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HEART FAILURE AND IMAGING

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Complete Heart Block, Severe Ventricular Dysfunction, and Myocardial Inflammation in a Child With COVID-19 Infection

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ABSTRACT

A young child presented with severe ventricular dysfunction and troponin leak in the setting of coronavirus disease-2019. He developed intermittent, self-resolving, and hemodynamically insignificant episodes of complete heart block that were diagnosed on telemetry and managed conservatively. This report is the first description of coronavirus disease-2019-induced transient complete heart block in a child. (**Level of Difficulty: Intermediate.**)

CASE PRESENTATION

A 10-year-old boy presented with a 7-day history of fever and viral symptoms including fatigue, cough, diarrhea, vomiting, myalgias, and nonpruritic rash that spread to the trunk. His vital signs were notable for sinus tachycardia (130 beats/min), tachypnea (respiratory rate, 24 breaths/min), hypotension (84/40 mm Hg), and normal oxygen saturation (98% on 2-l nasal cannula). His physical examination was notable

LEARNING OBJECTIVES

- To be aware of the possibility of heart block in children admitted with COVID-19 and myocardial dysfunction.
- To understand the benefit of a multidisciplinary approach in addressing potential pathophysiological components leading to the development of arrhythmia in COVID-19 patients with cardiac involvement.

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ABBREVIATIONS AND ACRONYMS

ACE-2 = angiotensin-converting enzyme-2

AV = atrioventricular

CHB = complete heart block

COVID-19 = coronavirus disease-2019

IL = interleukin

ref = reference range

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

for appearing drowsy but easily arousable, normal work of breathing, a gallop on cardiac examination, cool extremities, and delayed capillary refill at 4 s.

PAST MEDICAL HISTORY

He had a history of pityriasis lichenoides chronica. He had no personal or family history of congenital heart disease, immunodeficiency, or autoimmune disease.

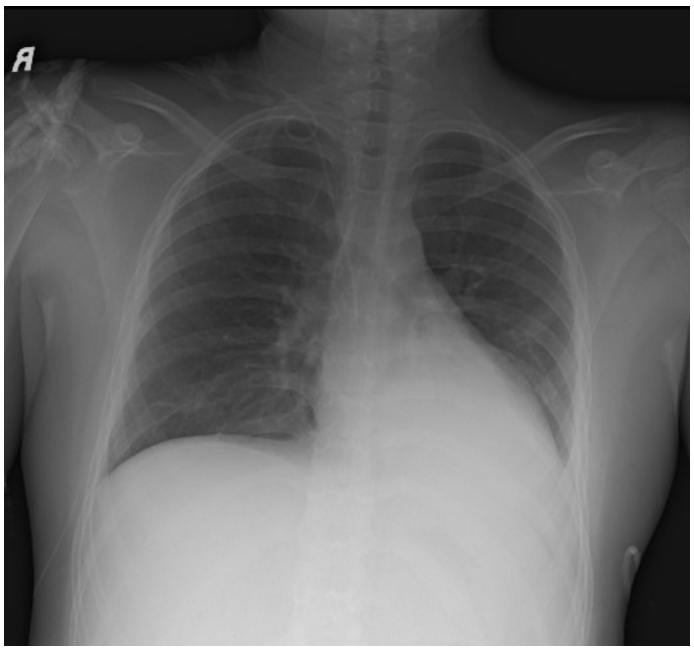
DIFFERENTIAL DIAGNOSIS

The differential diagnosis included viral-induced myocarditis or underlying cardiomyopathy unmasked by an acute viral illness.

