mL, ferritin max: 2869 ng/mL), progression of hepatic cytolysis (GOT max: 100 U/L, GPT max: 70 U/L) and kidney failure (creatinine max: 0.75 mg/dL).

Cardiac magnetic resonance imaging (CMR) performed at day 3 confirmed biventricular systolic dysfunction (left ventricular ejection fraction: 41%, right ventricular ejection fraction: 46%) with small pericardial effusion, mild subepicardial Gadolinium enhancement of the lateral wall and signs of diffuse edema (**Fig. 1**).

His pulmonary chest scan on day 3 showed bilateral pneumopathies of the inferior lobes with bilateral pleural effusions without glass-ground opacities. A nasopharyngeal swab realized on admission came back positive for SARS-CoV2 on real-time reverse transcriptase polymerase chain reaction assay (PCR) (N1 gene at 36.1 cycle thresholds [CT], E gene at 36.3 CT). Furthermore, a PCR on the stools, which was collected at day 6, was also positive (N1 gene at 39 CT and RdPR gene at 39 CT). The child had high titers of both Ig A and Ig G on the serum sample at day 6 (Ig A: 8.39; Ig G: 10.90, using enzyme-linked immunosorbent assay Kit). Screening for other infectious cardiotropic pathogens yielded negative results (nasopharyngeal PCR for adenovirus, coronaviruses NL63, 229E, OC43 and HKU1, enterovirus, parainfluenza, influenza and mycoplasma pneumoniae; throat culture; parvovirus B19 serologies; blood cultures).

He received IV immunoglobulins (2 g/kg given in 2 days). Dobutamine (max: 8.5 μ g/kg/min) was stopped at day 2 and followed by Milrinone (max: 0.6 μ g/kg/min) until day 3.

As COVID-19 was rapidly confirmed, and as he was developing a life-threatening condition possibly related to a massive inflammatory storm given the inappropriate IL-6 level, Tocilizumab (2 doses of 8 mg/kg²) was administered according to our national COVID-19 guidelines.³ Surprisingly, the cervical

cellulitis-like presentation disappeared after the first dose of Tocilizumab which was well tolerated and without any adverse effect until discharge. The cellulitis like was most likely a dermatologic feature of COVID-19.

Follow-up CMR performed a week later displayed normal systolic function and regression of myocardial edema (**Fig. 1**). The child was discharged on day 10 with a normal cardiac function and normalization of the blood impairments.

DISCUSSION

SARS-CoV2 is a new coronavirus that has been identified for causing a wide range of clinical symptoms.

As explained by the report of the China Medical Treatment Expert Group for COVID-19,⁴ the most common symptoms include fever, headache, fatigue, dry cough and shortness of breath. In adults, complications are mostly pneumonia and acute respiratory distress syndrome (ARDS).

Despite the observed frequent elevation of serum Troponin in COVID-19 adult patients, related to various putative mechanisms of cardiac injury,⁵ demonstrated cases of COVID-19-related myocarditis are scarce.

Fewer data about infection in children are available, but it seems clear that the pediatric population presents with less severe symptoms. A retrospective study by Lu et al⁶ examined the clinical characteristics of 171 pediatric COVID-19 cases. These children showed milder symptoms compared with adults: only 4 patients dropped their oxygen saturation <92% and 3 patients required intubation, all of them with comorbidities.

According to the Centers for Disease Control and Prevention, these findings seem to correlate with the pediatric population within the United States.⁷ To our knowledge, no published reports describing myocarditis related to COVID-19 in children are available yet.

Even if the fatality rate of COVID-19 in children seems incredibly low, there have already been mediatic reports of deaths among healthy children in different parts of the world including Europe, Asia and the United States. It is therefore an urgent priority to describe pediatric life-threatening events related to COVID-19 to increase their awareness and reduce death rate.

We describe one previously healthy boy presenting a life-threatening COVID-19 condition, requiring intensive care treatment and which manifested as myocarditis with cytokine storm and heart failure. He was rapidly identified as critical and was treated

consequently, leading to a good outcome. He also had a respiratory implication of SARS-CoV2 but not as severely described as in the adult ARDS.

The high clinical suspicion of myocarditis in our patient based on clinical course and elevated myocyte cytolysis markers was confirmed by the functional and structural CMR findings, combining main and supportive criteria according to the current guidelines⁸ and the revised Lake-Louise recommendations.⁹ Myocarditis due to viral infection has been widely described and associated to myocardial inflammation leading to necrosis and heart dysfunction. Other coronaviruses (Middle East Respiratory Syndrome Coronavirus) have already been identified as causative agents of myocarditis in adults.⁵ In the case of COVID-19, the physiopathologic process remains unclear, although both direct cardiac injury by SARS-CoV2 (eg, through ACE2 binding in the heart) and indirect damage through a toxic inflammatory reaction with cytokine storm seem plausible. Several adult autopsy reports revealed that there is a significant number of inflammatory cells in the alveoli of patients suffering from ARDS caused by SARS-CoV2.¹⁰ Nevertheless, no histologic changes were seen in heart tissue and no viral inclusions were identified in the lungs, suggesting indirect damage through the cytokine storm. Furthermore, high rates of inflammatory markers such as IL-6, Ferritin or CRP can be found in the blood of critical patients. Our patient with myocarditis responded to immunomodulatory treatment, with a complete reversal of myocardial edema, raising the hypothesis that SARS-CoV2 triggers an exaggerated inflammatory response causing heart damage. Further argument to highlight the physiopathologic process as a para-infectious inflammatory response to SARS-CoV2 in our patient is that viral load was low (high CT), suggesting that he was at the end of the infection but in the middle of the cytokine storm.

