Kawasaki Disease and MIS-C at a Community Children's Hospital in Pennsylvania: A Five-and-a-Half Year Retrospective Study

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Background
- Kawasaki disease (KD) is an acute vasculitis of childhood that affects medium-sized, extra-parenchymal muscular arteries, with a predilection for the coronary arteries.
- KD is one of the leading causes of acquired heart disease in children in developed countries. If untreated, 25% of patients will go on to develop coronary artery aneurysms. This risk is reduced 5-fold if treated with IVIG within 10 days of fever onset.[4]
- Diagnosis of classic KD requires presence of fever for at least 5 days, plus at least 4 of the following 5 key clinical features: changes in lips/oral cavity, bilateral conjunctivitis without exudate; polymorphous exanthem, erythema/edema of extremities and/or desquamation; cervical lymphadenopathy (≥1.5cm), usually unilateral.
- Incomplete KD should be considered in children with fever for ≥5 days and 2 or 3 clinical criteria (mentioned above) plus leukocytosis with neutrophil predominance, elevated ESR/CRP, and thrombocytosis.
- High-dose IVIG plus aspirin therapy within the first 10 days after fever onset has been shown to reduce the rate of coronary artery aneurysm formation from 25% to 5%.[4]
- In 2020 the world was struck by the COVID-19 pandemic, they described a high incidence of children with a severe form of KD called Multisystem Inflammatory Syndrome in Children (MIS-C).[5]

- These patients have presented with variable clinical manifestations including significant cardiac, respiratory, and gastrointestinal involvement, with variable expression of rash, red eyes and oral mucosal involvement.[6]

Study Aims & Objectives
- Describe and compare demographic, clinical, and laboratory features of children with complete and incomplete KD and MIS-C who were diagnosed and managed at the Lehigh Valley Reilly Children's Hospital in Allentown, Pennsylvania over a five-and-a half-year period.
- Evaluate the frequency of coronary artery aneurysm formation in our patient population.

Sample Size
- 113 charts were reviewed with a discharge diagnosis of KD or incomplete KD
- 33 patients met both diagnostic and inclusion criteria for KD
- 7 patients met diagnostic and inclusion criteria for MIS-C

Methods
- Patient charts were identified through querying the EPIC database during the time period of July 1, 2015-March 21, 2021 for the discharge diagnosis ICD-10 codes of Kawasaki disease (M30.3, Z87.39, I25.41) and ICD-10 codes of MIS-C (M35.81)

Inclusion and Exclusion Criteria
- *Inclusion*: Children age birth-18yo admitted at LVRCH over 5.5 years with discharge diagnosis of complete or incomplete KD or MIS-C.
- *Exclusion:* Children with a preceding cardiac condition, treatment at an outside hospital, or alternative diagnosis at discharge.

Results

Table 1. Demographics of Pediatric Patients

	All Patients (n=40)	Kawasaki Patients (n=33)	MIS-C Patients (n=7)
Age *median (IQR)[a]*	3.0 (5.0)	3.0 (4.0)	8.0 (10.0)
Gender n(%)			
Female	19 (47.5)	16 (48.5)	3 (42.9)
Male	21 (52.5)	17 (51.5)	4 (57.1)
Ethnicity n(%)			
Asian	3 (7.5)	3 (9.1)	0 (0.0)
Black or African American	7 (17.5)	6 (18.2)	1 (14.3)
Multi-racial	3 (7.5)	3 (9.1)	0 (0.0)
White or Caucasian	10 (25.0)	8 (24.2)	2 (28.6)

Hispanic or Latino	14 (35.0)	11 (33.3)	3 (42.9)
Other	1 (2.5)	0 (0.0)	1 (14.3)
Unavailable	2 (5.0)	2 (6.1)	0 (0.0)
Type of KD n(%)			
Complete	20 (50.0)	20 (60.6)	---
Incomplete	13 (32.5)	13 (39.4)	---
MIS-C	7 (17.5)	---	7 (100.0)