INVESTIGATIONS

Laboratory evaluation was notable for the following: an elevated white blood cell count (17,100 cells/μl) with neutrophilic predominance and lymphopenia (9,100 cells/ul; reference range [ref.]: 1.23 to 2.69 cells/ul); elevated high-sensitivity troponin (84 ng/ml; ref: 0 to 14 ng/l); brain natriuretic peptide (2,000 pg/ml; ref.: 0 to 100 pg/ml); and inflammatory markers (C-reactive protein, 22 mg/dl [ref.: <0.5 mg/dl]; ferritin, 1,138 ng/ml [ref.: 10 to 320 ng/ml]; and D-dimer, 3.1 μg/ml [ref.: <0.5 μg/ml]). The chest radiograph was consistent with mild viral pneumonia (**Figure 1**).

FIGURE 1 Chest Radiograph on Admission Demonstrating Coarsened Interstitial Lung Markings and Hazy Retrocardiac Opacification



The electrocardiogram showed sinus tachycardia at 140 beats/min and a normal conduction interval (PR interval, 140 ms). The echocardiogram revealed normal left ventricular size (left ventricular end-diastolic volume 112 ml; *z*-score +0.8) and severe left ventricular systolic dysfunction with an ejection fraction of 32% (*z*-score −6.8) (Video 1). Coronary arteries were normal, and there was no evidence of wall motion abnormalities. Results of real-time polymerase chain reaction were positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) from nasopharyngeal swab. Evaluation for common infections associated with myocarditis identified no other active infectious cause (**Table 1**).

MANAGEMENT

He was started on bilevel positive airway pressure for respiratory support and afterload reduction. He was also started on epinephrine and norepinephrine infusions. He received 2 doses of intravenous immune globulin at 1 g/kg within the first 48 h of admission as an empirical treatment for potential myocarditis. In light of his hyperinflammatory state consistent with cytokine storm syndrome, multidisciplinary consultation led to the early initiation of immunomodulatory therapy (anakinra, 100 mg 3 times daily, and methylprednisolone, 2 mg/kg twice daily) and antiviral therapy (remdesivir, 100 mg daily after a 200-mg loading dose) on hospital day 1. Because of evidence of hypercoagulability and concern for related thrombotic complications, therapeutic anticoagulation was initiated with unfractionated heparin.

On day 2 of admission, his clinical status and hemodynamics began improving. He was transitioned from bilevel positive airway pressure to a regular nasal cannula. He was weaned from norepinephrine on day 2 and from epinephrine on day 6 of admission.

From a rhythm standpoint, he developed first-degree atrioventricular (AV) block 24 h into his admission, which resolved spontaneously by the following morning. However, on day 3 of his admission, he began to display bradyarrhythmias. Review of telemetry demonstrated transient, self-resolving episodes of complete heart block (CHB) with a narrow junctional escape rhythm of approximately 90 beats/min (**Figures 2A to 2E**). The longest episode lasted for 4 min, during which the patient remained hemodynamically stable and asymptomatic. Over the following days, he continued to have repetitive, self-resolving, and hemodynamically insignificant episodes of conduction block ranging from first-degree

TABLE 1 Diagnostic Evaluation for Potential Infectious Causes or Triggers of Myocarditis*

Test Name	Result	Interpretation	Reference Range
CMV IgM	<8.0 AU/ml	Not detected	≤29.9 AU/ml
CMV IgG	3.10 U/ml	Detected	≤0.59 U/ml
Cytomegalovirus PCR (blood)	Not detected	Not detected	Not detected
EBV Capsid antigen, IgM	<10.0	Not detected	≤35.9 U/ml
EBV antibody to EA-D, IgG	<5.0 U/ml	Not detected	≤8.9 U/ml
EBV Capsid antigen IgG	717 U/ml	Detected	≤17.9 U/ml
EBV antibody to NA, IgG	331	Detected	≤17.9 U/ml
Epstein-Barr virus PCR (blood)	21,257 copies/ml	Detected	Not detected
HSV IgM	0.56	Not detected	≤0.89 U/ml
HSV I/II Ab, IgG	0.28	Not detected	≤0.89 U/ml
Parvovirus IgM	0.11 IV	Negative	≤0.89 IV
Parvovirus IgG	6.11 IV	Positive	≤0.89 IV
Parvovirus B19 PCR (blood)	<199 IU/ml	Detected, below limit of quantitation	Not detected
Coxsackie A9 virus IgG	<1:8	Negative	<1:32
Adenovirus PCR (blood)	Not detected	Not detected	Not detected
Enterovirus PCR (blood)	Not detected	Not detected	Not detected
Ehrlichia and *Anaplasma* PCR (blood)	Negative	Not detected	Not detected

