

Multisystem inflammatory syndrome in children and complete atrioventricular block: What have we learned so far and where do we go from here?

Mehta *et al.* describe two patients with complete atrioventricular (AV) block during the COVID-19 pandemic that required insertion of a temporary pacemaker.^[1] Both patients had evidence of complete AV block and poor cardiac output with clinical laboratory evidence consistent with multisystem inflammatory syndrome in children (MIS-C). Both patients were treated with similar regimens including isoproterenol and epinephrine in the acute setting along with intravenous immunoglobulin (IVIG) and steroids and both required placement of a temporary transvenous pacemaker. While one patient had a recovery to sinus rhythm with intact AV conduction within 5 days of presentation and remained in sinus at 2 months of follow-up, the second patient did not have recovery of AV conduction. The second patient remained in complete AV block at 10 days after presentation and had a permanent dual-chamber pacemaker placed and remained in atrial-sensed and ventricular-paced rhythm at 1 month of follow-up. The authors postulate an immune-mediated reaction, similar to the hypothesized pathophysiology of MIS-C and myocardial dysfunction, which directly affected the conduction system and led to AV block and subsequent hemodynamic changes.

The etiology of AV block in pediatric patients with structurally normal hearts includes congenital AV block, inherited AV block including skeletal myopathies and muscular dystrophies, cardiomyopathies including hypersensitivity or infiltrative processes, and infectious causes such as myocarditis and Lyme disease.^[2] The estimated prevalence of congenital AV block is 1/15,000–20,000 and the prevalence of the other forms of AV block in pediatric patients is not well described.^[3]

Abnormal AV conduction associated with MIS-C has been described in the literature. Choi *et al.* described 32 patients (median age 9 years) admitted for MIS-C at a single center with a 19% incidence of 1st degree AV block and median PR interval of 225 ms. The finding of 1st degree AV block was demonstrated at a median of 8 days after symptom onset with resolution 3 days after. In their cohort, there was a single patient with a PR interval >300 ms but no advanced AV block.^[4] Regan *et al.* reported on a cohort of 63 children (median age 10 years) with MIS-C and found a 25% incidence of 1st degree AV

block that persisted at follow-up evaluation in only 2 (3%) patients.^[5] In their cohort, there were no patients with higher-grade AV block. Clark *et al.* reported an international cohort of MIS-C patients and found a single case of complete AV block in an MIS-C patient requiring extracorporeal membrane oxygenation (ECMO) support and an additional patient with intermittent advanced 2nd degree AV block, both of which resolved during their clinical course and did not require temporary pacemaker implantation.^[6] Dionne *et al.* reported a group of 25 MIS-C patients with a 20% incidence of AV conduction abnormalities and four patients who advanced to high-grade 2nd or 3rd degree block.^[7] The four patients with high-grade AV block presented with cardiogenic shock and decreased left ventricular function on echocardiogram. These patients required vasoactive support, but no temporary pacing was required and all had resolution of their conduction abnormalities within 1 week of presentation. Interestingly, all patients with advanced AV block had elevation in their brain natriuretic peptide (BNP) levels but no increase in troponin. There is a single report of a pediatric patient requiring temporary pacemaker implantation in the setting of likely MIS-C. Domico *et al.* report an 11-year-old patient with clinical criteria consistent with MIS-C and evidence of coronary dilation on echocardiogram but negative SARS-CoV2 polymerase chain reaction testing.^[8] Throughout the hospital course, the patient had worsening of their clinical status and developed high-grade 2nd degree AV block with hemodynamic compromise and required temporary pacemaker implantation with significant clinical improvement. With ventricular pacing, the patient improved substantially, and pacing was no longer required after approximately 48 h. In addition to conduction abnormalities, there has been a report of sinus bradycardia without hemodynamic compromise in a 27 month-old patient with suspicion of MIS-C, but the patient improved without intervention and no pacemaker implantation was required.^[9]

The association between AV block and infectious causes such as myocarditis and Lyme carditis appears to have the most direct correlation to the cases of AV block associated with MIS-C. AV block associated with both Lyme carditis and myocarditis is hypothesized to occur secondary to a host inflammatory response to acute

infection (spirochete in Lyme carditis and multiple different organisms in the case of myocarditis) and direct effect on the AV conduction system. There have been multiple reports of AV block associated with both myocarditis and Lyme carditis in pediatric patients and while the reported incidence of AV block in adult myocarditis has been reported to be 16%,^[10] reports in pediatric patients are less well-documented. Kalpatthi *et al.* describe a 7-month-old patient with myocarditis based on the presence of elevated troponin and decreased cardiac function who developed advanced 2nd degree AV block that required isoproterenol infusion. This patient was treated with both IVIG and steroids and had reversion to sinus rhythm and intact AV conduction 2–3 days after treatment.^[11] Batra *et al.* described a 7-year-old with endomyocardial biopsy-proven acute myocarditis who acutely developed high-grade 2nd grade AV block that progressed to complete AV block requiring a temporary transvenous pacemaker. The patient was treated with vasoactive medications including dopamine and milrinone along with both IVIG and steroids and had return of AV conduction within 3 days.^[12] In cases of pediatric patients with Lyme carditis, the reported incidence of AV conduction disturbances is 29%. Most cases are 1st degree AV block and documented cases of complete AV block associated with Lyme carditis are quite rare,^[13] especially compared with adults, where an incidence of complete AV block in Lyme carditis of 49% has been reported.^[14] Silver *et al.* reported two teenagers with evidence of acute Lyme infection (IgM+) and complete AV block that required isoproterenol infusion. One of the patients required temporary pacemaker implantation, but both had normalization of AV conduction with ceftriaxone and steroid therapy.^[15] Cases of AV block associated with fulminant myocarditis due to diphtheria infection have been reported in pediatric patients, but unfortunately, cases have led to patient death despite temporary pacemaker insertion and aggressive therapy.^[16-18]

