Title: Unveiling BCG Site Reactivation in Kawasaki Disease: A Diagnostic Clue with Implications for Infants and Coronary Artery Aneurysms

Abarna Thangaraj, Rakesh Kumar Pilania, Archan Sil, Ridhima Aggarwal, Manpreet Dhaliwal, Saniya Sharma, Ankur Kumar Jindal, Pandiarajan Vignesh, Deepti Suri, Amit Rawat, Surjit Singh

Introduction: Kawasaki disease (KD) is the commonest childhood vasculitides. BCG site reactivation is a soft marker of KD. In this study we have reported the patients with KD exhibiting BCG site reactivation.

Materials and methods: We have reviewed records of all children who were diagnosed with KD over the period January 1994 - June 2023. Diagnosis of KD was based on according to American Heart Association guidelines. Children with KD and BCG site reactivation were analyzed in detail.

Results: From 1994 to June 2023 there were total of 1245 KD patients. Of these, 18 patients were found to have BCG site reactivation. Male to female ratio is 1.6 :1. Median age at diagnosis was 6 months. Median duration of fever before diagnosis is 10 days. The commonest presentations were bilateral conjunctival suffusion and redness of lips which are seen in 83.3% (n=15) and 77.8% (n=14) respectively. Half of the patient had maculopapular rash. Perianal or perineal rash is seen in 5 patients (28%), while periungual peeling is seen in 50% of the patients. Periungual peeling was noticed from 2 to 10 days after diagnosis. Extremities edema is seen in 7 (38.8%) patients. Unilateral cervical lymphadenopathy was the uncommonest manifestation seen in only 2 (11.1 %) patients. Nail changes like chromonychia and onychomadesis was noticed on follow up in 4 and 1 patient respectively. Irritability was noticed at admission in 8 patients (44.4%). Nearly 3/4th of the patient had anemia. Neutrophilic leukocytosis is seen in 62%. Thrombocytopenia is noticed in 2 patients, rest of them had thrombocytosis. 2D-echocardiography (2D ECHO) revealed coronary artery abnormalities (CAAs) in 8 patients, including giant coronary aneurysms in 3 patients. All

patients received intravenous immunoglobulin (IV IG) (2gms/kg). IV IG resistance was seen in 2 patients requiring higher immunosuppressants like Infliximab (5-10mg/kg single dose). Primary Intensification was done in 7 patients who had risk factors of CAA or had CAAs in initial 2D ECHO. Of the 7 patients 2 of them received cyclosporine (5mg/kg for 6 weeks) and 3 of them received oral steroids (6 weeks) also. Two patients had persistent aneurysm in follow-up. In addition to CAAs, one patient presented systemic artery aneurysms involving common iliac, internal iliac, subclavian, and axillary arteries, while another had a thrombus in the left anterior descending coronary artery.

Conclusion: While BCG site reactivation is regarded as a pathognomonic marker in the diagnosis of KD, it is observed in only 1.5% of patients within our KD cohort. This phenomenon is primarily noted in infancy. Alarmingly, nearly half of the children with KD exhibiting BCG site reactivation developed CAAs despite timely diagnosis and management.

Kawasaki disease – Not just coronary artery aneurysm

A 2-year-old boy illness was diagnosed to have Kawasaki disease (KD) at 1 year of age. He was treated with intravenous immunoglobulin, infliximab, corticosteroids and oral cyclosporine. 2D-echocardiography at presentation showed a giant aneurysm in the right coronary artery (RCA), left anterior descending artery (LAD), and left main coronary artery (LMCA) with thrombus in LAD. He was started on low weight molecular-weight heparin, aspirin, and atorvastatin. CT-coronary angiography on a 128-dual source platform showed RCA shows three discontinuous fusiform aneurysms with thrombus in distal RCA. LMCA at the bifurcation shows a fusiform aneurysm, LAD shows a giant thrombosed aneurysm, and multiple collaterals are noted in the periphery of this aneurysm which is seen reconstituting distal LAD. LCx is normal, LV apex showed a pseudo-aneurysm.

Title: Computed tomography coronary angiography findings in three adults with angina – sequelae of missed Kawasaki disease in childhood

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Abstract:

Background: Kawasaki disease (KD) is the commonest vasculitis in children less than 5 years. Diagnosis of KD is clinical with no pathognomonic laboratory tests. In the vast majority (75-90%) it's self-limiting and thus can easily be missed. We herein describe CT coronary (CTCA) angiography findings in 3 adult patients who were referred to rule out coronary artery disease.

Methods: We report 3 adult patients who presented with cardiac ischemic symptoms and on (CTCA) found to have coronary artery abnormalities possibly due to missed KD in early childhood.

Results: Three patients in the age group of 38-45 years presented with complaints of chest pain, and exercise intolerance without any risk factors of coronary artery disease (CAD) were included in this study. On evaluation, these had normal 2D Echocardiography and treadmill test. However, CTCA showed coronary artery aneurysms (CAAs) without any features of coronary artery disease (atherosclerotic plaque/s or stenosis) History obtained from their parents was suggestive of untreated KD during childhood

Conclusion: Missed KD can present in young adults with clinical features of myocardial ischemia. On CTCA if coronary artery aneurysms are seen without characteristics or features of coronary artery disease diagnosis of missed should be considered.

Title: CT coronary angiography is the preferred imaging modality for left circumflex coronary artery in children with Kawasaki disease: 9 years of experience from a tertiary centre in North India

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ABSTRACT

Background and objectives: Kawasaki disease (KD) is a systemic vasculitis with predilection for coronary arteries. Two-dimensional transthoracic echocardiography (TTE) has hitherto been the preferred imaging modality for assessment of coronaries in children with KD. TTE, however, has several limitations. For instance, coronary artery abnormalities (CAAs) involving left circumflex artery (LCx) can be missed on TTE. In this study, we have evaluated the involvement of LCx in children with KD on computed tomography coronary angiography (CTCA) performed on a 128-slice dual source platform.

Methodology: Diagnosis of KD was based on American Heart Association (AHA) guidelines. Radiation optimized CTCA was performed in 225 children with KD over a period of 9years (November 2013 – December 2022). TTE was performed on the same day, or a day prior to, or after CTCA. Patients were managed using AHA based treatment protocols.

Results: On CTCA, involvement of LCx was seen in 41/225 (18.2%) patients with KD. However, TTE detected LCx abnormalities in only 16/41 patients. Four patients(9.75%) had isolated LCx involvement. CTCA showed 47 CAAs in LCx in 41 patients. Aneurysms (40 fusiform; 2 saccular) were seen in 39 patients; setnoses in 3; thrombosis in 2. One patient had an aneurysm and a stenosis, while 2 patients had only stenoses. Thromboses and stenoses had both been missed on TTE. Giant aneurysms in LCx were seen in 6patients. Proximal LCx

aneurysms were seen in 39patients - of these, 12had distal extension as well. Distal LCx aneurysms, in absence of proximal involvement, were seen in 6 patients. Two patients had non-contiguous multiple aneurysms. Based on finings of the CTCA, treatment protocols had to be modified in 3/41 (7.3%)patients.

Conclusions: Abnormalities of LCx were seen in 18.2% (41/225) patients on CTCA. Majority of these had been missed on TTE. Isolated LCx CAAs were seen in 4 patients. CTCA should be the preferred imaging modality for assessment of LCx. Our findings have important implications for treatment planning and follow-up of children with KD.TTE alone is inadequate for assessment of LCx in children with KD.

Key words: Kawasaki disease, Coronary artery abnormalities, Left circumflex coronary artery, Computed tomography coronary angiography, Transthoracic echocardiography

ORAI1 gene polymorphisms in children with Kawasaki Disease: A study from north-west India

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Introduction: Pathogenesis of Kawasaki disease (KD) remains an enigma and new insights have suggested genetic predisposition of KD. ORAI1 is a calcium (Ca2+) channel protein involved in store-operated Ca^{2+} entry pathway required for activation of lymphocytes. Association of *ORAI1* gene with risk of KD was reported in Japanese children. We evaluated polymorphisms in *ORAI1* gene in Indian children with KD.

Methodology: This is an observational study conducted from June 2018 to December 2019 enrolling children with KD. As baseline prevalence data of *ORAI1* polymorphism in north Indian population is not available, 50 healthy adult controls were also enrolled for the study. Patients with KD were divided into KD with coronary artery abnormalities (KD with CAA) and KD without CAA for sub-analysis. DNA was extracted and amplified by conventional polymerase chain reaction technique using primer of exon 2 of *ORAI1*. Sequencing of DNA was, then, done using Sanger's chain termination method.

Results: Fifty children with KD and healthy adult controls each were enrolled with 25 children having CAA. Three different polymorphisms in *ORAI1* gene were identified viz. rs3741596 at c.652A>G p.Ser218Gly, rs3825175 at c.798T>C p.Thr266Thr and rs3741595 at c.546 C>T p.Ile182Ile. The AA and AG genotype of rs3741596 were found in 45 (90%) and 5 (10%) respectively in KD group. Whereas, all the 50 controls had AA genotype. There was statistical significant difference of variants of rs3741596 between the two groups (p-0.022). Whereas, no

statistically significant difference was observed for polymorphisms of rs3825175 and rs3741595 between the two groups. Polymorphisms of *ORAI1* was also not significantly different between KD with CAA and without CAA.

Conclusions: This is the first study in Indian population to explore the association of KD with *ORAI1* gene. The study provides evidence to support association of polymorphism of *ORAI1* with KD susceptibility. Further studies with a larger sample size are required to confirm this finding.

Title: Nail pitting in an infant with Kawasaki disease - An unusual clinical finding

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Case narrative: A 7-month-old boy presented with fever, generalized maculopapular rash, redness of eyes and swelling around left side of neck. Investigations showed hemoglobin 60 g/L, total white cell counts $18.2x10^9$/L ($N_{75\%}L_{21\%}M_{3\%}E_{1\%}$), platelet count $175x10^9$/L, elevated C- reactive protein (67 mg/L; N <6). He was noted to have congestive cardiac failure, pericardial effusion and mild mitral regurgitation, requiring mechanical ventilation and inotropic support at 4th week of illness. SARS-CoV-2 antibodies were positive. A possibility of Multisystem inflammatory syndrome in children versus Kawasaki disease (KD) was considered. He initially received intravenous immunoglobulin (IVIg; 2g/kg), oral prednisolone (2mg/kg/day and then tapering), digoxin, enalapril, and furosemide. A 2-dimensional(D)-echocardiogram done at 10th week of illness showed giant aneurysms of left anterior descending artery (LAD) with thrombus. He was thereafter referred to our institute for further evaluation. The 2D-echocardiography confirmed giant aneurysms of LAD (14.9 mm; +47.2 Z) with thrombus, left circumflex (4.39mm; +11.48Z), and right coronary artery (RCA) (4.17 mm; +9.5Z). As the N-terminal pro B-type natriuretic peptide (NT-proBNP) (3807 pg/mL; N<125), creatine kinase-MB fraction (42 IU/L; N:5-25) and troponin T (58.6 ng/L; N: 12.7- 24) were still elevated, he was treated with a second dose of IVIg (2g/Kg); infliximab (10 mg/kg); oral prednisolone (2mg/kg/day, tapered and stopped over 6 weeks); cyclosporine (3mg/kg/day); low molecular weight heparin (2mg/kg/day) and aspirin (5mg/kg/day). Nail examination at 2 weeks of follow-up showed nail pitting over multiple nails with Beau's lines (**Figure 1**).

Nail changes are seen in patients with KD usually in the convalescent phase. Various nail changes described are Beau's lines, leukonychia, orange-brown chromonychia (1), onychomadesis, Muehrcke's lines and pincer nail deformity (2,3). To the best of our

knowledge, nail pitting has not been previously reported in patients with KD. This appears to be an unusual manifestation of KD.

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Figure Legends

Figure 1

A: image showing nail pitting (asterisk) and Beau's line (red arrow) in fingernails. Zoomed image showing the nail pitting (focused image)

B: Toenails showing onychomadesis of right great toe (black arrow); nail pit (asterisk); Beau's line (red arrow)

Case report - A child with Kawasaki disease and acute pancreatitis: An atypical presentation

Disha N, Reva Tyagi, Suprit Basu, Rakesh Pilania, Manphool Singhal, Surjit Singh,

Introduction

Kawasaki disease is a systemic vasculitis of unknown etiology. Gastrointestinal manifestations like hydrops of the gall bladder and hepatic dysfunction are common findings in children with KD. However, KD causing acute pancreatitis is relatively rare and we present a case of 11-year-old boy.