*All serological samples were collected before administration of intravenous immune globulin. Other (all negative or non-reactive): blood culture; respiratory pathogen PCR panel (includes adenovirus, coronavirus [HKU1, NL63, OC43, 229E], human metapneumovirus, human rhinovirus/enterovirus, influenza A [2009H1N1, H1, H3], influenza B, parainfluenza virus types 1 to 4, respiratory syncytial virus, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, Bordetella parapertussis*); Lyme IgG and IgM; rapid plasma reagin; HIV combination antigen/antibody; rapid strep.

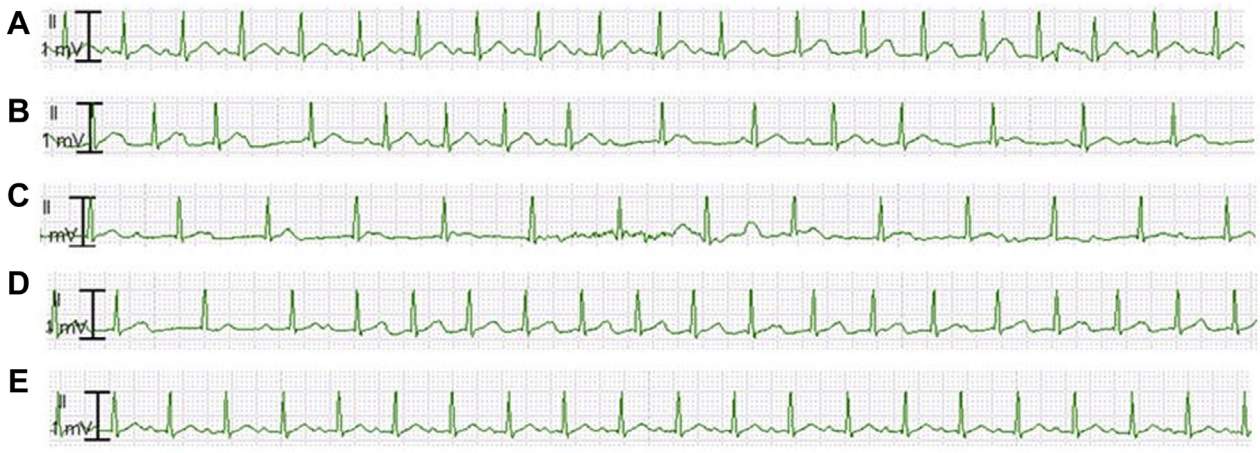
Ab = antibody; CMV = cytomegalovirus; EA-D = early antigen-diffuse; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenously; NA = nuclear antigen; PCR = polymerase chain reaction.

AV block to second- and third-degree AV block. All episodes resolved within a few minutes without intervention.