A hypothesis to explain the death of children occurring during COVID-19 could be that some predisposed children might be more susceptible to cardiac damages from the cytokine storm triggered by COVID-19 rather than the usual respiratory distress syndrome typically observed in adults. Deep analysis of pediatric life-threatening infections is necessary to better understand children's specific risk factors.

CONCLUSION

During this time of pandemic, where telemedicine is becoming a common practice, it is essential that whenever any sign of potential gravity is present at a child's evaluation, urgent clinical care is provided to identify potential life-threatening COVID-19 such as myocarditis.

Therefore, clinicians should be aware of the cardiac involvement of SARS-CoV2 in children and search for any signs of myocarditis when taking care of unwell children with proven or suspected COVID-19 as prompt diagnosis can be lifesaving.

We also raise concerns that cardiac injury could be due to the disproportionate host immune response to SARS-CoV2 rather than through direct damage by the virus itself.

ACKNOWLEDGMENTS

We thank the patient and his family for granting permission to publish this article.

REFERENCES

1. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020.
2. Ministerio de Sanidad. Documento de manejo clínico del paciente pediátrico con infección por SARS-CoV-2. 2020.

3. Recommendations by the high council of infectious diseases about COVID-19 in Luxembourg. 2020. Available at: <https://sante.public.lu/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/covid-19/covid-19-annexes/covid19-strategie-therapeutique.pdf>. Accessed April 14, 2020.
4. Guan W, Ni Z, Hu Y, et al. China medical treatment expert group for Covid-19. clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.
5. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020;17:259-260.
6. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med.* 2020;382:1663-1665.
7. CDC Covid-19 Response Team. Coronavirus disease 2019 in children—United States, February 12–April 2. *CDC Morbidity and Mortality Weekly Report.* 2020.
8. Caforio AL, Pankuweit S, Arbustini E, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34:2636-2648, 2648a.
9. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol.* 2018;72:3158-3176.
10. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;8:420-422.

ACUTE INFLAMMATION AND ELEVATED CARDIAC MARKERS IN A TWO-MONTH-OLD INFANT WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION PRESENTING WITH CARDIAC SYMPTOMS

Vania Giacommet, MD,* Valeria Anna Manfredini, MD,* Giulia Meraviglia, MD,* Caterina Francesca Peri, MD,* Anna Sala, MD,* Emma Longoni, MD,* Alessio Gasperetti, MD,† Marta Stracuzzi, MD,* Savina Mannarino, MD,‡ and Gian Vincenzo Zuccotti, MD§

Abstract: Severe acute respiratory syndrome coronavirus 2 infection in children mainly shows a milder course. In complicated cases, it is unknown whether inflammation is predictive of disease severity, as in adults. Moreover, cardiac involvement is anecdotally described. We report the case of a 2-month-old infant with severe acute respiratory syndrome coronavirus 2 infection presenting with fever, tachycardia and elevated interleukin-6, who was diagnosed with myocarditis and treated with immunoglobulins.

Key Words: coronavirus disease 2019, infant, myocarditis, interleukin-6, infection

Accepted for publication April 29, 2020.

From the *Department of Pediatrics, Luigi Sacco Hospital, ASST-Fatebenefratelli-Sacco, University of Milan, Milan, Italy; †Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland; ‡Department of Pediatric Cardiology, V. Buzzi Children's Hospital, Milan, Italy; and §Department of Pediatrics, ASST-FBF-Sacco, Vittore Buzzi Children's Hospital, University of Milan, Milan, Italy.

The authors have no funding or conflicts of interest to disclose.

Address for correspondence: Valeria Anna Manfredini, MD, Department of Pediatrics, Luigi Sacco Hospital, ASST-Fatebenefratelli-Sacco, University of Milan, Via G.B. Grassi 74, 20157 Milan, Italy. E-mail: manfredini.valeria@asst-fbf-sacco.it.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/INF.0000000000002750

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a public health emergency worldwide. In adults, the disease varies in its clinical presentation from a flu-like syndrome with fever, cough, myalgia and/or fatigue to respiratory failure as the major leading cause of death. Despite respiratory symptoms are dominant in complex cases, cardiac involvement has been lately described as a clinical complication. In adults with