Bilateral axillary aneurysms with early thrombotic changes in an infant: Thebad sequalae of missed Kawasaki disease!

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Coronary aneurysms in untreated Kawasaki disease (KD) are well known to occur and sometimes are accompanied with systemic aneurysms. We describe the case of a male infant who presented with bilateral axillary aneurysms, the sequelae of missed KD.

Case Report

A nine-month-old male infant, born of Indian parentage, presented with pulsatileswellings in both axilla for lasteight days. He was otherwise a well thriving child. At four months of age, he had fever which lasted for 19 days. It was associated with diffuse macular rashes, non-exudative conjunctivitis, cheilitis andstrawberry tongue. He was diagnosed as multisystemic inflammatory syndrome in children (MIS-C) andtreated with steroids;however,he did not receive immunoglobulin therapy. On examination, he had bilateral axillary swellings, 20 x 15 millimeters in size. Radial pulses were palpable and there were no signs of peripheral ischemia. The systemic examination was normal.

Investigations atfour months of ageshowed thrombocytosis (12,93,000/cu mm) and elevated inflammatory markers (C-reactive protein 139 mg/L, Erythrocyte sediment rate 120 mm/hour). The hemogram during current admission (9 months of age) showed marked thrombocytosis (650,000/cu mm), leukocytosis {20600 cells/cu mm (Neutrophils 14%/Lymphocytes 69%)} and raised inflammatory markers (ESR 45 mm).Ultrasonogram showed bilateral hypoechoic cystic saccular aneurysms of size 18 x 12 millimeters in right axilla and 29 x 15 mm over medial aspect of the left proximal arm, communicating with right and left axillary artery respectively. Color doppler showed a turbulent vascular flow in both aneurysms. Mild mural thickening was also noted in bilateral aneurysms with maximum depth 1.4 mm on right side and 1.7 mm on left side, indicating early thrombus formation. CT angiography confirmed the axillary aneurysms; however, other systemic arteries were normal. Echocardiogram showed giant aneurysms affecting multiple coronary arteries {Left main coronary artery 9 millimeters (ZScore 17.9), Left anterior descending artery 3.5 millimeters (Z score 9.4), Left circumflex artery 4.2 millimeters, and right coronary artery 3.5 millimeters (Z score 5)}. This was sequelae of severe infantile KD thatthe child had at the age of four monthsand considering the consequences and long-term significant morbidity associated withgiant coronaryaneurysms, he was treated with infliximab and steroids. The anticoagulation (low-molecular-weightheparin) and low-doseaspirin were added.

Conclusion

We describe a rare and serious complication due to missed KD.Giant axillary aneurysms are a challenge to treat and long term follow up with anti-coagulants for thrombosis prevention have to be balanced with chance of aneurysmal rupture.

Myocardial dysfunction on Cardiac Magnetic Resonance Imaging in children with Kawasaki Disease who had had spontaneous defervescence: anobservational study after a mean follow-up of 11.7 years.

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Introduction and objectives:A small proportion of children with Kawasaki disease (KD) have spontaneous defervescence. There is paucity of literature on long-term follow up of such patients. The present study aimedto evaluate changes in myocardium and coronary arteries in 10 patients with KD who had had spontaneous defervescence at least 8 years ago and had not received intravenous immunoglobulin(IVIg).

Methods: This prospective observational study was conductedbetween July 2021 and September 2022 in the Pediatric Allergyand Immunology Unit, Advanced Pediatrics Centre, the Department of Radiodiagnosis and Imaging, the Department of Cardiology,Post Graduate Institute of Medical Education and Research, Chandigarh. Tenpatients with mean interval of 11.7years(range 8-21 years)after spontaneous defervescence of KD underwentCardiac Magnetic Resonance Imaging(CMRI)on 3 Tesla – PhilipsIngeniaplatform. 2D-echocardiography(2DE)was also carried out the same day (Philips Epic 7). Diagnosis of KD was based on American Heart Association guidelines (2004).

Results: Mean age of the study cohort was 20.3years (range 16- 28 years). Of the 10 patients who underwent CMRI, 3 had lowejection fraction (EF). One amongst these alsohad elevated T1 values (1345ms in septum in midcavity and 1245ms in rest of the myocardium) suggestive of myocardial fibrosis. None of the 10 patients, however, had late gadolinium enhancement. None of the patients had any overt coronary artery abnormalities on 2DE.

Conclusion: One-third of patients with KD who hadhad spontaneous defervescence (and did not receive IVIg) were shown to have myocardial dysfunction on follow up.CMRI is a useful imaging modality in patients with KD on long term follow-up as it helps in assessment of myocardial function and changes in myocardium that are not picked on routine 2-DE. Results of our study suggest that children with KD can have significant non-coronary cardiac morbidity - our findings, however need to be confirmed on a larger cohort.