Table 2. Clinical Characteristics

	All Patients (n=40)	**Kawasaki Patients (n=33)**	**MIS-C Patients (n=7)**
Total Duration of Fever in Days *median (IQR)*[a]	8.0 (3.0)	8.0 (4.0)	9.0 (4.0)
Rash n(%)			
Yes	33 (82.5)	30 (90.9)	3 (42.9)
No	7 (17.5)	3 (9.1)	4 (57.1)
Skin Peeling n(%) (n=33[b])			
Yes	8 (24.2)	8 (26.7)	0 (0.0)
No	25 (75.8)	22 (73.3)	3 (100.0)
Conjunctivitis n(%)			
Yes	33 (82.5)	29 (87.9)	4 (57.1)
No	7 (17.5)	4 (12.1)	3 (42.9)
Cervical LAD n(%)			
Yes	24 (60.0)	21 (63.6)	3 (42.9)
No	16 (40.0)	12 (36.4)	4 (57.1)
Mucosal Involvement n(%)			
Yes	30 (75.0)	24 (72.7)	6 (85.7)
No	10 (25.0)	9 (27.3)	1 (14.3)
Erythema/Edema of Extremities n(%)			
Yes	27 (67.5)	24 (72.7)	3 (42.9)
No	13 (32.5)	9 (27.3)	4 (57.1)
Atypical Symptoms n(%)[d]			
Diarrhea	8 (20.0)	5 (15.2)	3 (42.9)
Abdominal pain	13 (32.5)	9 (27.3)	4 (57.1)
Vomiting	13 (32.5)	8 (24.2)	5 (71.4)
Arthritis or Arthralgia	5 (12.5)	5 (15.2)	0 (0.0)
None	19 (47.5)	18 (54.5)	1 (14.3)

Table 3a. Clinical Lab Values: Kawasaki Disease Patients

	Number of observations	Central Tendency (*mean[a]/median[b]*)	Dispersion (*s.d.[a]/IQR[b]*)
Hemoglobin admission *mean (s.d.)*	33	10.8	1.17
WBC admission *mean (s.d.)*	32	15.2	5.50
Platelet peak *median (IQR)*	24	466.0	398.25
ESR admission *mean (s.d.)*	27	76.2	31.85
CRP admission *median (IQR)*	30	76.9	105.08

Table 3b. Clinical Lab Values: MIS-C Patients

	Number of observations	Central Tendency (*mean[a]/median[b]*)	Dispersion (*s.d.[a]/IQR[b]*)
Hemoglobin nadir *median (IQR)*	7	8.3	1.90
WBC admission *mean (s.d.)*	7	6.6	1.41
Platelet admission *median (IQR)*	7	148.0	178.00
ESR admission *median (IQR)*	6	29.0	30.50
CRP admission *median (IQR)*	6	147.0	156.53
Albumin nadir *median (IQR)*	7	2.1	.90
Fibrinogen admission *mean (s.d.)*	6	432.8	73.93
Ferritin admission *median (IQR)*	5	649.0	820.0
BNP peak *median (IQR)*	4	2815.5	3157.00
D-dimer peak *median (IQR)*	7	5.3	3.33
Troponin peak *median (IQR)*	4	0.15	0.17

Table 4. Additional Lab Characteristics

	All Patients (n=40)	Kawasaki Patients (n=33)	MIS-C Patients (n=7)
COVID IgG n(%)			
Positive	7 (17.5)	0 (0.0)	7 (100.0)
Negative	4 (10.0)	4 (12.1)	0 (0.0)
Not Done	29 (72.5)	29 (87.9)	0 (0.0)
Rapid Viral Panel Positive n(%)			
Yes[a]	3 (7.5)	3 (9.1)	0 (0.0)
No	35 (87.5)	30 (90.9)	5 (71.4)
N/A	2 (5.0)	0 (0.0)	2 (28.6)
Blood Culture n(%)			
Positive	1 (2.5)	1 (3.0)	0 (0.0)
Negative	28 (70.0)	22 (66.7)	6 (85.7)
Not Done	11 (27.5)	10 (30.3)	1 (14.3)
Initial Echocardiogram n(%)			
Normal	39 (97.5)	32 (97.0)	7 (100.0)
Coronary Artery Abnormality	1 (2.5)	1 (3.0)	0 (0.0)