Case report

A 11-year-old boy presented with a fever for 4 weeks. He also had conjunctival congestion and maculopapular rash over the face and trunk in the first week of febrile illness that subsided spontaneously. Two weeks into the illness he developed acute abdomen radiating to his back associated with multiple episodes of non-bilious vomiting and poor oral intake. Physical examination showed peeling of the skin of palms and soles, Beau's line in multiple digits in palms, and sole (**Figure 1** A-D), and epigastric tenderness. Clinical diagnosis of Kawasaki disease (KD) was considered. The blood investigations revealed hemoglobin 11.2g/L, neutrophilic leukocytosis (total white cell counts $29.6x10^9$/L, neutrophils 84%), thrombocytosis (6.76×10^9/L), elevated levels of acute phase reactants (C-reactive protein: 140 mg/L; N<6.0, ESR: 24mm/first hour). Serum amylase (324U/L; N:28-100) and lipase (249 U/L; N:13-60) were also raised. Serum pro-brain natriuretic peptide was elevated (463 pg/ml; N<0-125). Serum calcium 10.2mg/dl (8.8-10.2) and serum triglyceride 186mg/dL (<100) were within normal limits. He was non-reactive for hepatitis B, hepatitis C, and cytomegalovirus. Ultrasonography of the abdomen showed a bulky pancreas and distended gall bladder (**Figure 2**). Given the clinical and corroborative laboratory findings, KD was considered as a possible

cause of acute pancreatitis. He was managed conservatively for pancreatitis with intravenous fluids and analgesics. He was given intravenous immunoglobulin (2 gm/kg) and the fever resolved instantly. Post IVIg, inflammatory markers showed C-reactive protein: 39.2mg/L; N<6.0, Serum amylase (34U/L; N:28-100) and lipase (37 U/L; N:13-60). 2D-echocardiography revealed normal coronary artery assessment with LMCA:2.72mm(-0.9Z), LAD 2.7mm(+0.6Z), RCA 2.6 mm(-0.48Z). After 48 hours of IVIg infusion, pain abdomen subsided and oral feeds were initiated initially in clear liquid form and later solid feeds. Acute pancreatitis is an unusual complication of KD and has been reported occasionally and its presence usually leads to delay of diagnosis of KD. Pancreatitis with KD is easily managed with IVIg and supportive treatment.

Discussion

KD presenting with acute pancreatitis is quite rare and often missed when child presents with abdominal pain, vomiting and jaundice. So, a high index of suspicion is required to diagnose these cases timely.

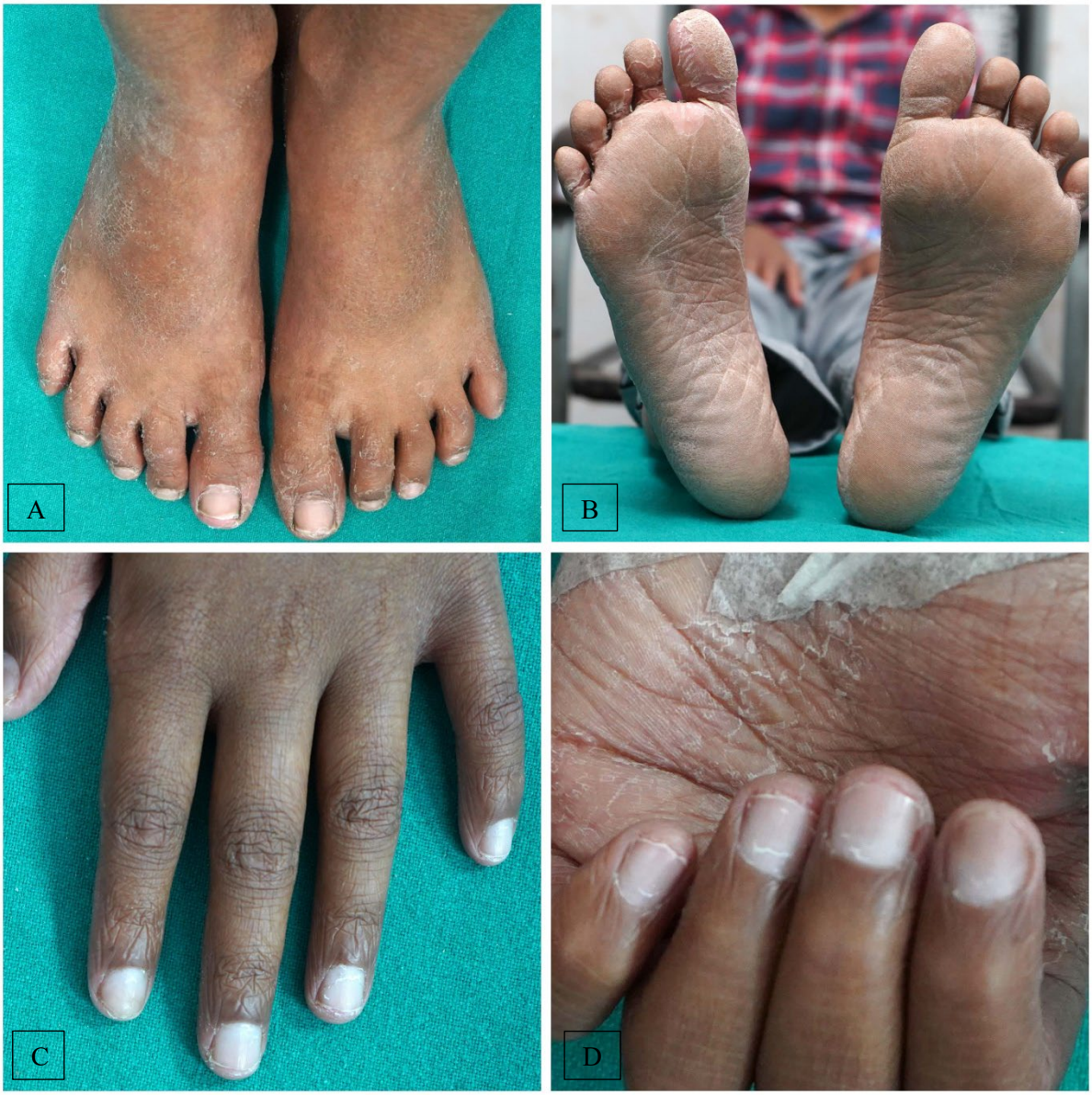

Figure1: Periungual desquamation of hands and feet

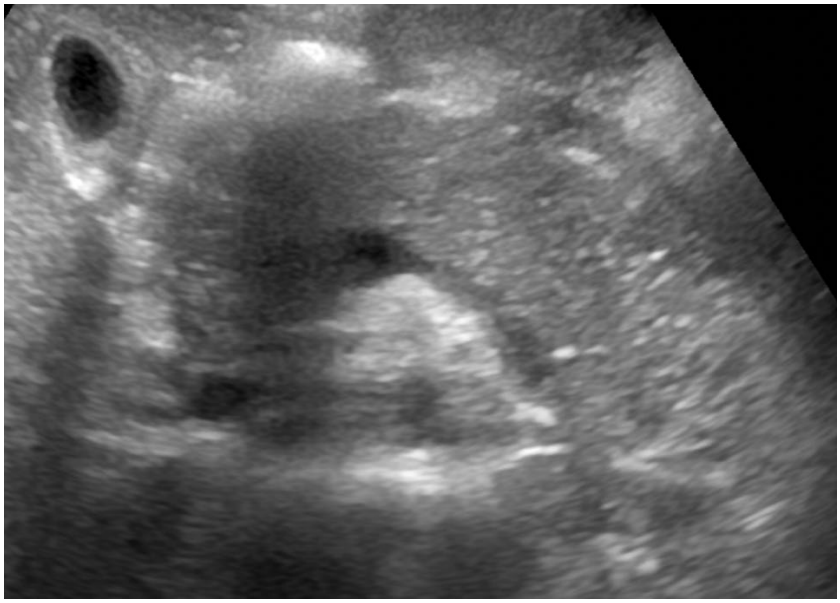

Figure 2: Ultrasonographic findings showing bulky pancreas with hyperechogenecity

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CATASTROPHIC COMPLICATION OF DELAYED DIAGNOSIS OF KAWASAKI DISEASE:

Gayathri C V, Archan Sil, Abarna Thangaraj, Ankur Jindal, Surjit Singh, Manphool Singhal

An eight-year-old boy, developmentally normal, had a high-grade fever for 45 days and right-sided neck swelling. He was treated with multiple courses of antimicrobials elsewhere, given persistent fever, cervical lymphadenopathy, neutrophilic leucocytosis, and elevated inflammatory parameters. Later, when he developed redness of eyes and cracking of lips, he was referred to our center because of suspicion of Kawasaki disease. At presentation, he had Bilateral conjunctival suffusion and red-cracked lips. 2D ECHO at our institute showed Giant aneurysms in the Left anterior descending (15.5 mm–34 Z score) and right coronary (8.5 mm-14.3 Z score) arteries. His blood investigation revealed normocytic anemia, neutrophilic leucocytosis, thrombocytosis, an ESR of 70mm/hr, and a CRP of 34mg/L. With a diagnosis of Kawasaki disease with Giant coronary aneurysms, he was treated with Infliximab, IVIg 2g/kg, Cyclosporine 5mg/kg/day, steroids, also on Low Molecular Weight Heparin, and atorvastatin. CT Coronary Angiography was done, which showed a pan coronary artery aneurysm (fusiform aneurysm and dilatation of all main coronaries with their branches) with partial thrombus in the Right Coronary artery. Peripheral arterial Doppler for the involvement of other vessels was found to be within normal limits. Despite receiving immunomodulators, his echocardiography in follow-up after four months shows similarly sized coronaries. The child currently continues to receive Low molecular weight heparin, atorvastatin, and antiplatelet drugs. This case report signifies the need to have a high suspicion of Kawasaki disease in all children with prolonged fever, including older children, as initially, the disease may be incomplete. We also emphasize the importance of early echocardiography in children with prolonged fever and early treatment with IVIg to prevent catastrophic complications of aneurysms, thrombus formation and prolonged treatment with anticoagulants.

MicroRNA-145 and MicroRNA-320a are upregulated in children with Kawasaki disease and are surrogate biomarkers for disease severity

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Background: Genetic biomarkers have been increasingly explored in association with Kawasaki disease (KD). MicroRNAs are small noncoding RNAs that regulate gene expression. Differential expression of miRNAs has been recently reported in Japanese and Chinese children with KD. This is the first study on role of miRNA in patients with KD from India.

Objectives: To assess microRNA-145, miRNA-320a and miRNA-499 in a cohort of North Indian Children with Kawasaki disease

Methodology: This study involves 30 children with KD along with 20 febrile age-matched controls. Diagnosis of KD was based on American Heart Association 2017 criteria. miRNA isolation was carried out from plasma followed by RNA quantification and cDNA synthesis. Quantification of miRNA expression was done by real-time polymerase chain reaction (RT-PCR).

Results: Of 30 children with KD enrolled for the study, 9 had coronary artery abnormalities (CAAs). Patients with KD showed significant increase in levels of miRNA-145 (p=0.0009) and miRNA-320a during acute stage (p= 0.0001) when compared with febrile controls. Gene expression of miRNA-145 (p=0.0003) and miRNA-320a (p=0.0001) was also significantly higher in acute stage as compared to convalescent stage. miRNA-145 (p=0.08) and miRNA-

320a (p=0.06) expression was higher in KD children with CAAs as compared to KD children without CAAs. There was no difference of expression of miRNA 499 in children with KD when compared to controls (p= 0.54).

Conclusion: This study shows that miRNA-145, miRNA-320a are significantly elevated in children with KD. These miRNA genes may have a role in regulating gene expression of TGF-β pathway and TNF-α expression during the acute stage of KD. Elevations of miRNA-145 and miRNA-320a in KD may be pointers to disease severity and may mandate more aggressive forms of therapy.

Profile Of Kawasaki Disease With Coronary Artery Aneurysms: Data From A Tertiary Care Centre In Eastern India

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Introduction

Aims and Objectives: To study the clinico-epidemiological profile, baseline investigations, treatment given and response to therapy in patients diagnosed as Kawasaki Disease with Coronary Artery Aneurysms.