Kawasaki Disease meandering around common gastrointestinal symptoms: A diagnostic conundrum

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- **Background:** Kawasaki disease (KD) is thecommonest childhood vasculitis. Gastrointestinal(GI) symptoms can occasionally be the forerunner of KD and may pose a diagnostic challenge to treating physicians.There is paucity of literature on GI presentationsof KD.
- **Aims:**To evaluate children with KD who had predominant GI presentations.
- **Methods:**We analysed case records of all childrenwithKD with GI presentations during the period January 1994-April 2021.Diagnosis of KD was based on American Heart Association criteria.
- **Results**: From January 1994 to April 2021, we diagnosed 1078children with KD. Of these, 24(19 boys; 5 girls) had a GI presentation.All had GI symptoms during acute phase of disease.Median age at diagnosis was 3.5 years (range 4 weeks-13 years). Manifestations included acute gastroenteritis(n=8); blood in stools(n=3); upper gastrointestinal bleed due to duodenal ulcer(n=1);abdominal distension, vomiting, features suggestive of subacuteintestinal obstruction, intussusception(n=2); colitis (n =3); mesenteric mass(n=1), ulcers in colon(n=1); gall bladder perforation(n=1); jaundice(n=7) and acute fulminant liver failure(n=1).Delays in diagnosis ranged from 7 days-4 weeks. Twentychildren respondedto single dose of IVIG (2g/Kg);3 children required a second dose of IVIG, infliximab was given in one case. 2-D

echocardiography examination revealed normal sized coronary arteries in 21 patients. One patient with acute fulminant liver failure had left main coronary artery(LMCA) aneurysm (2.8mm;+2.7z)and macrophage activation syndrome and succumbed to illness.Two patients with jaundice had multiple aneurysms (LMCA= 6.17 mm (+7.42); LAD=4.68mm(+6z); RCA= 7.5mm (+10.63Z))and dilated right coronary artery (4.2 mm) respectively.

Conclusions: None of the GI symptoms are part of the AHA criteria. GI presentation of KD is not uncommon and may create diagnostic confusion for the treating physician. One must not overlook the common characteristic features and laboratory criteria in presence of such unusual findings because they can help in early diagnosis and management of KD, ultimately reducing morbidity.

Title: Kawasaki Disease Shock Syndrome - Our experience at Chandigarh, North India

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Background:

Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause

that preferentially affects the coronary arteries. KD usually seen in children below the age of S. Cardiovascular manifestations can be prominent during acute phase of KD and can lead to significant morbidity and mortality (1). Coronary artery abnormalities (CA) can occur in 15-20% of untreated patients (2). Hemodynamic instability can also occur during the acute phase of the illness and may present as shock. This is an unusual presentation of KD and the diagnosis can be easily missed. We report here two cases who presented with fever and hypotensive shock, and was diagnosed as Kawasaki disease shock syndrome (KDSS). Approximately 5% patients with Kawasaki disease (KD) can present with cardiovascular collapse- the KD Shock Syndrome (KDSS). This is an unusual presentation of KD and is often confused with septic shock. As a result, the diagnosis can be easily missed. We report the profile of patients with KDSS from a cohort of 1014 KD patients at Pediatric Rheumatology Clinic, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, North-West India.

Patients and methods: 1014 children were diagnosed to have KD during the period January 1994-December 2019. Case files of patients with KDSS were retrieved and clinical details recorded.

Results: Of the 1014 cases during the period 1994-2019, 35 (19 boys; 16 girls) had hemodynamic instability. Median age at diagnosis was 7 years (range 6 months-14.5 years).

All patients required inotropic support. Infection triggered KD was seen in 7 patients and most common organism was Staphylococcus aureus. Initial diagnosis of toxic shock syndrome (TSS) had been given in 18 (51.4%) patients. Thrombocytopenia was seen in 13 (37.14%). We were able to perform NT-proBNP in 18 patients and median value was 921.5 (225-9450) pg/mL. First line treatment was intravenous immunoglobulin (IVIg) therapy. Second line therapy was required in 13 patients infliximab in 5; second dose IVIg in 4 and glucocorticoids in 7. Coronary artery abnormalities (CAs) were seen in 7 (20%) - of these, two had giant aneurysms in left anterior descending coronary artery and right coronary artery. Seven had severe myocardial dysfunction secondary to myocarditis. We recorded one death amongst the patients with KDSS.

Discussion and Conclusion: Both KDSS and TSS can present to the Emergency Room with fever, rash, and shock. Clinical differentiation between the two entities is crucial as management protocols for the 2 conditions are completely different. Delays in recognition of KDSS are not uncommon and may result in avoidable morbidity and occasional mortality. Patients with KDSS are at an increased risk of developing CAAs.

Gene expression analysis of inflammation-induced endothelium dysfunction markers in Kawasaki disease patients from North India

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Abstract: Kawasaki disease (KD) is an acute medium vessel vasculitis, predominantly affecting children <5 years of age. It is the most common childhood vasculitic disorder causing inflammation of the medium sized coronary arteries. The initial inflammatory insult to the endothelium during the acute phase of KD leads to endothelial injury, while the persistent chronic & smouldering inflammation during the chronic phase leads to endothelial dysfunction.

Design and Methods: Present study highlights mRNA levels of inflammation-induced endothelium dysfunction markers in patients with KD from India. KD patients were enrolled at different time intervals in 3 groups (20 each) as per AHA guidelines and 20 age matched healthy controls.

Group 1: KD diagnosed > 6months-1.5 years; **Group 2**: >1.5 - 3 years ; **Group 3**: > 3 - 4.5 years prior to enrollment

1. Flowcytometric analysis for reactive oxygen species, nitric oxide estimation and characterization of circulating endothelial cells and endothelial progenitor cells was carried out using different antibodies tagged with different fluorochromes.
2. Complementary DNA (cDNA) converted from extracted whole blood RNA was used to perform real-time PCR analysis. Genes for inflammation and endothelial dysfunction were selected as listed in Table 1. Comparison of fold change [2^(-ΔΔCT) method] between patients and controls were performed using the Mann-Whitney Utest.