a. All 3 positives were positive for Rhinovirus/Enterovirus

Table 5. Treatment and Follow-up

	All Patients (n=40)	Kawasaki Patients (n=33)	MIS-C Patients (n=7)
IVIG Doses n(%)			
One Dose	30 (75.0)	25 (75.8)	5 (71.4)
Two Doses	8 (20.0)	7 (21.2)	1 (14.3)
No Doses	2 (5.0)	1 (3.0)	1 (14.3)
Aspirin n(%)			
Yes[a]	38 (95.0)	32 (97.0)	6 (85.7)
No	2 (5.0)	1 (3.0)	1 (14.3)
Steroids n(%)			
Yes	7 (17.5)	3 (9.1)	4 (57.1)
No	33 (82.5)	30 (90.9)	3 (42.9)
ECHO Follow-up n(%)			
Normal	29 (72.5)	24 (72.7)	6 (85.7)
Abnormal	1 (2.5)	1 (3.0)	0 (0.0)
Not Done	10 (25.0)	8 (24.2)	1 (14.3)
ECHO follow-up CAA (n=30) n(%)			
Yes	1 (3.3)	1 (4.0)	0 (0.0)
No	29 (96.7)	24 (96.0)	6 (100.0)
Coronary Aneurysms Present n(%)			
Yes[c]	1 (2.5)	1 (3.0)	0 (0.0)
No	39 (97.5)	32 (97.0)	7 (100.0)
Lost to follow-up n(%)			
Yes	13 (32.5)	11 (33.3)	1 (14.3)
No	27 (67.5)	22 (66.7)	6 (85.7)

Discussion

- At our institution, MIS-C was seen in children of older school age compared to KD which was seen in younger children.
- There was no significant difference in disease prevalence between males and females which is inconsistent with literature that suggests a male predominance in both KD and MIS-C.[1]
- Black/African American and Asian children diagnosed with KD and MIS-C appear to be over-represented compared to the population of Black/African American and Asian children in our community.
- In the MIS-C patients, GI symptoms were more prevalent compared to the KD patient population.
- Lab values seen in our study were consistent with reported known laboratory findings in KD[2] with elevated inflammatory markers, hypoalbuminemia, and thrombocytosis
- MIS-C also had elevated inflammatory markers but tended to have thrombocytopenia and anemia. D-dimer and BNP were elevated, likely indicating a hypercoagulable state and myocardial strain which is a hallmark feature in MIS-C[1]

- There was only one patient who had a coronary artery aneurysm (CAA) based on initial ECHO and follow up ECHO, and this was in the KD patient group. This is lower than the reported 10-15% in the literature[3]
- Of note, almost one-third (32.5%) of all patients were lost to follow up and never received a follow up ECHO.

Conclusions

There are a lot of similar features between KD and MIS-C including an inflammatory component and cardiac involvement. GI symptoms appear to be more prevalent in patients with MIS-C. Overall, both diseases are treated very similarly. Further research can be done to compare outcomes in KD and MIS-C patients treated with similar protocols.

Limitations
- Small sample size which limits the power of our study
- Data is limited to what was documented in the EPIC database since this was retrospective. It is possible that some clinical features were present but not specified in EPIC.

References

1. Lee, Pui, et al. "Distinct Clinical and Immunological Features of SARS-COV-2-Induced Multisystem Inflammatory Syndrome in Children." *The Journal of Clinical Investigation*, 23 July 2020, www.jci.org/articles/view/141113/pdf.
2. McCrindle, Brian W., et al. "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association." *Circulation*, 29 Mar. 2017, www.ahajournals.org/doi/10.1161/CIR.0000000000000484.
3. McCrindle, Brian W., et al. "Medium-Term Complications Associated With Coronary Artery Aneurysms After Kawasaki Disease: A Study From the International Kawasaki Disease Registry." *Journal of the American Heart Association*, 28 July 2020, www.ahajournals.org/doi/10.1161/JAHA.119.016440.
4. Newburger, Jane W., et al. "Kawasaki Disease." *JACC*, Journal of the American College of Cardiology, 12 Apr. 2016, www.onlinejacc.org/content/67/14/1738.abstract.
5. Verdoni, Lucio, et al. "An Outbreak of Severe Kawasaki-like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic: an Observational Cohort Study." *The Lancet*, Elsevier, 13 May 2020, reader.elsevier.com/reader/sd/pii/S014067362031103X?token=3BBED107BB1940849D2CF40FA698D2C31D490D0F4A304CB47FE4B275EE56AFB7723C225D96BF2DDA72ED09B13701B7E9.
6. Whittaker, Elizabeth, et al. "Clinical Characteristics of Children With SARS-CoV-2–Associated Pediatric Inflammatory Multisystem Syndrome." *JAMA*, American Medical Association, 21 July 2020, jamanetwork.com/journals/jama/fullarticle/2767209.