Methods: This is a retrospective observational study on patients diagnosed as Kawasaki disease with CAA as per AHA 2017 guidelines from a tertiary care centre in Eastern India. The study period was January 2020 to August 2023

Results: 108 patients were diagnosed as KD during this study period of whom 101 patients were included (7 were excluded because of incomplete data). Table 1 demonstrates the profile of patients with small, medium and giant aneurysms versus those without CAA. Table 2 demonstrates the clinic-epidemiological profile and median investigation of those with and without CAA.

39/101 (38.6%) patients developed CAA at diagnosis or follow up of whom 35 (34.7% of 101) had aneurysms at diagnosis. 23 patients (59%) had small CAA, 14 (36%) had medium CAA and 2 (5%) had giant CAA.

All patients who had small CAA regressed on follow up.

Amongst the 14 patients who had medium CAA, 1 had intraluminal thrombus formation, 12 received anticoagulants, 6 have completely regressed, 1 had persistent aneurysm at 6 month follow up. 7 patients presenting over the last 6 months have achieved partial regression.

Two patients who had late diagnosis around 2 weeks had giant aneurysms, received Infliximab plus steroids and Cyclosporine along with anticoagulants. One has significant reduction in size (presently +3.8Z) whereas the other is lost to follow up.

Conclusion: Infants have a higher incidence of medium and large CAA. Those with giant CAAs had a later diagnosis. Thus infantile onset disease and diagnosis beyond 10 days of onset were associated with larger CAAs at diagnosis.

(In comparison to data till 2019 where the incidence of CAAs were 21% , since 2020 there has been a manifold increase of CAAs to 38.6% with increasing number of children presenting with CAAs at diagnosis. The number of giant CAAs have however reduced from 3% to 1.6%.)

Table 1: Profile of patients with small, medium and giant CAA versus those without CAA

	Small CAA	Medium CAA	Giant CAA	No CAA
Total number	23	14	2	62
Median age (months)	15.5	11.5	12mo	18
Number of IVIG resistant	1 (4.3%)	1 (7.1%)	0	10 (16.1%)
Number of Incomplete KD	11 (47.8%)	8 (57.1%)	1 (50%)	33 (53.2%)
Number of Males	16 (26.0%)	11 (78.6%)	1 (50%)	40 (64.5%)
Duration of illness prior to admission (median days)	7	8	11	5.5
Duration of illness at diagnosis	9	10	14	7
CAA at diagnosis	21 (91%)	13	2	
Additional therapy				
Steroids	18	1		12
IFX	2	14		8
IFX plus steroids	3	2		3
IFX plus steroids plus cyclosporin		3	2	

Table 2: Profile of patients with CAA versus those without CAA

	CAA	Non CAA
Total number	39	62
Age in months (median)	12	18
Males (number/percentage)	28	40
Incomplete KD (number/percentage)	23	33
Median duration of fever prior to admission (days)	7	5.5
Median duration of fever at diagnosis (in days)	9	7
IVIG resistance (number/percentage)	2	10
Investigations (median)		
Hb (gm/dl)	9.1	9.5
TLC	18300	17465
Neutrophils percentage	46	68
Platelets (/cmm)	394000	446000
ESR (mm/hr)	79	92
C reactive Protein (mg/L)	106.2	101
SGPT (U/L)	42	23.5
SGOT (U/L)	25	25
Albumin (g/l0	3.2	3.5
Total bilirubin (mg/dl)	0.33	0.23
Sodium (meq/l)	133	133

PREDICTING IVIG RESISTANCE IN KAWASAKI DISEASE : PROPOSAL FOR AN INDIAN SCORING SYSTEM

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Introduction: Various risk scoring systems have been developed to predict Intravenous immunoglobulin (IVIG) resistance in Kawasaki disease (KD), however, they have not been found to be useful in other ethnicities.

Objectives: The aim of the study is to produce a set of cutoff values for the parameters that would best predict IVIG resistance in Kawasaki Disease in the Indian cohort of patients.

Methods: The analysis involves predicting the IVIG resistance label of patients for different cutoff values of the parameters and calculating the accuracy of the predictions based on the ground truth labels. The analysis tried to keep the basic framework of the 3 Japanese scoring methods in the new method proposed. Dataset was divided into training and test datasets, with the training dataset having more data, and being used to produce the scoring mechanism, and testing dataset being used to compare accuracy of proposed new model to the established methods. The training dataset comprised of 70 patients, 22 being IVIG resistant. The testing dataset had 45,15 were IVIG resistant. Both datasets combined is called Full dataset. For each predictor used in all of the scoring methods, a list of possible points to be tested for being the potential new cutoffs in the scoring mechanism were generated.4 different scoring mechanisms were tested:

- Scoring based on original Kobayashi, where the cutoff (=/>5), all the original Kobayashi predictors (but new cutoff value predicted for each), and the greater/lower than signage corresponding to each predictor was re-used.
- On Sano and Egami, in a similar way.

- A new scoring method, using a structure similar to the established scoring methods, but selecting predictors based on Logistic Regression and testing different values of the cutoff for best performer. For each mechanism, the corresponding predictors and their list of values on which to test them were used to generate a grid. For each proposed mechanism, the set of predicted labels for IVIG Resistance was calculated iteratively for each set of points on the grid, and the sensitivity and specificity were calculated. The set of values of the predictors that resulted in the best prediction accuracy were noted.To allow the proposed cutoff values of predictors in the scoring mechanism to generalize well to unseen future data, a K-fold cross validation (with K=5) approach was used. The choice of predictor values that give the highest mean accuracy is chosen as optimal for the problem. This allows the proposed scoring mechanism to have high accuracy.

Results: The above analysis was done for all 4 of the proposed scoring mechanisms; the Kobayashi based approach produced best results. Using the same variables used in Kobayashi, and running an analysis on the training dataset, we came up with the following new values of the variables.
Sodium=133, fever=4 days, AST=100, Neutrophils=84%, CRP=17 mg/dl, age=21months, platelet=6 lacs. The signs are what was used in the original Kobayashi study for each of the variables (eg. for Sodium it was <=) (Table 1) Table 2 demonstrates the sensitivity and specificity of the proposed and the original Kobayashi score.

Table 1: Proposed risk scoring system

Parameter	Points
Age ≤ 21 months	2
Fever ≤ 4 days	2
ALT ≥100 U/L	1
CRP ≥ 17mg/dl	2
Platelet ≤ 600000/cmm	1
Sodium ≤ 133	2
Neutrophil ≥84%	2
Risk of IVIG resistance if total score ≥5	

Table 2: Sensitivity and Specificity of the Proposed and the Original Kobayashi Score

	New proposed score (based on Kobayashi score)	Original Kobayashi score
Test data		
Sensitivity	0.8	0.66
Specificity	0.43	0.5
Full data		
Sensitivity	0.9	0.75
Specificity	0.52	0.56

Conclusion: The proposed values can be seen to have better sensitivity than the original values on the Indian cohort. It will act as a better guide for screening patients for possible IVIG resistance and thus enable initiation of early aggressive therapy.

Association Of Intravenous Immunoglobulin Resistant Kawasaki Disease With Development Of Coronary Artery Aneurysms: A Post 2020 Analysis From A Tertiary Care Centre In Eastern India

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Introduction: 10-20% of Kawasaki Disease (KD) patients develop recrudescent or persistent fever after intravenous immunoglobulin (IVIG) and this has been associated with an increased risk of developing coronary artery aneurysms (CAA). However, in our cohort post 2020 it was observed that majority of the patients who had persistent/recrudescent fever after IVIG did not have CAA at diagnosis or follow up.

Aims and objectives: To compare the baseline clinico-epidemiological profile in KD patients with CAA and those with IVIG resistance as defined by AHA 2017 guidelines and determine the odds of development of progressive/persistant CAA in IVIG resistant KD.

Materials and Methods: This is a retrospective analysis of data on patients diagnosed as KD at a tertiary care centre in Eastern India. The study duration was January 2020 to August 2023. IVIG resistance was defined as per AHA 2017 guidelines. Those whose fever subsided after IVIG therapy were considered as IVIG responders.

Results: A total of 108 patients were diagnosed as KD during the study period of whom 101 are included. 39 had CAA at diagnosis or follow up, and 12 had IVIG resistance. Only 2 of the IVIG resistant patients developed CAA. 37 patients who developed CAA were IVIG responders.

The following table describes the subgroups of IVIG responders and IVIG resistant patients (Table 1) in relation to CAA.

Table 1

		Progressive/persistent CAA : **No**	Progressive/persistent CAA : **Yes**	
I	IVIG resistant	10	2	12
II	IVIG responder No CAA	52		52
III	IVIG responder with CAA			37
IIIa	CAA at diagnosis, partial/ complete regression after IVIG	21		

IIIb	CAA developed after IVIG therapy		2	
IIIc	CAAs at diagnosis, increasing size by atleast >1z or persisting after IVIG/ IVIG plus additional therapy		14	
	Total			101

The odds ratio of IVIG resistant KD for developing CAA in our cohort during the study period was 0.9 with CI 0.18 to 4.5 (p=0.9) and relative risk 0.93 (CI 0.24 to 3.5) which indicates that IVIG resistant fever was less likely to develop CAA in our population.

Drawbacks: This is a retrospective study with small study population.

Conclusion: Traditionally it is known that IVIG resistance has increased probability of CAA development, analysis of this contemporary cohort of patients from 2020 onwards did not support that fact.

Future Scope: The need of the hour is to assess risk factors for development of CAA irrespective of response of fever to IVIG.

Clinical Profile of Kawasaki Disease– Experience from a tertiary care center in South India

Jyothi Janardhanan[1], Neha Singh[1], Sagar Bhattad[1]

Affiliation:
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Introduction:
Kawasaki disease (KD) is an acute multisystem inflammatory disease involving medium-sized blood vessels (vasculitis) that most commonly affects infants and young children.

Objective:
To study the clinical profile of Kawasaki Disease in patients at a tertiary care center in Bangalore, India.

Methods:
A retrospective review of clinical records was performed and patients with KD, diagnosed during the study period (Feb 2017 to August 2023) were included. Clinical and laboratory profiles~~, including echocardiograms,~~and clinical outcomes were reviewed. Factors contributing to intravenous immunoglobulin (IVIg) refractoriness and coronary artery abnormalities (CAA) development were assessed. A p-value <0.05 was considered as significant.

Results:
73 children with KD presented to the center during the study period. The mean age at presentation was 34.64 ± 29.73 months. Males were predominantly affected ~~involved~~(n=49, 67%). The mean duration of fever was 9.50 ± 4.47 days. Mucosal involvement and rashes (71%) were the most common clinical abnormalities, followed by eye signs (59%) (Table 1). Incomplete KD was seen in 39 patients (53%). Overall, 33 patients (45%) developed~~had~~ CAA ~~development~~. 97 % of patients received intravenous immunoglobulin (IVIG) along with~~plus~~ aspirin as the first line of treatment, while, 53 % of them needed intensification of treatment. A total of 23 children in the cohort were refractory to IVIg treatment (32%). Those with mucosal changes and lymphadenopathy seemed to have refractory KD(p=0.01). Children with IVIg refractory KD were at higher risk of developing CAA(p=0.004) and were more likely to present with incomplete KD(p=0.02). H~~Factors affecting the refractoriness of the disease include mucosal changes and lymphadenopathy (p=0.01). Those with refractory disease were found to be associated with coronary artery abnormalities(p=0.004) and incomplete KD (p=0.02).~~ ~~H~~emoglobin was significantly lower in the group with coronary artery involvement (p = 0.005). On follow-up, the majority of the CAA was resolved (91%). ~~What happened to CAA on follow-up? How many resolved?~~

Conclusion:

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We hereby present one of the largest single-center cohort of Kawasaki disease from South India. A majority of our patients had incomplete KD and a significant proportion developed CAA.