Results: Real-time PCR analysis for intra group 1 revealed elevated CXCL8, pecam-1, osteopontin in KD patients with coronary artery aneurysms (CAA) as compared to KD patients without CAA (p=0.038), (p= 0.05) , (non-significant) respectively. Increased levels of endoglin, resistin, VEGF-A and leptin was found in patients without CAA as compared to patients with CAA (non-significant). Intragroup

analysis for group 2 showed increased Pecam-1, CXCL8, resistin, osteopontin and decreased levels of leptin, pentraxin-3 in KD with aneurysms as compared to patients without CAA (non-significant). Levels of endoglin, VEGF-A were comparable. Intragroup analysis for group 3 patients revealed elevated VEGF-A, CXCL8, Leptin, Pentraxin-3, resistin in patients with CAA as compared to KD without aneurysms while pecam-1, endoglin and osteopontin were comparable in both. Significant difference was also found for *Leptin* gene in intergroup analysis (1&2) in patients without CAA.

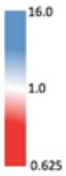
Conclusion: Real time analysis revealed altered gene expression in Kawasaki disease patients with aneurysms.

Keywords: Endothelial, inflammation, Real-time PCR analysis, angiogenesis

Table 1:

S. no.	Gene	Full forms	Function
1.	*CXCL8*	C-X-C motif chemokine ligand 8	Inflammatory cytokine
2.	*Pecam-1*	Platelet endothelial cell adhesion molecule	Migration of leukocytes, formation of vessels, and integrin activation
3.	*Pentraxin -3*		Inflammatory mediator
4.	*ENDOGLIN*		Pro-angiogenic, protects endothelial cells and regulates NO-dependent vasodilatation
5.	*VEGF-A*	Vascular endothelial growth factor	Induces proliferation and migration of vascular endothelial cells
6	*Leptin*		Pro-inflammatory and promotes angiogenesis
7	*Resistin*		Increases expression of endothelin-1, MCP-I, cytokines and upregulates adhesion molecules
8	*Osteopontin*		Pro inflammatory cytokine, controls monocyte adhesion , migration, survival, differentiation

Figure 1: Heat map representing fold changes of various genes in Intragroup analysis (Group 1, 2, 3) in patients with KD and HC.



Group 1

	KD without CAA										KD with CAA										HC															
Target	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19		HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC
CXCL8	0.14	5.48	0.10	0.91	0.32	0.09	0.37	0.67	0.28	0.75	0.01	8.46	477	0.69	0.03	3330	8.92	0.03	0.24		0.96	0.18	0.44	0.10	0.25	2.81	1.71	0.25	0.22	0.64	0.49	3.14	1.60	0.61	1.01
Pecam-1	1.04	1.37	0.82	0.46	0.50	0.65	0.47	0.74	0.50	0.40	1.90	1.11	0.67	0.66	1.37	0.95	0.62	0.46	0.13		1.33	0.82	0.91	0.69	0.94	1.54	0.88	1.20	0.95	1.16	0.80	1.07	1.29	0.69	1.13
Pentraxin-3	0.36	1.30	0.48	1.55	0.95	1.74	0.49	1.11	6.54	0.75	1.70	0.95	0.44	1.30	NA	1.02	0.32	1.75	0.80		1.14	0.57	1.55	0.89	1.11	1.01	1.01	1.36	0.72	0.98	0.95	1.07	0.62	1.24	1.29
Endoglin	0.66	1.03	1.12	0.54	0.23	1.00	0.19	0.75	0.96	0.72	0.93	0.91	0.57	0.88	1.42	0.40	0.59	0.58	0.39		1.05	1.17	0.81	1.42	0.64	1.10	0.61	1.41	1.16	0.92	0.78	1.40	0.81	1.03	1.19
VEGF-A	0.96	1.69	1.08	0.56	1.07	0.82	0.25	1.62	2.00	0.74	1.02	1.68	1.27	1.11	0.57	0.70	0.54	0.49	0.61		1.13	1.11	0.80	0.73	1.10	1.24	0.92	1.52	0.71	1.00	1.00	1.00	1.02	0.89	1.11
Leptin	0.17	0.70	1.21	0.15	0.13	1.29	0.17	0.25	0.28	0.52	NA	0.15	1.07	0.31	NA	0.52	0.18	0.17	0.24		1.65	1.12	0.54	1.13	0.36	2.49	0.63	0.45	1.38	0.63	1.03	1.54	2.47	0.27	1.53
Resistin	2.82	0.27	0.39	0.56	2.75	0.97	1.77	2.74	0.81	0.57	0.86	0.36	0.32	0.59	1.61			2.00	0.40		0.86	1.81	0.64	1.07	1.51	0.62	2.36	1.60	0.42	2.36	1.34	0.31	0.56	0.87	2.05
Osteopontin	0.71	0.61	1.57	1.87	0.19	0.82	1.41	0.25	1.04	0.27	0.12	0.66	0.34	4.76	3.41	0.80	0.91	0.04	0.04		1.07	1.95	0.48	0.73	1.44	0.95	0.63	1.73	0.56	0.63	2.39	0.66	1.97	0.81	0.63
GAPDH	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Group 2