DISCUSSION

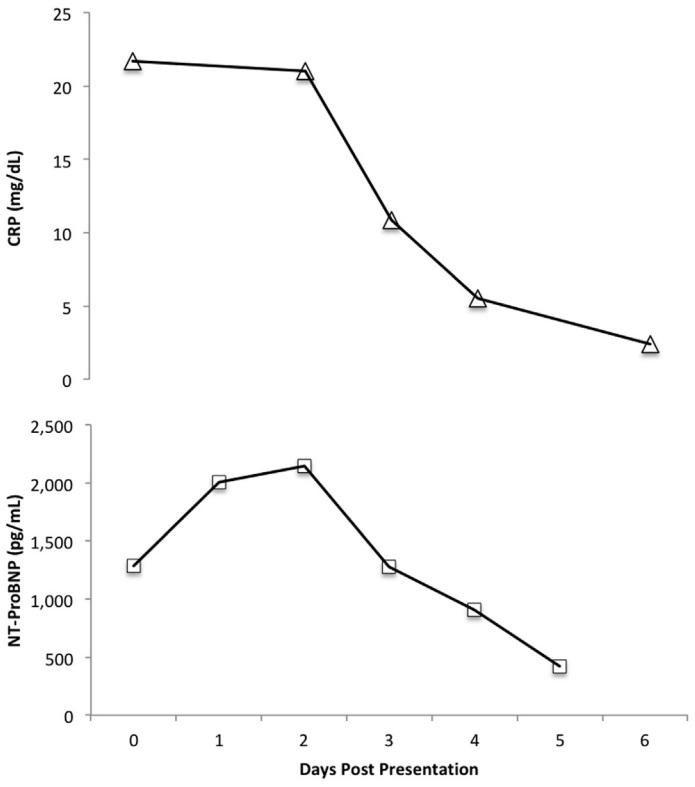
Myocardial involvement with the novel coronavirus, ranging from mild troponin leak to fulminant myocarditis, is well reported in adults and occurs in 8% to 28% of adults infected with SARS-COV-2 (1). Furthermore, acute cardiac injury portends poor outcomes (1,2). Children with coronavirus disease-2019 (COVID-19) appear to have a much milder form of the disease compared with adults, and they rarely progress to severe disease and multiorgan dysfunction (3–5). The largest pediatric cohort from China, of

FIGURE 2 Telemetry Rhythm Strips Showing the Progression From Normal Sinus Rhythm to CHB Followed by Resumption of Normal Conduction Within 4 Min



(A) Normal PR interval followed by first-degree atrioventricular block with prolonged PR interval at 280 ms. **(B)** Second-degree Mobitz I. **(C)** Complete heart block (CHB) with a narrow junctional escape rate ~90 beats/min. **(D)** First-degree atrioventricular block. **(E)** Sinus rhythm with a normal PR interval at 160 ms.

FIGURE 3 NT-ProBNP and CRP Plotted Against Day of Admission



CRP = C-reactive protein; NT-ProBNP = N-terminal pro-brain natriuretic peptide.

2,135 patients (728 confirmed and 1,407 suspected cases), showed that 94% of children had moderate disease severity or less, and there was only a single death, whereas severe disease was most common in neonates (5). Of 171 children with confirmed SARS-CoV-2 who were treated at the Wuhan Children's Hospital, only 3 patients with pre-existing conditions required intensive care support, and there was a single death (3). In a large systematic review of more than 1,000 children infected with COVID-19, Castagnoli et al. (4) reported a single case of severe COVID-19 infection, occurring in a 13-month-old child who achieved full recovery. Because of the recent emergence of COVID-19, data on its effects on the myocardium in children, and more specifically the conduction system, are scarce.

A large retrospective single-center case series of 138 hospitalized patients in China showed that 7% of the total cohort developed acute cardiac injury, and 16.7% had unspecified arrhythmias (6). There is a single case report of an adult woman admitted to the hospital with COVID-19 and respiratory distress requiring intubation who developed a single episode of transient CHB with prolonged pause on day 14 of her illness (7). She required cardiopulmonary resuscitation before resumption of normal sinus rhythm. Compared with our patient, she had a normal echocardiogram.