Table 1

	(n-73)
Age (month)	34.64 ± 29.73
M: F	49:24
Complete: Incomplete	34: 39
Clinical Features	
Duration of fever (days)	9.50 ± 4.47
Eye sign	43(58.9 %)
Mucosal Changes	52(71.2%)
Lymphadenopathy	17(23.3%)
Extremity	28(38.4%)
Rashes	52(71.2%)
Perianal peeling	12(16.4%)
Irritability	28(38.4%)
Respiratory Symptoms	10(13.7%)
Shock	3(4.10%)
Abdominal Pain / Diarrhoea	10 (15.1%)
Seizure	3(4.1%)
Hematological Parameters	
Hb (g/dL)	10.28 ± 1.42
TLC (cells/cu mm)	15527 ± 8256.7
Platelet (cells/ cu mm)	622000 ± 3.64
CRP (mg/l)	83.5 ± 79.2
ESR (mm/hr)	62.84 ± 35.51
AST (U/L)	25.73 ± 21.59
ALT (U/L)	21 ± 19.3
Cardiac Findings	
Coronary dilatation	33(45%)
MI	1 (1%)
LV dysfunction	6(8%)
Valvular regurgitation	3(4.1%)
Aortic Root dilation	3(4.1%)
Pericardial Effusion	3(4.1%)
Treatment	
Methylprednisolone	28(38.3 %)
Infliximab	11(15%)

IVIG	71(97.2%)
Aspirin	73(100%)
Dual Anti Platelet	5(6.8%)
Warfarin / LMWH	5(6.8%)

A study of the clinical profile of infantile Kawasaki disease in children at a tertiary care center in South India

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Affiliation:
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Introduction:
Kawasaki Disease (KD) is an acute, self-limiting systemic vasculitis of small and medium vessels and occurs mainly between six months and five years of age.

Objective:
To study the clinical profile of infantile Kawasaki Disease in patients at a tertiary care center in Bangalore, India.

Methods:
All children presenting to the center from February 2017 to August 2023, diagnosed to have infantile KD, were retrospectively included in the study. The clinical and laboratory parameters were analyzed. Factors contributing to intravenous immunoglobulin (IVIg) refractoriness and coronary artery abnormalities (CAA) development were assessed. A p-value <0.05 was considered as significant.

Results:
A total of 26 children with infantile KD presented to the center during the study period. The mean age of presentation was 7.76 ± 3.29 months. Males were predominantly affected~~involved~~ (73%). Incomplete KD was seen in 69% of children. The mean duration of fever was 9.46 ± 4.81 days. Rashes were the commonest clinical abnormality ~~for the group~~, followed by mucosal involvement (96% and 84.6 % respectively). 53.8 % of infants had coronary artery dilatation. Amongst this, two children had giant aneurysms of the left main coronary artery (LMCA). One child had bilateral axillary aneurysms. 46% of these children had refractory KD. ~~, although, it was not clinically significant(p=0.29).~~96 % of ~~these~~ children in our cohort~~children~~ were treated with IVIg, and 69% required intensification with methylprednisolone and infliximab~~. (how many were given primary intensification and how many treated for refractory KD).~~ All patients ~~were started on~~received aspirin. ~~I The average time to become afebrile~~for defervescence ~~after treatment with IVIG was 1.2 ± 0.478 days. I~~n this cohort, a prolonged duration of fever was associated with a higher risk of development of CAA(p=0.01). ~~his cohort, extremity changes and lymphadenopathy were found to be associated with incomplete KD (p=0.005 and p=0.007).~~

Conclusion:
Infants are more likely to present with incomplete KD and at higher risk for IVIG resistance and CAA.~~.~~ We hereby present 26 patients with infantile KD.

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Infantile KD(n=26)	
Age (months)	7.76 ± 3.29
M: F	19:7
Complete: Incomplete	8: 18
Duration of fever (days)	9.46 ± 4.81
Eye sign	20 (76.9%)
Mucosal Changes	22(84.6%)
Lymphadenopathy	3(11.5%)
Extremity	9(34.6%)
Rashes	25(96.1%)
Perianal peeling	6(23%)
Irritability	15(57.6%)
Respiratory Symptoms	3(11.5%)
Shock	1(3.8%)
Abdominal Pain / Diarrhoea	7(26.9%)
Seizure	2(7.6%)
Laboratory parameters	
CRP (mg/L)	73.00 ± 60.69
ESR (mm/hr)	65.9 ± 32.59
Platelet (cells/cu mm)	723000 ± 4.31
Hb (g/dl)	9.69 ± 1.61
TLC (cells/cu mm)	16715.63 ± 8152.161
AST (U/L)	35.31 ± 27.21
ALT (U/L)	28.87 ± 21.25
Treatment	
Methylprednisolone	13(50%)
Infliximab	5(19.2%)
IVIG	25(96.1%)
Aspirin	26(100%)
Dual Anti Platelet	2(7.6%)
Warfarin / LMWH	2(7.6%)
Post-treatment	
Time to become afebrile after IVIG (days)	1.2 ± 0.478
Time to discharge (days)	4.84 ± 4.54

Kanika Arora[1], Deepti Suri[1], Amit Rawat[1], Surjit Singh[1]

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Role of Innate cells in pathogenesis of Kawasaki disease

Introduction: Kawasaki disease (KD) is an acute systemic vasculitis of childhood that does not have a known cause or aetiology. Innate lymphoid cells (ILC), Gamma Delta T cells (GD)T cells, Natural killer T cells (NKT) are being increasingly recognized to have a pathogenic role in causation of disease. Alterations in these cells have been seen in other vasculitis disorders like Behcet's disease and Takayasu arteritis.

Methodology: Diagnosis of KD was based on American Heart Association 2017 criteria. All patients were treated with intravenous immunoglobulin (IVIg) and aspirin. Different type of Innate lymphoid cells (ILC1, ILC2,ILC3) were assessed in control n=20, n=20 (Pre IVIg and post IVIg) using CD45 APC H7, Lineage- FITC, CD127 PE, CD294 Percp Cy5.5, CD117 BV421, CD56/16 BV 510.Gamma delta T cells were assessed in Control=20, n=20 (Pre IVIg and post IVIg) using CD45 APC-H7, TCR αβ APC,TCR γδ BV421, CD3 PerCpcy5.5. Natural killer T cells were assessed in control, pre IVIg and post IVIg using CD45 APC-H7, CD7 APC, CD3Percpcy5.5, CD56 BV510 and CD16 BV510.Flow cytometric analysis was performed using markers specific for innate lymphoid cells, gamma delta T cells and natural killer T cells.

Results

Innate lymphoid cells were characterized as CD45+, Lin-, CD127+ ILC1 were characterized as CD45+ Lin- CD127+, CD294- and CD117-. ILC2 were characterized as CD45+ Lin- CD127+ CD294+ CD117-. ILC3 were characterized as CD45+ Lin- CD127+ CD294- CD117+. Total Innate lymphoid cells and subsets were analyzed using CD45, Lin-, CD127, CD294, CD117, CD56/16. Percentage of total ILCs were higher in pre IVIg (Mean ± SD 2.7(0.34-4.5) as compared to controls 0.5(0.1-2.2). ILC2 subpopulation was lower in pre IVIg 4.9(0.6-27.6) patients and increased in post IVIg patients 11(0.51-24.2) as compared to control 12.4(2.7-32). ILC1 populations were increased in pre IVIG patients 88.3(8.5-96.6) as compared to control 65.5(34-85.6). ILC3 were reduced in pre IVIg patients 4.2(0.8-21) and post IVIg patients as compared to control 17.8(1.82-41.9). NK cells were increased both in pre IVIg 7.5 (1.1-16.8) and post IVIg 7.4 (0.5-19.2) patients. Gamma Delta T cells were increased 6.185(2.7-24) in pre IVIg condition than post IVIg 5.575(2.4-14.8) condition. No significant change in NKT population in acute patients as compared to control.

Conclusion: Innate immune cells (Total ILC, ILC type 1 and GDT) were increased in KD, ILC type II, ILC type III, and NKT were decreased in KD suggesting acute activation of innate pathways.

OBJECTIVES: There is a paucity of literature on long term myocardial sequelae in patients with Kawasaki Disease (KD) who have had transient coronary artery abnormalities (CAAs) resolving on IVIg administration. The present study aimed to evaluate the long-term changes in myocardium and coronary artery in patients with KD who have had transient CAA and had received IVIg using 2D-echocardiography and cardiac magnetic resonance imaging (CMRI). In this study, transient CAAs resolved in 12 weeks' time after therapy.

METHODS: This prospective observational study was conducted between July 2021 and September 2022. 10 patients with mean age of 17.1 years (range 15-21 years) with mean age at time of diagnosis of 4.16 years (range 11 months-7 years) underwent CMRI on 3 Tesla machine - Philips Ingenia, 2D-transthoraic echocardiography on the same day.

RESULTS: Echo during the present study revealed no myocardial dysfunction or coronary abnormality in all patients except in one, in whom there was aneurysms of RCA (2.45 z) and LMCA (2.87 z) detected on 2D echo. CMRI confirmed same findings in the same patient. CEMRI also showed CAAs in 03 patients (Z scores of 2.79, 2.12, 2.97) with 1 patient showing elevated T1 values with no perceivable late gadolinium enhancement with rest of them having normal MRI findings.

CONCLUSION: Patients with KD who have transient CAAs on 2D echo during the acute stage and did receive IVIg do have long-term coronary or myocardial sequelae on follow up CMRI. Areas of fibrosis as detected in 1 of our case (elevated T1 values). The study is quite revealing that majority of patients on follow up in the clinical context of KD with transient CAAs at initial illness, have impact on cardiac function with no or minimal myocardial fibrosis. Further CMRI is a useful imaging modality in patients with KD on long term follow-up as it helps understand the myocardial function and changes in myocardium which are not picked by routine 2-D echocardiography.

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

Authors:

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5: Professor and Head, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh.

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 aimed to 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 conducted between July 2021 and September 2022 in the Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, the Department of Radiodiagnosis and Imaging, the Department of Cardiology, Post Graduate Institute of Medical Education and Research, Chandigarh. Ten patients with mean interval of

11.7 years (range 8-21 years) after spontaneous defervescence of KD underwent Cardiac Magnetic Resonance Imaging (CMRI) on 3 Tesla – Philips Ingenia platform. 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 low ejection fraction (EF). One amongst these also had elevated T1 values (1345 ms in septum in mid cavity and 1245 ms 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 had had 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.

Title: Kawasaki Disease-Like Presentation in a Child with Chronic Granulomatous Disease: A Diagnostic Challenge

Author: Dr. Manvi Choudhary, Dr. Anu Maheshwari, Dr. Deonath Mahto, Dr. Rajan Garg

Department of Pediatrics, Lady Hardinge Medical College

Introduction: Chronic Granulomatous Disease (CGD), a hereditary immune deficiency caused by gene mutations, impairs reactive oxygen species (ROS) production, leading to ineffective microorganism clearance. This results in recurrent infections and potential hyper-inflammatory autoimmune manifestations. Kawasaki Disease (KD), a childhood vasculitis, has associations with primary immunodeficiencies like CGD, highlighting the intricate relationship between immunological disorders and pediatric cardiology.

Case summary: This case concerns a 3-year-old girl born to consanguineous parents, who experienced recurrent respiratory symptoms .At 3 months, she was diagnosed with pneumonia and treated at a private hospital. Her symptoms recurred at 11 months, characterized by a persistent high-grade fever and cough. Despite initial empirical treatment with intravenous antibiotics and anti-tuberculosis therapy (ATT), her condition did not improve. Further investigations, including bronchoscopy and bone marrow aspiration, yielded no definitive diagnosis.

Extensive workups, including tuberculosis screening, ACE levels, Ig profile, and HIV serology, all returned normal results. Flow cytometry revealed an increased CD4 to CD8 ratio, while markers for LAD (leukocyte adhesion deficiency) were negative. A neutrophil oxidative index test indicated reduced values, suggestive of CGD, a rare immune disorder. Prophylactic treatment with septran and itraconazole was initiated.

At 14 months, she experienced another episode of severe pneumonia, necessitating a 21-day course of intravenous antibiotics. Subsequently, at 36 months, she presented with fever, cough, and rapid breathing. Blood investigations revealed severe anemia, marked neutrophilic leucocytosis, elevated inflammatory markers, and notable LMCA dilation, resembling Kawasaki Disease (KD). Intravenous immunoglobulin (IVIG) therapy reduced LMCA dilation, and prednisolone treatment alleviated her symptoms. This complex case underscores the diagnostic challenges and importance of considering rare immune-related conditions like CGD and KD in pediatric patients with recurring symptoms.

Discussion: This case report details a 3-year-old girl with CGD diagnosed at age 1, exhibiting KD-like symptoms at age 3, including LMCA dilation. Similar cases have been reported, linking CGD and KD - like presentations. Autoimmunity in CGD may result from impaired pathogen clearance and heightened inflammation. Timely KD diagnosis is crucial in these immunodeficient children, as late recognition exacerbates morbidity and mortality. CGD type doesn't significantly affect symptom onset, though pneumonia episodes are more common in autosomal recessive CGD. Vigilant monitoring is essential due to a 3% recurrence rate of KD-like illness in these patients, emphasizing early investigation in unresponsive cases.