	Without CAA														With CAA														HC													
Target	P20	P21	P22	P23	P24	P25	P26	P27	P28	P29	P30	P31	P32	P33	P34	P35	P36	P37	P38	P39	P40	P41	P42	P43		HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC
CXCL8	0.13	2.56	1.18	1.07	44.7	2.36	0.56	0.07	0.47	0.76	0.49	1.22	1.87	2.02	7.69	4.27	3.65	2.69	30.4	0.49	0.09	0.15	0.39	8.73		2.69	0.37	1.51	0.60	1.10	2.11	1.69	0.28	2.35	0.48	0.89	5.65	0.88	0.20	1.00
Pecam-1	0.12	0.75	0.86	0.66	0.92	0.89	0.42	0.52	0.81	1.23	0.69	0.97	0.89	0.44	1.60	0.58	0.85	0.81	0.52	0.76	0.76	0.67	0.86	1.23		1.00	1.00	1.76	0.84	0.68	1.15	0.83	1.05	1.30	0.75	1.03	1.39	0.88	0.82	1.00
Pentraxin-3	0.38	0.86	0.56	0.66	1.22	4.05	1.77	1.09	1.18	14.4	0.51	2.34	1.27	1.36	3.05	1.04	0.39	1.11	1.19	0.41	3.42	0.84	0.55	1.07		0.88	1.14	1.39	0.92	0.78	0.83	0.86	1.40	1.11	1.35	0.67	1.03	0.79	1.23	1.00
Endoglin	0.43	1.01	0.89	0.77	1.41	0.98	1.19	0.97	0.96	3.04	0.54	1.12	0.74	0.68	1.21	0.74	0.63	1.19	1.11	0.67	0.95	1.10	1.15	0.64		0.68	1.48	1.18	1.29	0.66	1.00	0.94	1.06	1.37	0.97	0.75	1.03	0.80	1.21	1.00
VEGF-A	0.36	0.50	0.71	0.56	1.01	0.90	1.67	1.42	1.25	5.32	1.49	3.05	0.86	1.23	6.66	0.75	0.58	0.88	1.33	0.31	1.12	0.98	0.35	0.72		1.02	0.98	1.71	0.86	0.68	0.81	0.87	1.41	1.41	0.84	0.84	1.12	0.78	1.14	1.00
Leptin	0.28	1.65	0.85	4.19	4.78	6.90	0.21	0.69	0.99	3.21	0.47	2.34	0.18	0.83	0.29	0.64	3.46	3.25	0.38	1.03	1.49	0.19	0.25	0.23		0.63	1.58	2.49	1.13	0.36	1.08	1.04	0.89	0.62	0.98	1.65	1.38	0.72	5.82	1.00
Resistin	0.23	0.27	0.31	0.63	0.60	0.41	0.79	1.61	0.61	2.42	0.10	0.33	0.29	0.24	1.44	0.81	0.44	0.74	0.25	0.44	0.89					1.17	0.86	0.62	1.07	1.51	1.01	1.23	0.80	1.23	1.40	0.58	2.49	0.97	0.42	1.00
Osteopontin	0.01	1.79	2.68	0.67	0.31	2.31	0.43	0.86	1.01	4.59	0.20	0.59	1.08	0.71	0.56	4.12	5.80	1.63	0.61	0.79	0.02	0.14	1.26	0.74		1.11	0.90	0.95	0.73	1.44	1.32	1.07	0.71	2.60	0.36	1.06	1.91	0.49	1.07	1.00
GAPDH	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00		1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Group 3

	Without CAA										With CAA										HC															
Target	P44	P45	P46	P47	P48	P49	P50	P51	P52	P53	P54	P55	P56	P57	P58	P59	P60	P61	P62	P63	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC	HC
CXCL8	1.70	0.85	1.89	0.76	0.57	0.28	0.35	0.31	3.22	1.05	0.58	2.52	8.80	0.64	0.27	0.14	8.34	0.49	0.11	0.70	1.52	1.61	0.51	3.47	1.04	0.28	1.22	0.49	0.25	0.45	1.87	1.20	0.25	1.14	3.51	1.60	0.61
Pecam-1	0.61	0.92	0.54	0.35	0.85	0.84	0.68	0.51	1.13	0.67	0.75	1.71	0.90	0.39	0.79	0.53	0.55	0.49	0.72	0.61	1.05	1.03	0.92	0.96	1.64	0.64	1.05	1.29	0.74	0.82	0.97	1.26	1.46	0.74	0.92	1.29	0.69
Pentraxin-3	2.41	2.62	2.08	1.90	0.48	0.93	1.43	1.36	1.53	NA	1.77	4.15	0.82	2.12	2.20	5.43	313	2.73	1.16	1.75	0.66	1.30	1.16	1.39	0.82	0.87	1.32	0.88	0.86	1.21	0.78	1.06	1.73	0.95	0.61	0.62	1.24
Endoglin	1.30	1.05	0.79	0.60	0.69	0.79	1.09	1.11	1.17	1.58	1.27	2.22	0.70	0.33	0.81	0.80	17.8	1.08	1.00	0.96	1.14	1.13	0.77	1.01	1.04	0.95	1.22	0.70	1.17	1.03	1.06	0.91	1.21	0.83	1.00	0.81	1.03
VEGF-A	2.35	2.23	1.18	0.66	0.84	0.64	1.58	1.51	1.12	1.07	1.01	4.19	1.21	0.67	1.27	1.06	6.30	1.10	1.35	0.78	0.89	1.14	0.99	1.17	1.33	0.64	1.10	1.03	0.88	0.93	1.07	1.00	1.57	0.64	1.00	1.02	0.89
Leptin	1.04	3.12	1.89	0.68	0.87	1.14	0.91	0.20	2.09	0.17	0.69	0.38	1.33	8.20	0.21	1.33	113	0.17	0.31	0.51	1.36	0.88	0.83	2.55	0.96	0.41	0.64	1.75	0.89	0.92	0.90	1.21	1.61	0.45	1.38	2.47	0.27
Resistin	0.32	0.21	5.09	0.87	0.45	1.11	0.80	0.63	1.77	2.00	0.39	0.61	0.41	3.54	1.01	0.58	9.84	0.43	0.87	0.42	1.00	0.80	1.25	0.78	1.33	0.96	1.80	1.53	0.36	1.41	1.39	0.51	1.49	1.60	0.42	0.56	0.87
Osteopontin	1.08	0.76	1.00	0.15	1.69	0.72	1.78	0.63	1.41	0.04	1.44	4.13	0.59	0.15	0.45	0.38	NA	0.24	0.84	0.85	0.93	0.91	1.18	2.51	1.01	0.40	0.79	2.00	0.63	0.43	2.50	0.92	1.03	1.73	0.56	1.97	0.81
GAPDH	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

