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The Electrocardiogram in Multisystem Inflammatory Syndrome in Children: Mind Your Ps and Qs

Since its first description in Wuhan province in December 2019, coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has disrupted the health and economic welfare of millions of people around the world. Children were initially thought to be spared from severe disease.[1-3] However, in spring 2020, initial reports from Italy and the UK described a new multisystem inflammatory syndrome in children (MIS-C), with features of cardiovascular involvement and Kawasaki syndrome.[4-6] As of December 2020, almost 1300 cases of MIS-C and 23 deaths from this syndrome had been reported to the US Centers for Disease Control and Prevention.[3] MIS-C seems to crest about 1 month after the peak for positive SARS-CoV-2 testing in a region, and many children have antibodies to SARS-CoV-2 at presentation, suggesting that MIS-C is caused by a postinfectious inflammatory response.[7-10]

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Children with MIS-C typically present with fever, hypotension, multiorgan involvement, and markedly elevated inflammatory markers. The great majority of those affected have cardiovascular complications, which may include shock, ventricular dysfunction, coronary artery dilation and aneurysms, or arrhythmias.[7,8,10-12] Whereas acute cardiovascular involvement is frequent, its causes and long-term sequelae remain active areas of investigation. Potential pathophysiologic mechanisms include dysregulated inflammation, direct viral cardiomyocyte toxicity, and microvascular dysfunction, which in turn may cause not only shock and myocardial dysfunction, but also abnormalities of the cardiac electrical conduction (including bradyarrhythmias, tachyarrhythmias, and electrocardiogram [ECG] changes).[7,8,10-14]

In this volume of *The Journal*, Regan et al describe a review of ECGs obtained during hospital admission and follow-up of patients with MIS-C.[15] They found ECG abnormalities during the illness in the majority of patients (n = 42 [67%]). Findings included interval prolongations, decreased amplitude, and T-wave inversion. Most of those abnormalities were seen during hospital admission, improved before hospital discharge, and normalized at outpatient follow-up. All intervals, including PR, QRS, and QTc, were prolonged in patients with MIS-C during hospitalization. Depending upon the interval type (ie, PR, QRS, or QTc), 6%-11% of patients had conduction or repolarization delays for age at time of admission, 7%-17% during hospitalization, 2%-12% at time of discharge, and 2%-3% at the time of follow-up. PR prolongation was the most frequently encountered conduction delay (n = 16 [25%]) and the last one to normalize, with first-degree atrioventricular block (AVB) in 12% of patients at time of discharge (vs 2%-3 % with QRS or QTc prolongation at discharge). The authors also described an abnormal PR:heart rate slope, defined as a paradoxical lengthening of the PR interval at increasing heart rates in patients with a ≥5 bpm difference in heart rate on ≥2 ECGs. This finding supports conduction system involvement, beyond the expected PR prolongation due solely to changes in autonomic states.

Two pediatric series have reported conduction abnormalities in 19%-20% of patients with MIS-C.[13,14] One series described first-degree AVB with no progression to higher grade AVB whereas the other reported progression to second- or third-degree AVB in 75% of patients with first-degree AVB.[13,14] The first series describing first-degree AVB found no significant difference in cardiac enzymes, inflammatory markers, and ventricular dysfunction between patients with and without AVB, similar to findings of Regan et al.[14,15] The other series reported that all patients with AVB required admission to the intensive care unit (unrelated to conduction abnormalities) and had echocardiographic evidence of ventricular dysfunction.[13] In all series, the conduction abnormalities peaked during hospitalization, at a median of 6 days after onset of symptoms.[13,14] Although the etiology of AVB in MIS-C remains unclear, we hypothesize that it could be caused by inflammation and edema of the conduction tissue. Conduction abnormalities, including complete heart block, have also been described in viral myocarditis unrelated to coronavirus disease-2019, which is characterized by an inflammatory infiltrate of the myocardium on histopathology.[16]

The hypothesis that conduction disturbances in MIS-C result from diffuse myocardial inflammation and edema is supported by findings of decreased voltages and T-wave changes. The authors have described a sequence of ECG changes, including low QRS amplitude on admission, followed by precordial T-wave flattening and inversion, which normalized before discharge.[15] These dynamic ECG changes have been observed in a variety of conditions often associated with transient ventricular dysfunction, including pericarditis, myocarditis, acute coronary syndrome, myocardial contusion, and Takotsubo or stress cardiomyopathy.[17-21] Despite their frequency, little is known about the pathogenesis of those ECG findings, sometimes referred to as Wellen's

AVB	Atrioventricular block
ECG	Electrocardiogram
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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phenomenon. A case series described myocardial edema on cardiac magnetic resonance imaging associated with transient T wave inversion in the anterior precordial leads, supporting edema and inflammation as an underlying mechanism.[17,18] Similar mechanisms may be responsible for ECG changes in patients with MIS-C. Prior series have described elevated brain natriuretic peptide in 78-100% patients, elevated troponin in 50-95%, ventricular dysfunction in 35-100%, and coronary artery dilation/aneurysm in 14-48%.[8,10-12] A study using cardiac magnetic resonance imaging in 20 patients 11-29 days after MIS-C diagnosis found abnormal strain in all patients and myocardial edema in half of the patients.[22] Similar to ECG changes described in this manuscript, the finding of myocardial edema did not correlate with ventricular function (ejection fraction and strain). More recently, a study using functional echocardiographic assessment with deformation measures (global longitudinal strain, left atrial strain) showed that all patients with MIS-C had evidence of diastolic dysfunction, with decreased strain measurements compared with normal subjects, suggesting that myocardial involvement may be more frequent than initially thought.[23]

In summary, using serial ECGs in a single-center series, Regan et al provide a comprehensive study of ECG abnormalities during hospitalization for MIS-C, with findings of changes in ECG voltages, T-wave polarity, and conduction times. These frequent and transient ECG changes during the course of illness may reflect systemic inflammation and myocardial involvement during hospitalization for MIS-C, even in patients with preserved systolic function on echocardiogram. This emphasizes the importance of rigorous cardiology follow-up of all children who have had MIS-C, including those without ventricular dysfunction or coronary dilation during the acute phase. Multimodality cardiac testing will help us elucidate the pathophysiologic changes, their importance for long-term cardiac health, and risk of sudden cardiac death with return to play. ■

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