Cardiology in the Young

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Original Article

Cite this article: Shehab N and English RF (2023) Describing our experience with the effects of multisystem inflammatory syndrome in children with COVID-19 on the cardiovascular system. *Cardiology in the Young* **33**: 2312–2314. doi: 10.1017/S1047951123000173

Received: 20 June 2022
Revised: 23 December 2022
Accepted: 11 January 2023
First published online: 1 February 2023

Keywords:
MIS-C; myocarditis; COVID-19; cardiac biomarkers; ejection fraction; pericardial effusion

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Describing our experience with the effects of multisystem inflammatory syndrome in children with COVID-19 on the cardiovascular system

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Abstract

Cardiac involvement with multisystem inflammatory syndrome in children can include coronary artery abnormalities, ventricular dysfunction, conduction abnormalities, arrhythmias, pericarditis, and myocarditis. We report the cardiac findings in 34 patients with multisystem inflammatory syndrome in children admitted to a single institution. We looked at patient age, sex, brain natriuretic peptide levels, troponin levels, ejection fraction, presence of pericardial effusion, valvular changes, need for inotropic agents, and electrocardiogram findings. Our data showed that elevated brain natriuretic peptide did not predict troponin elevation and vice versa. Additionally, troponin rise was not a reliable marker for decreased left ventricular ejection fraction. All changes tracked were proven to be transient and resolved after initiating steroids, Intravenous immune globulin (IVIG), and occasionally anakinra.

Multisystem inflammatory syndrome in children was first described in April 2020[1] as a Kawasaki disease-like illness with multiorgan involvement. Patients present with mucocutaneous, conjunctival, gastrointestinal, haematologic, renal, respiratory, and/or cardiac symptoms. Based on the available literature, cardiac involvement with multisystem inflammatory syndrome in children can include coronary artery abnormalities, ventricular dysfunction, conduction abnormalities, arrhythmias, pericarditis, and myocarditis.[2–6]

We report the cardiac findings in patients with multisystem inflammatory syndrome in children admitted to a single institution. LV systolic function, brain natriuretic peptide levels, troponin levels, pericardial involvement, and electrocardiogram findings were assessed. We tracked the progression of these findings during hospitalisation and after discharge.

Materials and methods

This is a retrospective single-site chart review of patients less than 18 years of age with multisystem inflammatory syndrome in children admitted to Wolfson Children's Hospital in Jacksonville, Florida between October 2020 and October 2021.

A central computerised patient database was used to identify potential subjects. Patient information collected was specific to the hospital admission encounter for the multisystem inflammatory syndrome in children illness and included patient age, sex, brain natriuretic peptide levels, troponin levels, ejection fraction, presence of pericardial effusion, valvular changes, need for inotropic agents, and electrocardiogram findings. The progression of those findings was evaluated as well. Patients with multisystem inflammatory syndrome in children with existing cardiac pathologies prior to the diagnosis of multisystem inflammatory syndrome in children were excluded.

Definitions

Multisystem inflammatory syndrome in children

Per the CDC, children under the age of 21 are diagnosed with multisystem inflammatory syndrome in children when they present with fever for at least 24 hours in addition to laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalisation in greater than two organ systems (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological) and with no alternative plausible diagnosis. Patients must be positive for current or recent COVID-19 infection by reverse-transcriptase polymerase chain reaction, serology, or antigen test; or known or suspected COVID-19 exposure within the 4 weeks before the onset of symptoms.[7]

LV dysfunction

LV systolic dysfunction is defined as a subnormal LV ejection fraction. Borderline LV function is defined by LV ejection fraction between 50 and 55% and definite dysfunction is defined by LV ejection fraction <50%.

BNP levels

The reference range of brain natriuretic peptide levels per our institution was 1–100 pg/ml.

Troponin levels

The reference range of troponin levels was <0.04 ng/ml.