KD –Kawasaki disease
HC –Healthy control
CAA-Coronary artery aneurysms

CLINICAL PROFILE, NATURAL HISTORY OF KAWASAKI DISEASE WITH CORONARY ARTERY INVOLVEMENT IN CHILDREN AT TERTIARY CARE HOSPITAL

BACKGROUND

Kawasaki disease is an acute febrile illness of children, globally with highest incidence in Asian children. Approximately 20-25% of untreated children develop coronary artery abnormalities (CAA) including aneurysms, whereas<5% of children treated with intravenous immunoglobulin (IVIG) develop CAA. Coronary artery aneurysms from KD contributes about 5% of acute coronary syndromes (ACS) in adults <40 years of age. Hence, this study was undertaken to study clinical profile, natural history of Kawasaki disease which can be used to early diagnosis and to reduce complications in children with Kawasaki disease in a tertiary care center.

OBJECTIVES

To determine the severity of coronary artery involvement in a child with Kawasaki disease and the association with inflammatory markers, Covid19 and response of treatment.

METHODOLOGY

This prospective observational study was conducted at the department of Rainbow Children's Hospital and perinatal Centre, Hyderabad, India, from 6th November 2020 to 31st December 2021. 40 patients aged below 18 years with Kawasaki disease with involvement of coronary arteries were included. Data regarding age, sex, clinical andlaboratory parameterswere collected. 2D echowas done and patients were managed accordingly. During the period of study, children were followed after 1-2 weeks and 1-6 months of initial treatment along with 2D echo findings. The improvement in coronary artery involvement were documented in the children after the treatment.

RESULTS

In our study, higher incidence of KD was observed in the 1-5 year age group children with a male preponderance. The youngest child diagnosed with KD was 3 months of age. More children was diagnosed with incomplete KD (mean days-9.75 days) than complete KD (6.54).Fever is the most common symptom followed by oral mucosal changes and the least common symptom, Erythema and induration at the BCG site was found in our study. There was no statistical significance found with increasing value of inflammatory markers like CRP (p-value=0.16), ESR (p-value=0.19) and IL6 (value=0.27), Ferritin (p-value=0.09) with severity of arterial involvement, because of

less number of study population and only 32 children were investigated for ferritin and 17 children for IL6.No significant statistical (p-value=0.11) association found between reaction with covid antibodies and severity of arterial involvement.

Of the 40 patients, 18(45%) had LMCA involvement, 31 (77.5%) had LAD involvement, 19 (47.5%) had RCA involvement and 19(47.5%) with more than one artery involvement.LAD was the most commonly involved artery. There were 09 dilatations, 23 small aneurysms, 06 medium aneurysms, 02 large aneurysms in our study population. After the 6 months follow up, majority of the arterial involvement changed to normal except one large aneurysm in LMCA changed to small aneurysm, total 03 large aneurysms in LAD and RCA still remained the same. Thirty nine (97.5%) children received IVIG treatment followed by high dose aspirin in 35(87.5%) children, 02(5%) received 2nd dose of IVIG, 17(42.5%) received methylprednisolone, 04(10%) received Infliximab.

CONCLUSION

KD is mainly a clinical based diagnosis. In < 1 year of age, Incomplete KD was mostly commonly. After 6 months follow up, all the dilatations and aneurysms became normal except in 2 children with persistence of large aneurysms. No statistical significance noted with increasing values of inflammatory markers with severity of arterial involvement. Two refractory cases were seen in 6months old child and in 23 months old child.

EFFECT OF TREATMENT INTENSIFICATIONWITH INFLIXIMAB ON MODERATE TO GIANT CORONARY ARTERY ANEURYSMS IN KAWASAKI DISEASE WITH RESPECT TO TIME OF ADMINISTRATION

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BACKGOUND

In Kawasaki Disease (KD) intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysms (CAA) to 5%. Treatment intensification with corticosteroids or infliximab (IFX)has been proposed for children presenting with CAA at diagnosis. There is paucity of data on the effect of IFX, after IVIG, on medium to large CAAs with respect to time of administration of IFX and CAA regression.