Kawasaki disease in PICU: Clinico-epidemiological profile and inflammatory markers -Experience from a tertiary Care Centre in Eastern India

Dr Mrinmoy Roy*, Dr Debadatta Mukhopadhyay**, Dr.Ashok Kumar Mondal***, Dr.Dilip Pal €

*JR, **Associate Professor, ***Professor and HOD, € Professor and Principal, Dr B C Roy Post graduate Institute of Paediatric Sciences

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ABSTRACT :

BACKGROUND

Kawasaki disease, a type of muco-cutaneous syndrome is an acute, self-limiting, systemic vasculitis of unknown etiology mainly affecting infants and children. It is the most common cause of acquired heart disease in children affecting the coronary arteries leading to aneurysmal lesions, arterial thrombotic occlusion and even may cause sudden death. Occasionally children may present with severe illness or shock , requiring admission in PICU.

OBJECTIVE

To identify the predictors of severity and outcome of children with Kawasaki disease requiring PICU admission.

METHOD

This was an observational study, over a period of 1 year in a tertiary care centre in Eastern India.. Children with Kawasaki disease admitted in the PICU were included in the study. Details of the patients were noted including socio-demographic factors such as Age, Sex, Gender, Address, and anthropometric data . Clinical history with detailed clinical examination findings, investigations and and specific management given after admission were recorded in the data sheet.

Statistical calculations were done using Statistical Packages for the Social sciences (SSPS)v25.0 software. Significant differences between groups to be determined using the chi square test or Fischer exact test where appropriate.

RESULTS

Among 11 patients of diagnosed Kawasaki disease who were admitted in PICU , 10 survived and one patient succumbed. There were 6 boys(55 %) and 5 girls(45 %) Seven patient were below 5 years(64%). All except one patient had high grade fever and were admitted within 7 days. Only one had late presentation with fever for 15days and that patient died. One patient had cutaneous manifestations simulating SJS. 9 (82%) presented

with shock. 8 of 11 children (73%) had loose stool and vomiting, all of whom required positive pressure ventilation, prolonged ICU stay and 1 died. Among them, 80 % patient had anaemia, hypoalbuminemia seen in all patients(100%). Increased ferritin(>1000) seen 3 patient(27%) (treated as KD with HLH), all had prolonged PICU stay and one of them died. Increased procalcitonin (>1) seen in 8 patients(73%). 90% (10 out of 11) of the children with KD in PICU required positive pressure support , 6 invasive ventilation(55%) and 5 required NIV (45%).

CONCLUSION

All patients presenting with diarrhoea had a stormy course and required positive pressure ventilation.

All patients in PICU had hypoalbuminemia and fever> 7days

We lost the child who had diarrhoea, increased ferritin>1000, and hypoalbuminemia (<2.5).

Limitations : This is a pilot study and is being extended to compare with those children with Kawasaki disease who did not require PICU admission.

Title page: Chromonychia in a child with multi-inflammatory syndrome in children (MIS-C): A sign of hyperinflammatory state?

Authors: Mugundhakumar Balashanmugam[1], MBBS; Abarna Thangraj[1], MD; Pallavi L Nadig[1], MD; Rakesh Kumar Pilania[1], DM

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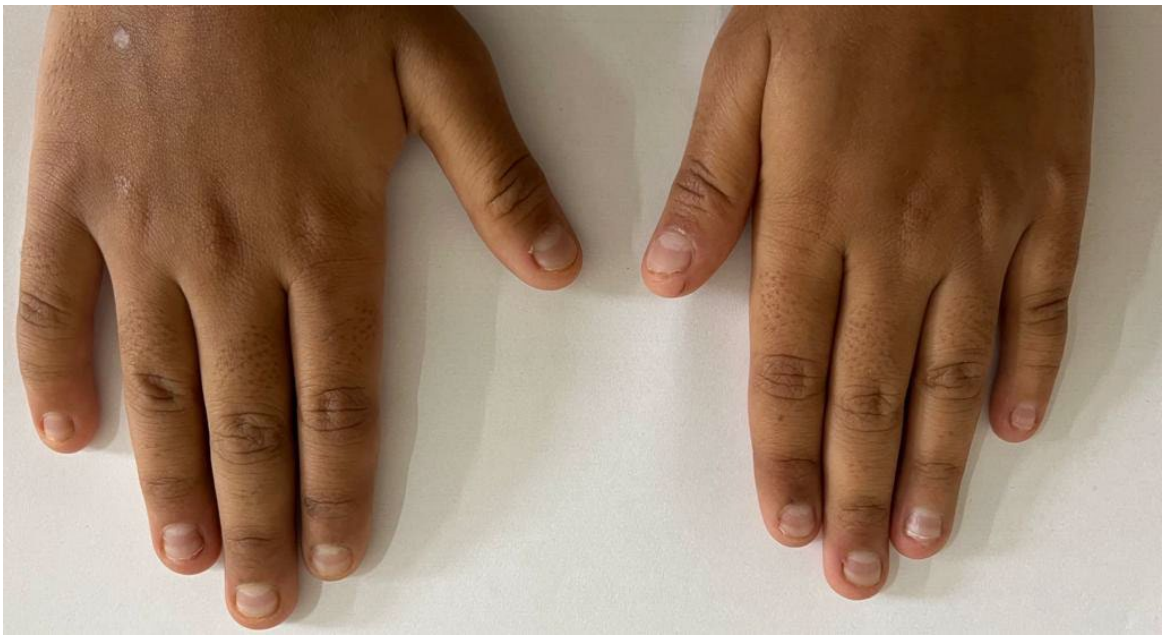
Case details: An 8-year-old girl presented with fever, generalized maculopapular rash, conjunctival congestion, abdominal pain, vomiting and loose stools for 4 days and features of shock. Investigation revealed anemia (84 g/L), lymphopenia ($0.46*10^9$/L), with platelet count $57x10^9$/L. Inflammatory markers [erythrocyte sedimentation rate (ESR) 43 mm/hour; C-reactive protein (CRP) 276 mg/L (N<6); serum ferritin 1590 ng/ml (N< 366); D-dimers 948 ng/ml (N < 250); IL-6 364 pg/ml (N <7)], Pro BNP level [13940 pg/ml (N: 0-125)] and anti-SARS-CoV-2 antibody titres were elevated [7403 IU/ml (N< 10)]. Her infective workup was negative. Diagnosis of multi-inflammatory syndrome in children following COVID-19 infection (MIS-C) with cardiogenic shock was proffered. 2D-echocardiography showed ejection fraction of 20% with dilated left main coronary artery (LMCA) (+2.36z) and aneurysm in the left anterior descending artery (LAD) (+3.86z). She was treated with intravenous immunoglobulin (2gm/kg), 5 doses of pulse methylprednisolone (30mg/kg) followed by oral prednisolone, aspirin, and supportive management. On 3rd week of illness, she developed orange-brown horizontal lines over all fingernails suggestive of chromonychia (Figure).

Figure: Orange-brown transverse line in nails seen in all fingers- Chromonychia



Title: Follow-up CT coronary angiography in children with Kawasaki disease: Our experience at a tertiary care centre in North India.

Authors: Munish Arora, Manphool Singhal, Rakesh Kumar Pilania, Abarna Thangaraj, Ankur Kumar Jindal, Pandirajan Vignesh, Deepti Suri, Surjit Singh

Background: Coronary artery abnormalities (CCAs) can occur in up to 25% of children with KD who have not received Intravenous Immunoglobulin. Transthoracic 2D-Echocardiography (2DE), hitherto the imaging modality of choice, has several limitations. Computed Tomography Coronary angiography (CTCA) has enabled the comprehensive evaluation of coronary arteries in children with KD. This study pertains to interval CT coronary angiography in 15 children with KD at a tertiary care centre in North India.

Patients and methods:

CTCA was carried out on 128-slice dual-source CT scanner (Siemens, Erlangen, Germany) which is installed in our institute. Interval CTCA was performed in 15 children.

Results:

Median age at diagnosis of KD was 48 months [range 4-96 months]. Median interval between the first and second CTCA examination was 37 months [range 6-85 months]). Findings of CTCA at presentation revealed 21 aneurysms and 11 dilatations: left main coronary artery (LCA) – 5 aneurysm and 2 dilatation and ectasia in 1; left anterior descending artery (LAD) – 9 aneurysm, 1 dilatation; right coronary artery (RCA) – 7 aneurysm and 1 dilatation and left circumflex artery (LCx) dilatation in 6 patients. 6 patients had giant aneurysms (LAD – 5; RCA-3). Thrombosis and stenosis were noted in 3 patients each in initial CTCA and complex aneurysm with multiple skip lesions were seen in 3 patients. Interval CTCA was completely normalized in 5/15 (33.3%) patients. Remaining 10 patients showed persistent (albeit regressed/remodelled) coronary artery

aneurysms: LCA-5; LAD-8; RCA-7; LCx-2. Two patients had shown mural calcifications. Two patients in whom CTCA was performed at intervals of 37 months and 72 months after diagnosis of KD, revealed long segment stenosis in LAD and significant mural calcification. One patient developed thrombus in fusiform aneurysm of LAD after 42 months. Of the 3 patients with stenosis in initial CTCA, 2 patients had normal study after 60 months of follow up, one patient had progressive stenosis involving up to 80% of LAD. One patient developed stenosis in follow up which wasn't noticed in the initial CTCA.

Conclusions:

Children with KD and CAAs require prospective long-term follow-up as they may develop complications like thrombosis, stenosis, and calcifications. These complications can be missed by 2DE which is more subjective and is user dependent. CTCA provides more detailed and comprehensive evaluation in comparison to 2DE.

Immune dysregulation in Kawasaki disease: a report of 10 such cases

Introduction:

Kawasaki disease is the most common medium vessel vasculitis which usually occur in children less than 5 years of age. The cause of Kawasaki disease (KD), is currently unknown and many hypothesis have been proposed for the same.

In immune dysregulation disorders, the inability of the immune system to eradicate the pathogens and an exaggerated inflammatory response, may lead to the development of KD. Patients with immuno- deficiencies frequently present an incomplete form of KD. We present 10 patients in support of this hypothesis. Three patients were having nephrotic syndrome who had developed Kawasaki disease. Two patients were having haematological malignancy who had developed Kawasaski disease. Two patients were having HIV infection who had developed Kawasaki disease. One patient had nesidioblastoma who had presented with recurrent hypoglycemic episodes developed Kawasaki disease. One patient had PFAPA while one patient had autoimmune hepatitis. All the patients received IVIg for therapy of Kawasaki disease. One patient had resistant KD for which he was given infliximab as rescue therapy for KD.

Conclusions :

In this report we describe 10 patients of kawasaki disease who also had other immunological diseases (other than Primary Immunodeficiency). The association of KD and other immune-mediated conditions has been recognized, as has been recognized between KD and atopy and KD and psoriasis in children which suggests that patients with KD may have a general propensity toward immunodysregulation

Title: Neurological manifestations of Kawasaki disease - Our experience at tertiary care centre from North-Western India

Presenting Author: Pallavi L Nadig

Author: Pallavi L Nadig, Rakesh Kumar Pilania, Suprit Basu, Reva Tyagi, Saniya Sharma, Manpreet Dhaliwal, Ankur Jindal, Vignesh Pandiarajan, Deepti Suri, Amit Rawat, Surjit Singh

Introduction:

Kawasaki disease (KD) is a medium vessel vasculitis, presenting typically in children below 5 with characteristic features such as polymorphous rash, extremity changes, mucosal changes and conjunctivitis and cervical lymphadenopathy. Neurological features like cerebrospinal fluid pleocytosis, seizures, facial nerve palsy, paralysis of the extremities have been described. We here in report our experience on neurological manifestations in our cohort of KD.

Patients and methods: All children with KD from Chandigarh, who presented to Pediatric Allergy Immunology unit, Postgraduate Institute of Medical Education and Research, Chandigarh, a tertiary care center in north India from January 1994 - September 2022 were analyzed.