There is an interesting similarity between the clinical course of AV block in pediatric patients in cases of Lyme carditis and myocarditis (including diphtheria-associated myocarditis) and MIS-C. The presumed pathophysiology of a host inflammatory response after infectious insult can explain the findings of AV conduction disturbances in all cases and is consistent with the improvement or resolution of conduction abnormalities throughout the disease course, though the potential severity of diphtheria-associated myocarditis may be an outlier. Conversely, there is a potential difference between MIS-C and these other entities based on the ability for direct infectious effect on the conduction system, especially in cases of Lyme carditis. Furthermore, the severity of conduction disease does occasionally parallel the severity of the MIS-C infection, which has been documented

in cases of AV block and both myocarditis and Lyme carditis.

The authors, to our knowledge, report the only pediatric case of complete AV block temporally associated with MIS-C that required permanent pacemaker implantation.^[1] However, based on review of prior reports, the possibility that the second patient had preexisting complete AV block must be considered. Since all other MIS-C patients with heart block have had their AV conduction improve or normalize, there is a distinct possibility that this patient had complete AV block prior to the acute illness and had worsening of their clinical status due to the MIS-C infection. The authors used postoperative AV block pediatric guidelines to guide their decision on permanent pacemaker implantation, as there is no current guidance for AV conduction abnormalities related to MIS-C. Since this clinical situation is exceedingly rare, the authors made their decision based on available evidence and appear to have made the correct choice since the patient remained atrial sensed and ventricular paced at 1 month of follow-up.

As pediatric cardiologists, we are accustomed to making decisions without the benefit of large-scale clinical trials, but MIS-C has magnified this conundrum. Although the data regarding MIS-C have been substantial and the sharing of information across the globe has been beneficial to both physicians and patients, we continue to operate in a suboptimal situation. Although pediatric patients with a history of MIS-C have not developed long-term consequences to date, we remain in the infancy of follow-up of these patients and cannot reliably predict outcomes. This is amplified further in the cases of AV conduction disturbances which are rarer than cardiogenic shock secondary to MIS-C so there is an additional difficulty in predicting which patients will have long-term conduction disease. In cases of myocarditis, the use of cardiac magnetic resonance imaging (MRI) during acute illness and follow-up may allow for improved counseling regarding sports participation and long-term risk of ventricular arrhythmias and sudden death. Unfortunately, in most patients with MIS-C, cardiac MRI was not possible or feasible, so we cannot truly know the burden of inflammation and fibrosis and there are no documented case reports of pediatric patients with an abnormal cardiac MRI in the setting of MIS-C and abnormal AV conduction. In cases such as those presented by Mehta *et al.*, a cardiac MRI may give additional information if there is evidence of late gadolinium enhancement in the area of the AV node/His/Purkinje system.

The true importance of this case series is to highlight the potential for hemodynamically significant AV conduction disturbances in pediatric patients with MIS-C. While these cases are rare, the authors present two patients

that required temporary pacemaker implantation, one of which required implantation of a permanent system. While the majority of cases in the literature have not required acute intervention such as temporary pacing, most required intensive care support and vasoactive medications and there has been at least one documented case of cardiogenic shock and complete AV block secondary to MIS-C that required ECMO support.^[6] The cases presented by Mehta *et al.* had evidence of complete AV block on presentation, though other cases have shown acute worsening of AV conduction with progression to complete block. This highlights the importance of an elevated index of suspicion in addition to proper electrocardiographic and hemodynamic monitoring to increase the chance of prompt recognition and intervention. And it appears that with each passing week or month, we are faced with a new challenge. Recent reports of myocarditis with temporal association to the COVID-19 vaccine have increased and bear monitoring. Anecdotal cases of vaccine-related myocarditis appear to have a similar clinical presentation to MIS-C, so clinicians should be aware of these patients and the potential for the development of AV conduction abnormalities in addition to other changes related to MIS-C.

To close with an optimistic tone, cases of MIS-C, and more specifically AV conduction disturbances in MIS-C patients, are rare, especially compared to the incidence of COVID-19 in pediatric patients. As we continue to learn more about the long-term complications of MIS-C, we may be able to more accurately counsel our patients and families regarding the risks of recurrence of AV conduction abnormalities after initial presentation with advanced heart block. For the time being, proper follow-up, vigilance, and counseling of our families will be our greatest resource to properly recognize AV conduction abnormalities and prevent more severe outcomes.

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