AIMS AND OBJECTIVES:

To determine the duration to regression of medium to large CAA with respect to time of administration of IFX as administered in ≤3 days, 4 to 7 days, ≥8 days after the completion of first dose of IVIG in children with KD.

MATERIALS AND METHODS

This is a retrospective analysis of data of children with KD who received IFX(after IVIG) with medium to large CAA admitted between January 2016 to September 2022 at Institute of Child Health, Kolkata. Medium to large CAAs were present at diagnosis or developed on follow up echoespost IVIG. Medium CAA defined as CAA z score ≥5 to <10, large CAA as ≥10z or absolute dimension ≥8mm.

The duration of IFX administration was classified within ≤3 days, 4 to 7 days, ≥8 days after the first dose of IVIG. Data noted were size of CAAs on serial follow up echoes and the duration to regression of CAA was noted in three categories: reduction of CAA by atleast 1z score, reduction by 50% and complete regression as defined by CAA z score ≤2z.

RESULTS

From January 2016 to September 2022 a total 210children were diagnosed as Kawasaki disease. 24 (11.4%) patients received IFX post IVIG due to medium or large CAA.

16 of 24 patients had medium CAA. All of them has shown complete regression on follow up. Median time to complete regression was 180 days

8 of 24 had large CAA. 1 completely regressedby one year. 3 reduced by 50% by 6 months however there are persisting CAA in the follow up echo. 4 are awaiting follow up echoes.

12 patients received IFX ≤3 days after IVIG with a median age of 11months. 10 were males. 3 were IVIG resistant. 9 had medium CAA and 3 had large CAA.

8 received IFX 4- 7 days after IVIG with a median age of 23.5mo. 7 were males. 4 had medium CAA and 4 had large CAA. 3/8 were also IVIG resistant.

4 patients received IFX ≥8 days of IVIG. 3 were males. 3 had medium CAA and 1 had large CAA.

Duration to regression with respect to time of administration of IFX after IVIG in Medium CAA (Table 1) and in Large CAA (Table 2) is described below.

Table 1 Duration to regression with respect to time of administration of IFX after IVIG in Medium CAA.

	≤3 days (median days)(range) N=9	4- 7 days (median days) N=4	≥8 days (median days) (n=3)
Decrease in size of CAA by 1z (days)	14 (2-42 days)	35 (2wks-6wks)	42 (4wks - 6wks)
Decrease in size of CAA by 50% (days)	28 (2-8 wks)	42 (2wks – 6m)	180 (4wks - 6 mo)
Complete regression (days)	90 (6wks-6mo)	111 (6wks – 1yr)	180 (5mo - 1 yr) (n=2)

Table 2 Duration to regression with respect to time of administration of IFX after IVIG in Large CAA

	≤3 days (median days) N=3	4- 7 days (median days) N=4	≥8 days (median days) N=1
Decrease in size of CAA by 1z (days)	28 (n=3)	81	42
Decrease in size of CAA by 50%(days)	42 (n=1)	150	365
Complete regression (days)	365 (n=1)	-	-
Persistence (no of patients)		2	1
Awaiting follow up (no of patients)	2	2	

CONCLUSION:

From our cohort we noted therapy intensification with IFX results in regression of CAAs. Early administration preferably within 3 days post IVIG results in consistently better response. Delay in administration of IFX leads to delayed regression and persistence of giant CAA.

Expression of inflammasomes (NLRP3, AIM2, NLRC4) and underlying cytokines (Caspase 1 and IL-1β)in pre and post patients with Kawasaki disease

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Introduction

Kawasaki disease (KD) is an acute systemic vasculitis of childhood. Both innate and adaptive immune pathways are involved in pathogenesis. Inflammasomes are innate immune system receptors that regulate the activation of caspase-1 and induce inflammation. There is a paucity of information on the role of inflammasomes in KD.

Objective: To examine the expression of inflammasomes (NLRP3, NLRC4 and AIM2), caspase- 1 and Interleukin-1β (IL-1β) in treatment naive (pre intravenous immunoglobulin) and post IVIg treatment in children with KD.

Method: 9 patients with KD were enrolled in the study. Diagnosis of KD was based on American Heart Association 2017 criteria. All patients were treated with intravenous immunoglobulin (IVIg) and aspirin. Pre IVIg (n=9) and, 4-6 weeks after treatment, post IVIg (n=5) blood samples were collected. Expression of inflammasome (NLRP3, NLRC4, AIM2), caspase 1 and IL-1β were assessed by real time PCR in patients with KD and compared with normal controls.

Results: Real time PCR analysis was performed in 9 patients with KD (9 in acute stage; 5 post IVIg) and compared with four controls. There was a significant increase in NLRP3 expression in patients (p value=0.0017) as compared to controls. Significant decrease in IL-1β expression in post IVIg patients as compared to pre IVIg (p=0.0191). Significant increase was also seen in IL-1β (p value=0.0293) in pre IVIg patients as compared to control.

Significant decrease in AIM2 expression in post IVIg patients as compared to pre IVIg patients (p=0.0445). There was found a significant increase in AIM2 expression in pre IVIg patients as compared to control (p= 0.0259). No significant difference in expression of NLRC4 (p value=0.86).

Conclusion

Increased expression of NLRP3, caspase 1 and IL-1β in patients with acute KD suggests activation of inflammasome pathway in pathogenesis of KD. Blocking of this pathway may provide another therapeutic target for KD.