QT interval

Normal QTc is defined as less than 440 ms. QT interval between 440 and 460 was borderline. QT interval greater than 460 was considered prolonged. These criteria was used for all genders in our study.

First-degree AV block

Electrocardiogram shows PR interval >200 ms.

Right axis deviation

Electrocardiogram shows QRS angle >100 degrees.

Valve regurgitation

Valve regurgitation was graded based on the interpreting physician's qualitative assessment and colour flow mapping on ECHO.

Pericardial effusion

Severity of pericardial effusion is defined based on size. Trivial is seen only in systole, mild is <10 mm, moderate is between 10 and 20 mm, and severe is >20 mm.

Coronary artery dilation

Seen with z-score >+2.

Results

Forty-five paediatric patients were admitted to Wolfson Children's Hospital with multisystem inflammatory syndrome in children between October 2020 and October 2021. Thirty-four had cardiac involvement evidenced by elevation of brain natriuretic peptide or troponin, electrocardiogram changes, echocardiogram changes, and/or need for inotropes.

As seen in Table 1, the age of the patients with cardiac involvement ranged between 2 months and 16 years, and 28 were male.

After admission, patients with multisystem inflammatory syndrome in children were started on steroids ± Intravenous immune globulin (IVIG) as well as other immunomodulators if needed at the discretion of the rheumatologist. Thirty-one patients were started on IVIG and steroids. Three received only steroids and two received anakinra in addition to steroids and IVIG. Findings after admission are illustrated in Table 1.

Initial workup included complete blood count (CBC), comprehensive metabolic panel (CMP), inflammatory markers, troponin, and brain natriuretic peptide levels. Twenty-eight had elevated brain natriuretic peptide ranging between 102 and 4555 pg/ml. Eighteen had elevated troponin (0.05–16.34 ng/dl). Fifteen had both brain natriuretic peptide and troponin elevation. Twelve had brain natriuretic peptide elevated while troponin was within normal limits. Three patients had troponin elevated while brain natriuretic peptide was within normal limits. Four had neither brain natriuretic peptide nor troponin elevation.

Four patients with normal brain natriuretic peptide on admission had elevated brain natriuretic peptide 1–4 days after starting IVIG in addition to 28 patients that had further increase in brain natriuretic peptide after starting IVIG. Twenty-seven of the patients had brain natriuretic peptide elevation resolved by day 14.

Fifteen patients had elevated troponin 1–2 days after initiating IVIG; however, four had a decrease in troponin after starting therapy followed by transient elevation 4–5 days afterward. Seven had a steady decrease. Seven of these 15 patients had troponin levels within normal range prior to initiating IVIG.

Initial work up also included an electrocardiogram. Twenty-five patients had normal electrocardiograms. Three had QT prolongation, two had first-degree AV block, five had a right axis deviation, two had inferior T wave inversion, one had inferior ST depression and one had non-specific intraventricular conduction block.

Review of serial electrocardiograms, when obtained, revealed of the three patients with prolonged QT interval, two had normalisation of QT intervals at outpatient follow-up visits within 2 months after discharge. However, our data also showed that a total of four patients with previously normal QT interval developed prolonged QT during illness course. One patient had prolonged QT interval on days 6–14 which normalised at outpatient follow-up, one had prolonged QT interval days 2–6 which normalised at outpatient follow-up, and the other two patients were unfortunately lost to follow-up.

Table 1. Number of patients with specific cardiac changes on admission and during illness course

	Number of patients on admission	Number of patients during hospital stay	Total number of patient
Brain natriuretic peptide elevation	28	32	32
Troponin elevation	18	19	25
QT prolongation	3	7	7
AV block	2	2	2
Right axis deviation	5	5	5
T was inversion	2	2	2
ST depression	1	1	1
Non-specific conduction delay	1	1	1
Decrease in left ventricular ejection fraction	5	4	9
Mitral regurgitation	2	3	5
Pericardial effusion	10	18	18
Coronary artery dilation	1	3	4

https://doi.org/10.1017/S1047951123000173 Published online by Cambridge University Press

Other electrocardiogram findings included bradycardia on days 1 and 2 of admission after initiating therapy, one had first-degree AV block on day 1 which resolved on day 3, and one had first-degree AV block at presentation which never resolved. One patient with intraventricular conduction delay had a normal electrocardiogram at discharge as well as the one with right bundle branch block.