Results: Neurological manifestations were noted in 20 of 1187 patients (1.68%). Most common manifestation was generalized seizures which was seen in 9 patients. Others included encephalopathy (n=6), focal seizures (n=1), headache (n=4), transient visual loss (n=1), features of raised intracranial pressure (headache, extensor plantar, neck rigidity, papilledema) (n=2), and sensory neural hearing loss (n=1). Neuroimaging was carried out in 12 patients with various findings including transient hydrocephalus (resolved on follow-up imaging) (n=1), cerebral venous thrombosis (n=2), micro bleed (n=1), hypoxic injury (n=1), ring enhancing

lesion (n=1), and normal study in rest (n=6) of the patients. Lumbar puncture and cerebrospinal fluid (CSF) examination was done in 11 patients; 3 had SF pleocytosis, in rest 8 patients CSF study were normal. Concomitant gastrointestinal manifestations were seen in 6 patients, pulmonary in 5, KD shock syndrome in 2, macrophage activation syndrome in 1, scrotal gangrene in 1, and arthritis in 1. Coronary artery abnormalities were seen in 6 patients (coronary artery aneurysm in 2, coronary artery dilatations in 4 patients).

Conclusion: Neurological manifestations, though rare, are important cause of confusion in diagnosis of KD due to presentation which is indifferentiable to other causes of acute encephalopathies.

Thrombotic calcified aneurysm in a child with Kawasaki disease at 4 years of follow-up

Author sequence: Pallavi Nadig[2], Manphool Singhal[1], Rakesh Kumar Pilania[2], Tarun Sidhant[1], Surjit Singh[2]

Case details:

An 8-year-old boy was diagnosed with Kawasaki disease (KD) at the age of 4 years. He received intravenous immunoglobulin (2 g/kg) along with oral aspirin. At the time of presentation, transthoracic echocardiography (TTE) revealed a saccular aneurysm in the left main coronary artery (LCA) measuring 7.7 mm in diameter, a dilated left anterior descending (LAD) artery and a right coronary artery (RCA) aneurysm (4.0 mm in diameter). He was started on warfarin due to giant coronary artery aneurysm, and low-dose aspirin was continued.

CT Coronary angiography (CTCA) performed 4 years on follow-up showed dilated proximal RCA (2.8mm) and two fusiform aneurysms in mid-RCA (3.5 mm and 3.2 mm) along with mural calcifications. There was a fusiform aneurysm in distal LCA (8.4mmx12.5mm) extending into the proximal left circumflex coronary artery (LCx) and ramus intermedius coronary artery. A densely calcified saccular aneurysm (12.6mmx15.6mm) filled with hypodense contents suggestive of thrombus was visible in the LAD beyond its origin. Mid and distal segments of the LAD were markedly attenuated and showed bare opacification (likely from collaterals). Agatston's calcium scoring was 497, indicating a coronary age of more than 70 years (Figure 1).

This case emphasises the importance of CTCA in delineating the intricacy of coronary artery abnormalities in children with KD. This degree of coronary artery calcification in 4 years follow-up is dystrophic rather than atherosclerotic.

Legend for illustration

Figure 1:- CT angiographic images (a- volume rendered image-VR, b- curved reformatted image-CPR, and c-oblique coronal maximum intensity projection-MIP) show densely calcified saccular aneurysm (thick arrow in a) in proximal left anterior descending coronary artery (LAD) (12.6mmx15.6mm) filled with hypodense contents suggestive of thrombus (inset- arrow). Note markedly attenuated mid and distal LAD (arrowhead in a). Distal left coronary artery (LCA) demonstrates a fusiform aneurysm (8.4mmx12.5mm) (thin arrows in a & b) extending into the proximal left circumflex coronary artery (LCx) (arrowhead in b) and ramus intermedius coronary artery (interrupted arrows in a & b). Proximal RCA is dilated (2.8mm) with two fusiform aneurysms in mid-RCA (3.5 mm and 3.2 mm) along with mural calcifications (arrows in c).

Title: 7-month-old infant with incomplete Kawasaki disease, giant coronary artery aneurysm, coronary artery thrombus: Challenges in management during the acute phase

Authors: Pallavi Nadig, Rakesh Kumar Pilania, Prabal Barman, Manphool Singhal, Surjit Singh

Abstract:

Introduction:

Kawasaki disease is a medium vessel vasculitis of childhood with predilection to coronary arteries. Infants with KD often present with incomplete and atypical forms (40%) compared to older patients (10–12%). Delayed diagnosis and treatment, higher incidence of coronary arteries abnormalities, and greater intravenous immunoglobulin (IVIG) resistance frequently occur in KD infants. Here we describe a 7-month-old infant who presented with incomplete Kawasaki disease with giant coronary aneurysms complicated with thrombus.

Clinical description: A 7-month-old boy presented with fever, generalized maculopapular rash, redness of eyes and swelling around left side of neck. Investigations showed hemoglobin 60 g/L, total white cell counts $18.2x10^9$/L ($N_{75\%}L_{21\%}M_{3\%}E_{1\%}$), platelet count $175x10^9$/L, elevated C- reactive protein (67 mg/L; N <6). He was noted to have congestive cardiac failure, pericardial effusion and mild mitral regurgitation, requiring mechanical ventilation and inotropic support at 4th week of illness. SARS-CoV-2 antibodies were positive. A possibility of Multisystem inflammatory syndrome in children versus Kawasaki disease (KD) was considered. He received intravenous immunoglobulin (IVIg; 2g/kg) and oral prednisolone (2mg/kg/day initially and then tapering), digoxin, enalapril, and furosemide. A 2-dimensional(D)-echocardiogram done at 10th week of illness showed giant aneurysms of left anterior descending artery (LAD) with thrombus. He was thereafter referred to our institute for further evaluation. The 2D-echocardiography confirmed giant aneurysms of LAD (14.9 mm;

+47.2 Z) with thrombus, left circumflex (4.39mm; +11.48Z), and right coronary artery (RCA) (4.17 mm; +9.5Z). As the N-terminal pro B-type natriuretic peptide (NT-proBNP) (3807 pg/mL; N<125), creatine kinase-MB fraction (42 IU/L; N:5-25) and troponin T (58.6 ng/L; N: 12.7- 24) were still elevated, he was treated with a second dose of IVIg (2g/Kg); infliximab (10 mg/kg); oral prednisolone (2mg/kg/day, tapered and stopped over 6 weeks); cyclosporine (3mg/kg/day); low molecular weight heparin (2mg/kg/day) and aspirin (5mg/kg/day). Nail examination at 2 weeks of follow-up showed nail pitting over multiple nails with Beau's lines

Conclusion:

Diagnosis of Kawasaki disease in infants can be very challenging as they may not fulfil the epidemiological case definition from AHA-2017 and appears to run a more aggressive clinical course due to delay in with a significant risk of development of CAA even with IVIg treatment. High index of suspicion for KD is required in an infant presenting with unexplained fever lasting more than 5 days, and early initiation of IVIG and other adjuvant therapy is required.

ABSTRACT

Pulmonary Presentation of Kawasaki Disease: A diagnostic challenge

Piyush Chauhan, Avinash Sharma, Sandesh Guleria

Dr. Rajendra Prasad Government Medical College Tanda, H.P.

Background: Kawasaki disease (KD) is a multisystem medium vessel vasculitis of unknown etiology, affecting predominantly younger children. Pulmonary presentation is a rare (1.83%) manifestation in KD and can have adverse clinical consequences.

Objective: To report a child with atypical KD, who presented with empyema thoracis and subsequently developed clinico-laboratory features of KD.

Case

A 7-year-old male child presented to a hospital elsewhere with fever and cough for a week and difficulty in breathing for 2 days. On examination, he had tachypnea with chest retractions and dull percussion note with reduced breath sounds. Chest X-ray and ultrasonography thorax was suggestive of pleural effusion. Thoracostomy was done, pus was drained and its gram staining showed scanty gram-positive cocci. He was initiated on intravenous (I/V) ceftriaxone (100 mg/kg/day) and vancomycin (60 mg/kg/day), continued for 20 days. He continued to have fever. On day 20 of illness, the child had maculopapular rash over the whole body, edema of hands and feet and was then referred to our hospital.

At the time of presentation, he had fever (102^{o}F). He had pallor, cervical lymphadenopathy, edema on hands and feet and subsequently developed desquamation palms and soles. His pus culture was sterile. Investigations showed anemia, neutrophilic leucocytosis, thrombocytosis and elevated CRP and ESR. Possibility of KD was kept and he was given Intravenous Immunoglobulins (IVIG) which led to clinical improvement and no fever spikes were recorded after its administration. Echocardiography showed small aneurysm (Z-score of LCA=3.9, RCA=4.43). He was discharged on oral aspirin (5 mg/kg/day) and kept on follow up.

Conclusion: While pulmonary involvement in children with KD is not a common manifestation, it can result in diagnostic confusion. Possibility of KD should be kept in mind in young children with empyema with persistence of fever and clinico-laboratory features of KD. Timely diagnosis and treatment may prove lifesaving.

Ciclosporin is useful in severe Kawasaki Disease: Experience from a tertiary care centre in North-West India

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Background: Kawasaki disease (KD) is a medium vessel vasculitis of agnogenic origin. Although intravenous immunoglobulin (IVIg) is the standard of care, however, approximately 15-20% of patients remain refractory to conventional therapy. In addition, this subset of patients with KD has a higher propensity to develop coronary artery abnormalities (CAAs) with severe manifestations including macrophage activation syndrome (MAS), KD shock syndrome (KDSS) and atypical manifestations. It has been reported that ciclosporin can produce rapid defervescence and reduce CAA in IVIg-non-responders and severe forms of KD. We report the role of ciclosporin in 31 children with KD.

Methods: A review of medical records of all patients who were diagnosed to have KD during the period January 1994 - June 2023 in Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India was done. Case records of children with KD who had received ciclosporin were analysed in detail.

Results: Of the 1245 patients with KD, 31 patients (22 boys) received ciclosporin. Median age at diagnosis was 2 years (range 0.3-13 years). Indications for using ciclosporin were: MAS (2/31); KDSS (5/31), presence of CAAs (27/31); both KDSS and CAA (4/31); and

pancreatitis (1/31). Amongst the patients who had CAAs, 8 (26%), 2 (6%) and 17 (55%) had small, medium and giant aneurysms respectively. All patients had received IVIg (2g/Kg), corticosteroid (methylprednisolone 30 mg/kg/day for 3 days followed by oral taper. The dose of ciclosporin was 5 mg/kg/day, and it was tapered and stopped after a duration of 4 to 6 weeks. One patient died during hospital stay due to refractory MAS (he had also received tocilizumab and etoposide). Dimension of large CAAs (moderate and giant CAAs by z-score) normalised and/or reduced in size in 7/31 (23%) after a median duration of 540 days (range 330-730 days). Small CAAs normalised in 7/8 (88%) patients after a median duration of 10.5 days (range 2-35 days). None of the patients had any adverse event during therapy nor did any patient have any significant infection over a cumulative follow-up of 21596 patient-days.

Conclusions: In conclusion, our findings suggest that ciclosporin holds promise as an adjunctive therapy for intensifying treatment in IVIg non-responders and managing severe KD cases. Importantly, no adverse events were reported during the short course ciclosporin therapy, highlighting its safety profile.

Tryst of medium and large vessel aneurysms in a febrile infant: management conundrums

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Case report:

A 6-month-old boy was presented with fever for 20 days, conjunctival injection, and maculopapular rash over extremities. He had normal pulses and blood pressure. Hyperemia in the Bacille Calmette–Guérin vaccination site was noted. A clinical possibility of incomplete Kawasaki disease (KD) was considered. Investigations revealed leucocytosis (20.1×10^9/L, *N*: 4–11 $\times 10^9$/L; neutrophils 69%); thrombocytosis (612×10^9/L, N: 150–400 $\times 10^9$/L); and raised C-reactive protein (CRP: 87 mg/L, *N*: < 6). Two-dimensional echocardiography showed aneurysms involving the right coronary (RCA: 9.4 mm; + 24 Z), the left anterior descending (LAD: 6.4 mm; + 16.8 Z); the left circumflex (LCx: 3.2 mm; + 6.4 Z), and the left main coronary arteries (LMCA: 3.1 mm; + 4.6 Z). Computed tomography angiography (CTA) revealed aneurysms involving all four coronaries [largest: LAD and RCA]; abdominal aorta extending up to internal iliac artery; and left subclavian artery. He was administered intravenous immunoglobulin (2 g/kg) and infliximab (10 mg/ kg), oral cyclosporine (5 mg/kg/d), methylprednisolone (30 mg/kg/d × 3 days) followed by tapering doses of oral

prednisolone. Low molecular weight heparin (2 mg/kg/d), atorvastatin (5 mg/d), and aspirin (3 mg/kg/d) were also commenced. General well-being improved and inflammatory parameters also came down. However, persistent mild elevation in CRP was noted in the follow-up for which a second dose of infliximab (10 mg/kg) was administered at the 4th month of illness. At the 8th month of follow-up, the inflammatory markers were normal and the coronary artery aneurysms had only partially reduced in size (LAD: 5.25 mm, + 12.1 Z; RCA: 4.3 mm, + 7.9 Z). In view of unusual course of disease and systemic artery aneurysms, an underlying monogenic disease was also thought of; however, whole exome sequencing did not yield any pathogenic variants. For the management of large vessel vasculitis, a course of oral methotrexate was initiated (15 mg/m^2/week). After 2-years of follow-up, there has been minimal improvement in arterial dimensions, and he has developed calcifications in all 3 coronary arteries.