		Navraj	Sanvi 1	Seerat	Anmol 1	Krishu	Anmol 2	Shivansh	Ved	Riyansh	Vihan	Sharav	Rivan		
NLRP3	Pre	1.2	1.1	2.8	36.6	4.6	1.3	17.1	3283.9	98.4					
NLRC4	Pre	0.1	0.9	0.1	684.1	0.7	0.1	2.0	346.0	3.2		4.6	0.2		
AIM2	Pre	0.8	1.3	1.0	207.6	0.5	5.6	5.3	1075.8	25.2					
IL1B	Pre	0.3	1.8	1.4	192.5	1.3	0.0	21.7	2102.5	43.9	839.9	162.5	12.7		
Caspase 1	Pre	0.2	0.4	0.9	182.8	3.3	0.6	75.5	9539.7	67.9	98.8		1.6		
NLRP3	Post	0.3	6.0	10.4	2.2	0.5									
NLRC4	Post	0.2	0.2	0.0	0.7	0.0									
AIM2	Post	1.3	0.4	0.0	1.6	0.0									
IL1B	Post	0.0	0.2	4.5	0.1	0.0									
Caspase 1	Post	0.1	1.8	1.8	0.3	0.0									
		Rashmi pla	Sanchi plat	Sanchi plat	Rashmi pla	Kanika plat	Control 1 p	Control 2 p	Control 2	Rashmi sh	Sanchi she	C1 080520	C2 080520	C3 08052021	
NLRP3		0.6	1.6	0.7	1.2	1.2	1.0	0.9	1.1	0.8	1.2	1.6	2.4	0.3	
NLRC4		0.8	1.2	0.8	0.8	1.7	ND	0.0	1.4	3.5	0.3	0.6	1.1	1.4	
AIM2		1.3	0.8	0.3	0.9	3.0	1.1	0.7	1.3	2.3	0.4	0.6	1.0	1.6	
IL1B		0.5	1.8	0.0	8.8	2.8	0.9	0.8	1.4	ND	1.0	1.6	0.8	0.8	
Caspase 1		0.6	1.7	1.2	0.7	1.2	0.9	0.8	1.3	1.0	1.0	1.0	1.8	0.6	

Kawasaki Disease: Is Intravenous immunoglobulinAlone Adequate For The Child With Kawasaki Disease And Coronary Artery Lesions? A Retrospective Study Of 65 Children With Kawasaki Disease From A Single North Indian Centre

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Background:

Steroid use in Kawasaki disease (KD)iscontroversial and has swung from contraindicated, to maybe & now perhaps "should be given to all."(1)Currently, standard practice is to use IVIg for *all* children with KD and addupfront steroids to IVIg only for those children who are at risk of non- response to IVIg , if such children can be identified. (2)There is data to support the use of steroids at 2mg/kg/dayas an add on to IVIg for the child who is at high risk of non response to the 1stIVIg(3) At our center, over the last 18 years we have observed1. significant no. of children present with CALs&2.These children often donot respond to 1st dose of IVIG. Thus, from 2017 we changed our practice & added steroids to IVIG as an upfront therapy to children presenting with CALs.We audited our practice &present the data on 65 children with KD.

Objectives:

1. To study demographic & clinical profile of children with KD.
2. To study response rate of IVIg
3. To study the difference in response rate (if any) for the child with KD& CALs who was given only IVIg (pre 2017) or IVIg& steroids (post 2017)at first presentation

Materials and methods:

All children diagnosed with KD from Jan13 to Apr19 were included. Clinical &demographic details were recorded on predesigned proformas.CALs were defined by z score (Boston) of more than 2 in any coronary artery. Response to IVIG was defined as no fever 36 hours post IVIG completion. Patients given IVIG alone got high dose aspirin, with steroids only low dose was given.SPSS 17.0 was used for analysis.

Results: 65 KD patients reviewed.Clinical & demographic details in Table 1. CALs were present in 31(47.6%) children at diagnosis. Boys had more CALs at onset than girls(p=0.059)IVIg was given to all. Steroids as first line were given to 13(20**%):All** had CALs.A second dose of IVIG was required by 13(20%). Therapy detailed in Table 2.

IVIg alone had a poor response in those presenting with CALs. Addition of steroids to IVIG upfront was associated with significant increase in response in those with CALs(p=0.001)Details in table 3.

No factors predicted the response to IVIG alone(age, day of diagnosis, C reactive protein). A higher z score predicted poor response to IVIG alone($p<0.005$), thus reiterating the fact that steroids are helpful in KD patients with CALs

Kawasaki shock syndrome was seen in 2(3%) and macrophage activation syndrome in 1(1.5%),requiring high dose methylprednisolone(10-30mg/kg/day).

At median follow up of 14 months(IQR 8-15), CALs normalized in 27(86%),5 persisted to have abnormal CALs. (All had giant aneurysms at presentation, Z scores >10).

There was no mortality in this cohort.

Conclusions:

1. 47% KDpatients presented with CALs.
2. KD with CALs have poor response to IVIG alone vs IVIG with upfront steroids (p=0.001)
3. In addition to the well described scoring systems that predict a poor response to IVIG in the Japanese population, the presence of CALs and risk of non response to IVIG needs further study and replication in cohorts across the world.