Echocardiogram done showed that a total of five patients had definite LV dysfunction with ejection fraction between 26 and 50% on presentation which normalised over 1–7 days. Four had normal ejection fraction at presentation which decreased below 55% on days 2 and 3 and normalised afterward.

A total of two had greater than trivial mitral regurgitation on admission that was resolved during the hospital stay. However, three patients without MR on admission developed MR during stay.

A total of 10 patients had pericardial effusion on admission with one patient showing transient worsening of effusion to small-moderate at days 4–5 and 7 showing persistence of trivial-small pericardial effusion until the time of discharge. Eight patients had no pericardial effusion on presentation but developed a small pericardial effusion throughout admission.

A total of one patient had right coronary artery (RCA) dilation on admission and three had dilation of left anterior descending artery (LAD) and RCA that developed during hospital stay. This was resolved in two and improved in one; however, this patient was lost to follow-up to confirm resolution.

Nine of the patients with cardiac involvement required inotropes and vasopressors due to hypotension and poor perfusion. Duration of therapy ranged between 1 and 9 days.

Discussion

Based on our results, 75% of multisystem inflammatory syndrome in children patients had cardiac involvement. 82% of these patients were male. The cardiac manifestations in our study included: elevation of cardiac biomarkers, decreased LVEF, pericardial effusion, valvular dysfunction, coronary artery dilation, conduction abnormalities, and/or QT prolongation.

However, it is important to note that the findings were inconsistent. Twelve had elevated brain natriuretic peptide with normal troponin and three had elevated troponin with normal brain natriuretic peptide. Interestingly, elevated brain natriuretic peptide/troponin did not translate to decreased LV ejection fraction. There were no trends seen that could predict electrocardiogram changes or need for inotropes. It is essential to consider all data, in addition to the clinical history and the physical exam, when considering the possibility of cardiac involvement related to multisystem inflammatory syndrome in children.

While steroids and IVIG were the mainstay therapy of all multisystem inflammatory syndrome in children patients admitted to Wolfson Children's Hospital, some patients required anakinra as well due to the progression illness and worsening of cardiac findings. Based on case report studies, anakinra was found to be beneficial in patients with unfavuorable response to IVIG and steroids.[8–9]

After initiating therapy, transient worsening was seen with the elevation of brain natriuretic peptide, troponin, and electrocardiogram changes, as well as echocardiogram changes. One possible explanation for this was that the large volume infused (40 ml/kg) may have caused volume overload, especially in patients with myocardial dysfunction. However, the decline in those markers and improvement seen after just a few days was reassuring.

Similar to what was seen in other studies,[10] all changes tracked were proven to be transient lasting less than 2 weeks and resolved after initiating steroids, IVIG, and occasionally anakinra, including the LV ejection fraction.

It is important to note that since the study is retrospective in nature, data points are limited by the work up done at that time. Even though in some cases, complete resolution of abnormalities were not confirmed, resolution was expected based on the trend of data values at that time.

Conclusion

The cardiac involvement in our review included findings suggestive of an inflammatory process such as elevated brain natriuretic peptide and troponin, non-specific electrocardiogram changes and conduction abnormalities, decrease in LVEF, as well as valvular abnormalities, and pericardial effusion. Our data shows that symptoms related to multisystem inflammatory syndrome in children and cardiac involvement can be expected to resolve after initiating therapy. Worsening of cardiac markers and function was transient, however in some cases, severe enough to require inotropic support.

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

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