Points of discussion:

1. How to manage systemic artery aneurysms in KD?

2. Is there still a possibility of another etiology of the index case? How to proceed diagnostically?

Myocardial dysfunction on Cardiac Magnetic Resonance Imaging in children with Kawasaki Disease who had received intravenous immunoglobulin in acute phase of illness and had no coronary artery aneurysm: an observational study after mean follow-up of 14.2 years.

Authors:

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Introduction and objectives: Kawasaki Disease (KD) is vasculitis of unknown etiology with risk of coronary aneurysm. In this study, aim was to assess long term effect of KD on myocardial structure and function who had received intravenous immunoglobulins (IvIg) and had no coronary artery aneurysm in acute phase of illness using cardiac magnetic resonance imaging (CMRI).

Methods: This prospective observational study was conducted between July 2021 and September 2022. 10 patients with mean age of 19.2 years (range 13- 29 years) with mean age at time of diagnosis of 5 years (range 9 months – 12 years) underwent CMRI on 3 Tesla machine - Philips Ingenia, 2D-transthoraic echocardiography on the same day.

Results: Echo during the present study also revealed no myocardial dysfunction or coronary abnormality. But CMRI showed mild left ventricular systolic dysfunction in 3 of the 10 patients (EF <55% - 51%, 52%, 54%) with 1 patient showing focally raised native T1 values along posterior wall and at apex (focal fibrosis) and thrombosis in RCA with no perceivable late gadolinium enhancement with rest of them having normal MRI findings.

Conclusion: Patients with KD who had no coronary aneurysm on 2D echo and had received IvIg during the acute stage did not have long-term coronary or myocardial sequelae on follow up CMRI. Areas of focal fibrosis as detected in 1 of our case (elevated T1 values) and LV systolic dysfunction can be seen whose aetiology as of now remain elusive. The study is quite revealing that majority of patients on follow up in the clinical context of normal coronary arteries at presentation and have no major impact on cardiac function with no or minimal myocardial fibrosis. Further CMRI is a useful imaging modality in patients with KD on long term follow-up as it helps understand the myocardial function and changes in myocardium which are not picked by routine 2-D echocardiography.

Gene expression and protein levels of long-term endothelial dysfunction markers in patients with Kawasaki Disease from North India

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lntroduction

Kawasaki disease (KD) is an acute self-limited vasculitis with a predilection for coronary arteries. Children with KD may have abnormal expression of adipocytokines, proteins involved in vascular injury, remodeling and other inflammatory markers with altered cytokine profile and adhesion molecules that may last for prolonged periods and involved in accelerated coronary abnormalities.

Method

Present study highlights mRNA expression and protein levels of long term endothelial dysfunction markers in patients with KD. Patients were enrolled at different time intervals in 3 groups (20 each) as per AHA guidelines 2004 and 20 age & sex matched healthy controls. **Group 1**: KD diagnosed >6months-1.5 years; **Group 2**: >1.5 - 3years; **Group 3**: >3-4.5 years prior to enrollment. Patients with coronary artery aneurysms (CAA) were classified as per **Z score [Montreal (JASE 2011)]**.

Complementary DNA (cDNA) converted from extracted whole blood RNA was used to perform real-time PCR (ABI StepOnePlus). 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 U test. Concentration of protein levels were estimated by Luminex technique (Multiplexing array based on solid-phase bead-based sandwich immunoassay) using MAGPIX with Xponent software and analyzed by Belysa TM 1.2.0. Protein levels of resistin and osteopontin were measured using ELISA (Enzyme linked immunosorbent assay-Sandwich ELISA) and optical density was determined using a microplate reader (Tecan) at 450nm.

Results

Real-time PCR analysis for intra group 1 revealed upregulated CXCL8, pecam-1, osteopontin in KD patients with CAA as compared to patients without CAA (p=0.038, p= 0.05, non-significant) respectively. Intragroup analysis for group 2 showed increased CXCL8, osteopontin and down regulated expression of leptin in patients with aneurysms as compared to patients without CAA (non-significant). Levels of endoglin, pentraxin-3, VEGF-A were comparable. Intragroup analysis for group 3, revealed elevated VEGF-A, CXCL8, Pentraxin-3 in patients with CAA as compared to patients without aneurysms while pecam-1, endoglin and osteopontin were comparable in both.

Significantly elevated pentraxin-3 levels in KD patients (Group1: p=0.03, Group 2: p=0.01) than control suggests it as a definitive biomarker for the prediction of KD. Comparable values were noted in PECAM-1 levels in patients and healthy controls in all 3 groups. Elevated VEGF-A levels were observed in KD patients (Group 2: p=0.03) than control. Significantly elevated levels of pro inflammatory cytokine CXCL8 (Group1, 2 &3: p= 0.01, p=0.0001, p=0.04 respectively) and angiopoietin-2 (Group1, 2 &3: p= 0.0006, p= 0.0005, p= 0.009 respectively) was noted in patients as compared to healthy control. Higher serum resistin levels were observed in patients while no significant difference was found in patients with and without CAA. Significantly elevated osteopontin levels were observed in KD patients in all 3 groups than healthy controls ($p<0.0001$).

Conclusion

Real time analysis revealed altered gene expression profile in Kawasaki disease patients with aneurysms. Elevated levels of pro inflammatory cytokines suggest its role in pathogenesis of KD and progression of disease in patients with CAA. There is disruption of vascular homeostasis in KD patients and in patients with aneurysms with altered lipid metabolism. Elevated osteopontin level is associated with increased risk for vascular injury in KD patients suggesting its role as a potential biomarker for vascular inflammatory disease.

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

Assessment of pathogenesis of inflammation-induced endothelium dysfunction markers using flow cytometry in patients with Kawasaki disease from North India

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Introduction:

Kawasaki disease (KD) is an acute medium vessel vasculitis of childhood that leads to coronary artery aneurysms. Long-term complications are frequent that includes vascular endothelial dysfunction (ED). Oxidative stress plays an integral role in KD as it triggers reactive oxygen species (ROS) production. Abnormal immune system in KD is characterized by an overproduction of nitric oxide (NO) having role in triggering dysfunction. Circulating endothelial cells (CECs) are associated with vascular injury and circulating endothelial progenitor cells (EPCs) are capable of vasculogenesis and have association with cardiovascular risk factors.

Method:

Present study is a single centre, prospective study in North India that includes KD patients (diagnosed as per American Heart Association **(AHA) guidelines 2004**) at different time intervals with and without coronary artery aneurysms (CAA) (**Z score as per Montreal (JASE 2011)**. KD patients with CAA were further classified into transient and persistent aneurysms as per **AHA 2017**.

Group 1: Diagnosed prior >6 months-1.5 years **(N=19)**

Group 2: >1.5 - 3 years **(N=24)**

Group 3: >3 - 4.5 years **(N=22)**

Group 4: Age and sex matched healthy controls **(N=20)**

Flowcytometric analysis for ROS production by dihydrorhodamine assay (DHR 123 assay) is done to quantify the functional status of NADPH oxidase system to study oxidative stress by calculating delta mean fluorescence intensity (∆**MFI = MFI Stim - MFI Unstim**). Extracellular nitric oxide estimation (quantitative) is done by measuring nitrite and nitrate concentration by (Nitric oxide assay kit) in extracellular fluid (serum) to elucidate the pathophysiology of disease. Estimation of CECs **($CD45^{dim}/CD146^{+}/CD31^{+}/CD133^{-}$)** and EPCs **($CD34^{+}/CD309^{+}/CD133^{+}$)** was done by flow cytometry using specific antibody markers tagged with different fluorochromes, (Table 1) using a specific gating strategy, acquired on flowcytometer (Beckman Coulter Navios) and analyzed using kaluza software.

Results:

Maximum patients (56%) were <5 years, 12% were >10 years while 33% were between 5-10 years of age. Median age was 4 (range: 0.2-13) years. Male: female ratio was 10:3. All the patients had fever followed by peeling (81%), redness (80%), beau's lines (73%), strawberry tongue (71%), mucosal changes (62%), conjunctival congestion (62%), rash (61%), swelling (46%), lymphadenopathy (35%) and chromonychia (15%) patients. Family history was noted in one patient. All patients received IVIg (2gm/kg) and aspirin as standard treatment.

Levels of nitrite and nitrate was comparable among patients (group1, 2 &3), however higher nitrate levels was found in patients when compared to healthy control (non-significant). ∆MFI was higher in patients in group 2 when compared with healthy control (non-significant). In Intra group analysis of group 1, ∆MFI was higher in patients with CAA as compared to non-CAA and HC while in group 2&3 the values are comparable. Significantly elevated number of EPCs was found in patients in group 1, 2 & 3 (P=<0.0001, P=0.0001, P=0.0003) respectively as compared to healthy controls. Higher number of EPCs were noted in patients with aneurysms [(Group 2: P=0.01, Group 1, 3 (non-significant)] as compared to patients without aneurysms. Significantly elevated no. of CECs were noted in patients in group 1, 2 and 3 (P=<0.0001) as compared to healthy

control. Also higher number of CECs was observed in group 1 & 2 in patients with CAA as compared to patients without CAA that showed statistical significance (P=0.04, P=0.01 respectively).

Conclusion:

Nitrate levels may be high in patients & could be linked with disease pathogenesis but due to non-significant difference, validation in larger cohort is needed. No significant increase in the oxidative stress marker late after the acute illness in KD patients was found. Enumeration of EPCs can be used as a good screening marker in follow up patients other than ECHO. Increased no. of CECs reflects endothelial damage and may serve as early diagnostic tool. Higher no. of cells in KD patients without CAA highlights their progression to endothelial damage in future if not treated so, more close follow up is needed for these patients as they can be at high risk of developing aneurysms.

Antibody	**Fluorochrome**
Endothelial Progenitor cells (EPCs)	
7-AAD	
CD34	PE
CD309	PECY7
CD133	APC
Circulating endothelial cells (CECs)	
CD45	Percpcy5.5
CD146	PE
CD31	FITC
CD133	APC

THROMBOSIS WITH MULTIPLE CORONARY ANEURYSMS IN INFANTILE KAWASAKI DISEASE: A Case Series

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BACKGROUND

Kawasaki disease (KD) is an acute vasculitis of childhood that leads to coronary artery aneurysms in about 25% of untreated cases. This is a case series of 4 KD patients with multiple coronary aneursyms & thrombus, all presenting in infancy.

CASE SUMMARY

CASE 1: 3 months old boy presented with fever for 26 days. Echo showed LAD medium aneurysm with thrombus, LMCA small aneurysm & RCA dilatation, diagnosed as complete KD .Treated with Infliximab(5mg/kg) followed by IVIG (2gm/kg), oral steroids, ecospirin , LMWH at 2mg/kg/day. Since there was persistence of thrombus on day 7 echo, oral cyclosporin ,clopidogrel were started. 4 weeks echo showed increin diameter of LAD& LMCA aneurysm RCA dilatation progressed to small aneurysm , with resolution of prevoithrombus

CASE 2: 2 months old boy presented with high grade fever for 15 days with thrombocytosis, multiple giant aneurysms involving all major coronaries with thrombus in LAD. IVIG (2 g/kg)aspirin, LMWH, infliximab (5 mg/kg), streptokinase was administered .Repeat echocardiography after 24 hours showed complete dissolution of the clot. LMWH was

continued followed by oral warfarin. At 5 years follow-up, the child continues to have persistent giant aneurysm of LAD.

CASE 3

10 months girl presented on day 16 of fever. Diagnosed as complete KD, echo showed giant aneurysm in LMCA, distal RCA, LAD with clot 17x17mm , with pericardial effusion. Treated with IVIG, oral steroid, unfractionated heparin , alteplase. However during alteplase infusion baby succumbed to death due to myocardial infarction.