References:

1. Corticosteroids for the treatment of KD in children.CochraneReview 2017.
2. Diagnosis, Treatment, and Long-Term Management of KD.Circulation. 2017.
3. Efficacy of IVIG plus prednisolone for prevention of CALs in severe Kawasaki disease (RAISE study): Lancet 2012

Table 1: Clinical and demographic characteristics

Characteristics	
Male: females	45:20
Median age at diagnosis(years)	2.77 years (IQR 1.28-5.24)
Median time to diagnosis(days)	9 days (IQR 7-13)
Complete KD	31(48%)
Incomplete KD	31 (48%)
Atypical KD	3 (4%)
Seizures	1
Jaundice	1
Severe hemolytic anemia	1
Clinical features at presentation	
Oral cavity changes	48 (74%)
Non purulent bulbar conjunctivitis	48 (74%)
Rash	45 (69%)
Extremity changes(acute and subacute)	42 (65%)
Cervical lymphadenopathy	29 (45%)
Arthritis	19 (29%)
Irritability	13 (20%)
Urethritis	3 (5%)
BCG scar reactivation	2 (3%)
Complications	
Kawasaki shock syndrome	2(3%)
Macrophage activation syndrome	1(1.5%)
Sensori neural hearing loss	2 (3%)

Median C reactive protein	60.5mg/l(IQR 6-344)
Echocardiographic findings No CAL CAL at time of diagnosis	 33 (51%) 32 (49%)
Z scores(Boston criterion) <2 2-2.4 2.5-5 5.1-10 >10	 33 (51%) 4 (6%) 13 (20%) 9 (14%) 6 (9%)

Table 2: Details of therapy given per the echocardiographic finding

Patient profile	**Upfront therapy with IVIG alone**	**Upfront therapy with IVIG and IV steroid**	**No of patients given second IVIG only**	**No of patients given rescue with steroids AND second dose of IVIG**	**No of patients given only steroid after 1st IVIG failure and no 2nd dose of IVIG**	**No of patients given additional anti inflammatory therapy ie Infliximab Azathioprine Cyclosporin Others**	**No of patients given additional antithrombotic therapy: Clopidegrol Low molecular weight heparin**
KD with no CAL N=33	32	1* steroid for MAS	1	2	0	Infliximab 1** (for intolerance to IVIg)	0
KD with any CAL N=32	21	11	4	6	1	Infliximab 2 Azathioprine 1	LMW heparin 6 Clopidogrel 6
KD with CAL z 2-2.4 N=4	4	0	0	1	0	0	0
KD with CAL z 2.5-5 N=14	11	3	2	3	0	Infliximab 1	0

KD with CAL z 5.1-10 N=8	2	6	2	1	0	0	LMW heparin 2 Clopidogrel 2
KD with CAL z > 10 N=6	3	3	0	2	0	Infliximab 1	LMW heparin 3 Clopidogrel 4

Table 3: Response to IVIg(alone without steroids)and factors predicting response to IVIg

	Response to IVIg alone	**No response to IVIg alone**	**p value**
No CAL at onset	32(97%)	1(3%)	***0.001***
CAL at onset	20(62.5%)	12(37.5%)	
Age at onset <1 year	8 (66.7%)	4 (33.3%)	0.237
>1 year	44 (83%)	9 (17%)	
Diagnosis<day 10 of fever	33 (82.5%)	7 (17.5%)	0.524
Diagnosis >day 10 of fever	19 (76%)	6 (24%)	
Z scores <2	32(97%)	1 (3%)	**<0.005**
2-2.4	4 (100%)	0	
2.5-5	11 (78.6%)	3 (21.4%)	
5-10	2 (25%)	6 (75%)	
>10	3 (50%)	3 (50%)	

Intensive combination therapy for patients with Kawasaki disease with large coronaryartery aneurysms may improve outcomes – our experience from a tertiary care center in North India

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Background

Kawasaki disease (KD) is a common vasculitis in childhood. Literature suggestsgiantcoronary artery aneurysms (CAAs)generally do not regress. Our experience has shown that intensive combination therapy may result inregression of these abnormalities.

Objectives

To report the outcomes in patients with KDandlarge CAAsmanaged in Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, Chandigarh, India.

Methods

Data were collated from clinic records of patients with KD with large(including 'moderate' and 'giant') CAAs being followed during period January 2018 – December 2021.

Results

We identified 26 children with KD and large CAAs [moderate (n=10); giant CAAs (n=16)]. Male to female ratio was 5.6:1. Median age at diagnosis was 2 years. Treatment was initiated at median interval of 13 days from onset of fever.

Of 16 patients with giant CAAs, resolution was seen in 2 (12.5%),regression to mild CAAs was noted in 5 (31.25%) and persistence of aneurysms was seen in 9 (56.25%). Eight patients received treatment with intravenous immunoglobulin (IVIg), infliximab, cyclosporine, and steroids; 4 received treatment with IVIg and infliximab; 1 received treatment with IVIg, infliximab and steroids; and 1 received treatment with IVIgand steroids. Of the 8 patients who received all 4 drugs, 50% showed regression to mild CAAs, while 50% showed no change. The 2 patients that showed complete resolution of giant CAAs had received combination therapy with IVIg and infliximab.

Of ten patients with moderate CAAs, resolution was seen in 7 and regression to mild CAAs was seen in 3. No patients had persistence of aneurysms. Three patients received treatment with IVIg, infliximab, cyclosporine, and steroid; 4received treatment with IVIg and

infliximab; 2 received treatment with IVIg and steroid; and 1 received IVIg alone.

Conclusion

Treatment protocols incorporating intensive combination therapy may be necessaryfor patients with KD and large CAAs at presentation.