Our patient exhibited evidence of cytokine storm, with elevated ferritin, C-reactive protein, and procalcitonin, as well as markedly elevated soluble interleukin (IL)-2 receptor (14,800 pg/ml; ref.: ≤1,033 pg/ml), CXCL9 (chemokine [C-X-C motif] ligand 9, 1,575 pg/ml; ref.: ≤121 pg/ml), and IL-18 (1,427 pg/ml; ref.: 89 to 540 pg/ml) and elevated IL-6 (44 pg/ml; ref.: ≤5 pg/ml). The child's only pre-existing condition was pityriasis lichenoides chronica. Although there exists debate about the etiology of pityriasis lichenoides chronica, it can be characterized by benign clonal T-cell lymphoproliferation, which may arise as an aberrant immune response to an antigenic trigger, such as a viral infection (8). Whether this history suggests an underlying immunologic phenotype that contributed to the patient's hyperinflammatory state in response to SARS-CoV-2 infection remains to be determined.

Our patient improved significantly after initiation of immunomodulatory and antiviral therapy, although the relative contribution of either of these approaches cannot be discerned from this single case. A positive response to systemic glucocorticoids and intravenous immune globulin was reported in a single case of an adult patient with coronavirus fulminant myocarditis (9). Remdesivir has shown promise with in vitro activity against SARS-CoV-2, and early reports have noted a positive clinical response; however, trials are still underway to establish clinical efficacy (10). Additionally, anakinra has been applied with a favorable safety profile in adults with myocarditis from other causes (11). Our patient did not undergo a myocardial biopsy, so we cannot confirm that SARS-CoV-2 was directly responsible for myocardial injury or myocarditis. However, results of testing for some common infections often implicated in myocarditis were negative, except parvovirus (low-level viremia with a positive immunoglobulin G result), and Epstein-Barr virus viremia (with positive antibody to nuclear antigen and capsid immunoglobulin G), which both likely represent past infection with reactivation in the setting of acute illness.

The pathophysiology of myocardial injury secondary to SARS-CoV-2 is multifactorial, including

direct cardiotropic action of the virus mediated by its cellular receptor target: angiotensin-converting enzyme (ACE)-2, which is heavily expressed in adult cardiac pericytes (1,12). Furthermore, inhibition and down-regulation of ACE-2 result in an increased circulating level of angiotensin II, which has proinflammatory and vasoconstrictor properties, leading to microangiopathy (1,12). In adults with coronary artery disease, an oxygen demand-supply mismatch is suspected to play a role in the development of acute coronary syndromes, mediated by hypoxic respiratory failure and increased metabolic demand (1,11). Finally, cytokine storm secondary to down-regulation of ACE-2, as well as direct endothelial injury, may contribute to myocardial dysfunction (1,12).

The mechanism for COVID-19-induced heart block is not well studied, but we suspect that it is secondary to inflammation and edema of the conduction tissue, as part of the global myocardial injury process. The 2 potential mechanisms resulting in inflammation are direct viral invasion and immune-mediated injury (1). In our case, the patient had significantly elevated inflammatory markers, no other known risk factors for conduction disease, and a normal baseline electrocardiogram. With therapy, his inflammatory markers trended downward (**Figure 3**), and his episodes of heart block resolved, thus indicating that inflammation is likely the main cause of conduction disease in our patient.

FOLLOW-UP

The patient has had no recurrent episodes of CHB since day 4 of admission, and a repeat echocardiogram on day 12 of admission demonstrated low-normal biventricular systolic function.

CONCLUSIONS

Myocardial involvement in the form of dysfunction and conduction abnormalities appears to be a rare manifestation of SARS-CoV-2 infection in children (3–5). Nonetheless, evaluation for myocardial injury may be warranted in pediatric patients with symptomatic SARS-CoV-2 infection, particularly in patients whose clinical symptoms (e.g., dyspnea, hypoxia) seem out of proportion to chest imaging findings. Furthermore, children infected with COVID-19 who have myocardial involvement should be placed on continuous telemetry for close monitoring. Rhythm management should be guided by the patient's hemodynamics and clinical status. Additional studies are needed to identify the spectrum of rhythm disorders and cardiac involvement in pediatric patients with COVID-19 infections.

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KEY WORDS children, complete heart block, coronavirus, electrocardiogram, myocarditis, ventricular dysfunction

APPENDIX For a supplemental video, please see the online version of this paper.