CASE 4

6 weeks old male baby was admitted with fever for 2 days and high inflammatory markers. He was initiated on broad spectrum antibiotics, developed hypotension within 24 hours, was shifted to PICU and managed as septic shock. He was intubated and ventilated for 7 days. In view of persistent fever at day 10, increasing CRP, with progressive thrombocytosis, an echocardiography was done which showed proximal LAD giant aneurysm(+14.9Z), LMCA and RCA ectasias. IVIG was started followed by Infliximab. Echo after 7 days showed some regression in size of CAAs but there was a thrombus in LAD partially obstructing the lumen. LMWH 2mg/kg was initiated. Repeat echo after 7 days showed dissolution of clot. On follow up, the child had complete regression of aneurysms by 2 years of age.

Observation:

Over the last 16 years these were the 4 KD babies who presented with coronary thrombus at diagnosis. All were infants, had a late diagnosis beyond 10 days and all had LAD thrombus. One of them succumbed during thrombolysis, and although the clot could be dissolved in the other 3, 2 of them continued to have persistent aneurysms inspite of aggressive management.

A RETROSPECTIVE STUDY ON CLINICOPATHOLOGICAL PROFILE OF INCOMPLETE KAWASAKI DISEASE

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BACKGROUND:

AIMS AND OBJECTIVES: To evaluate the clinicopathological profile of children with incomplete Kawasaki disease and to compare with children of complete Kawasaki disease.

MATERIALS & METHODS:

Retrospective observational study done at Institute of Child Health Kolkata on children diagnosed with Kawasaki disease according to AHA 2017 criteria from January 2020 to August 2023.

RESULTS:

106 patients were diagnosed with Kawasaki disease from January 2020 to august 2023 of which 101 patients were included in this study. 53 % had incomplete KD with median age of 15 months , 20/101 were females and 34/101 were males diagnosed with incomplete KD.

	INCOMPLETE KD (N=54)	COMPLETE KD (N=47)
Median age(months)	15	18
% of infants	43	38
Male (%)	63	77
Female(%)	36	23
Median duration of fever prior to admission(days)	7	6
Median duration from admission to diagnosis (days)	1	1

Investigations (median)		
Hb (gm/dl)	9.6	9.1
TLC (/mm3)	17530	18000
Neutrophil (%)	59	69
Platelets (lakh/mm3)	4,90,000	4,20,000
CRP (mg/L)	85	130.5
SGPT (IU/ml)	25	33
Albumin (gm/dl)	3.5	3.1
Small aneurysm (%)	20 (11 patient)	21 (10pts)
Medium aneurysm(%)	14.8 (8 pts)	11(5pts)
Giant aneurysm(%)	1.85 (1pts)	2.1(1pts)
Multiple aneurysm (%)	20 (11pts)	21(10pts)
Thrombus(%)	3.9	
IVIG resistance(%)	7.4	23
Aneurysms at presentation (%)	35	34

CONCLUSION:

Patients with incomplete KD comprised half of the total number of KD patients. Infantile onset of disease had predominantly incomplete presentation, however no significant difference was found in the incidence of CAA as compared to complete KD.

Title: Peripheral gangrene in Kawasaki disease: Clinical conundrum

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Background: Kawasaki disease (KD) is medium vessels vasculitis affecting young children. Peripheral gangrene is an unusual complication in KD.

Patients and methods: Records of all children diagnosed with KD during 1994-2021 were analyzed. Clinical details of children who had peripheral gangrene were reviewed.

Case details: Of the 1078 children with KD diagnosed during 1994-2021, 4 developed peripheral gangrene. Patient 1: A 3-year-boy presented with fever, diffuse erythematous rash, and patchy gangrene of skin over thighs, left elbow and dry gangrene of bilateral toes. He also developed macrophage activation syndrome. Patient 2: 1-year-boy presented with fever, rash, and gangrene of digits of right hand and tips of right toes. Patient 3: 1-year-girl presented with fever, vomiting, loose stools, seizures and gangrene of bilateral feet and right little finger. She remained febrile during hospitalization and developed thrombocytosis, elevated inflammatory parameters, and periungual peeling. Patient 4: A 2-month-female presented with fever and black discoloration of toes that progressed to involve dorsum of both feet. All 4 patients developed periungual desquamation and Beau's lines. Echocardiography showed myocardial dysfunction in 2 patients (patient nos. 1 and 4); coronary arteries were normal. All 4 patients had elevated inflammatory markers, thrombocytosis and elevated NT-proBNP. Two patients (patient nos. 1 and 4) received

additional therapies - methylprednisolone in former and infliximab and pulse methylprednisolone in latter. All 4 patents received low molecular weight heparin (1 mg/kg twice a day; duration range 2-3 months) and oral aspirin. Prothrombotic workup (Factor V Leiden, Protein C, S and anti-phospholipid antibodies) was unremarkable in all patients. On follow-up gangrenous lesions improved in all four patients.

Discussion and conclusions: Peripheral gangrene is a rare manifestation of KD. It may occasionally be the only presenting clinical manifestation along with fever, thereby creating a diagnostic conundrum for the attending paediatricians.

Title: Challenging case of increasing size of giant aneurysm in a child with KD on follow-up

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Background: Kawasaki disease (KD) is the most common vasculitis in childhood. It is the leading cause of heart disease in the pediatric age group in the west. We present a 5-year-old boy who showed progression in the size of aneurysm during long term follow-up.

Case details: A 5-year-old boy presented to us with acute febrile illness along with redness of eyes, dry, cracked lips and strawberry tongue. Physical examination revealed non-exudative conjunctival injection along with changes of oral mucosa. Blood investigations revealed leucocytosis, elevated acute phase reactants (C-reactive protein- 78mg/L, erythrocyte sedimentation rate- 74 mm/hour) and elevated pro-brain natriuretic peptide (798pg/ml). Possibility of KD was considered. 2D-echocardiogram of the coronary arteries showed loss of tapering of left anterior descending artery [LMCA: 3mm (-0.08 z), LAD: 2.0mm (+1.13z), RCA: 2.3mm (-0.62z)]. Intravenous (IV) immunoglobulin was given @2g/kg and oral aspirin at anti-inflammatory dose with which the fever subsided. On follow up after 2 weeks he was found to have ectasia of left coronary artery [LMCA: 3.7mm (+3.42z), LAD: 2.5mm (+1.89z), RCA: 2.3mm (+1.28z), LCx: 2.7mm (+2.32z)] and aneurysm in the distal end of right coronary artery [5.8mm (+9.08z)] which was confirmed on computed tomography (CT) coronary angiogram (CTCA) on 128-slice dual source

platform. He received IV Infliximab (5 mg/kg). He was discharged on subcutaneous low molecular weight heparin (LMWH) which was later changed to oral warfarin 4 months later. He also received aspirin and atorvastatin. A repeat CTCA 5 years later (LMCA: 3.6mm, LAD: 2.5mm, RCA:2.7mm,LCx: 2.7mm) showed progression in the size of aneurysm in the distal right coronary artery [7.2 mm (+9.99z] but there were no calcification. Child has remained well since then. Factor Xa levels (0.48 IU/ml) and international normalised ratio (INR- ranging1.6 to 3.16) were monitored during follow up and were well within the expected range on anticoagulation.

Conclusion: This case highlights the role of CTCA in detailed visualization of coronary artery abnormities in children with KD. Though enlargement of a coronary aneurysm after the acute phase in KD is an extremely rare phenomenon, physicians should be aware of coronary sequelae including dilation of prior aneurysms. Growth of the coronary artery with somatic growth, abnormalities of the coronary arterial wall and hemodynamic factors are one of the many causes cited in the causation of aneurysm in the late period after KD.

Title: Anticoagulation in children with Kawasaki disease: our experience at Chandigarh, North India

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Objective: To describe safety and efficacy of antiplatelet and anticoagulation therapy (aspirin and low molecular weight heparin (LMWH)/warfarin) in a cohort of Kawasaki disease (KD) patients with moderate to giant coronary artery aneurysm.

Methods: Records of all children diagnosed to have KD during 1994-2022 were analyzed. Of the 1230 patients with KD, clinical details of children who had received aspirin and either LMWH/warfarin were retrieved.

Results: Fourty-five (3.6%) children (32 boys; 13 girls) with KD, were put on aspirin and LMWH/warfarin. Median age of diagnosis was 18 months (range 1.5 months-12 years). Thirteen children (28.9%) were < 1 year age at diagnosis. Twenty-three patients (50%) have received LMWH, while 10 (23.7%) received warfarin. Twelve patients received initially LMWH for 12-31 months duration followed by oral warfarin. Giant aneurysms were present in 41 patients while 4 patients had moderate-sized aneurysms. Thromboses developed in acute phase of disease in 5/38 (11.1%) and most common coronary artery affected was LAD. All patients were continued on oral aspirin (3-5 mg/kg/day) along with anticoagulation therapy and 6 patients also received a second antiplatelet agent (clopidogrel). Median

duration of LMWH was 19 months (range: 3-42 months), and median warfarin duration was 46 months (range: 2-126 months). In 22 patients we were able to monitor factor Xa activity and median activity was 0.46 IU/mL (0.32-0.81). Median INR in patients receiving warfarin was 1.55 (0.99-2.73). There were no significant complications related to anticoagulation in any of the patients, although parents frequently complained of local bruising. Serial 2D-echocardiogram during follow-up showed remodeling of coronary arteries. None of the patients developed thrombosis or symptomatic stenosis during follow-up. Duration of follow-up was 1614 patient-months.

Conclusion: Although the recommended INR in patients with KD and large aneurysm who are receiving anticoagulation therapy is 2-3, we maintained our patients on lower INR. Our results show that even on a much lower INR, these children have had no significant complications.

Title: Increasing incidence of Kawasaki Disease at Chandigarh during 2015-2019 – Are we following the trends in the developed world?

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Abstract:

Background: There is paucity of literature on epidemiological data on Kawasaki disease (KD) from developing countries. The present study aims is to estimate the incidence of KD during the period 2015-2019 at Chandigarh, North India.

Methodology: All children suffering from KD residing within the Union Territory [UT] of Chandigarh and diagnosed between January 2015-December 2019 were enrolled. Annual incidence rates were calculated using decadal growth rates on basis of National Census Data, 2011. Methodology was similar to previously published studies from our center pertaining to the periods 1994-2008 and 2009-2014. We computed incidence of KD in children aged <5 as well as in children aged <15 years. We also undertook linear trend analysis along with the prediction analyses using Holt-Winter's Additive Smoothing technique for KD cases <5 years and <15 years.

Results: During the period 2015-2019, 83 patients (66 boys, 17 girls) below 5 were identified to have KD in UT Chandigarh. Annual incidence rates during this 5 year period were 5.64, 9.25, 9.11, 9.87, and 9.72/100,000 in children below 5 and 2.65, 4.44, 3.86, 5.07, 4.74/100,000 in children below 15.There was increasing incidence of disease from 2015-2019. Mean age at diagnosis was 61 months (median=48 months; range: 12 days - 15 years). There is 53.1% increase in annual incidence of KD in children below 5, and a 53.7% increase in children below 15 during the period 2025-2019, as compared to our previous data from

2009-2014. Coronary artery abnormalities (CAAs) during the acute phase of illness were noted in 17.7% patients, while at 6 weeks of illness 7.6% of patients with KD had persistent CAAs. Trend analysis found a monthly rise of 0.02 cases among children below 5 and 0.0165 cases among children below 15, (p value < 0.0001). The forecast indicated a monthly increase of 0.0177 cases of KD among children aged 0-15 years during the period from 2020 to 2030

Conclusions: This study highlights that incidence of KD in Chandigarh has continued to show an upward trend over the period 2005-2019. This may reflect a true increase in KD incidence or may be due to increased ascertainment of disease as a result of increased awareness amongst pediatricians and physicians in this region. Seasonal occurrence of KD is like other studies. Despite treatment, CAAs were documented in 17.7% of patients with KD during the acute phase of disease. KD appears to be emerging as an important cause of acquired heart disease in children in North India.

Understanding F_c Gamma Receptors ($F_c\gamma Rs$) in pathogenesis of Kawasaki Disease

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Introduction: Kawasaki disease (KD) is an acute febrile systemic vasculitis that affects coronary arteries. Intravenous immunoglobulin (IVIg) is standard of care for patients with KD. Administration of high dose IVIg provides prompt anti-inflammatory effect, though its exact mechanism of action is not clearly understood. F_c gamma receptors ($F_c\gamma Rs$) are receptors for IgG. The constant region, F_c region (fragment, crystallizable), of IgG mediates the effector function. Altered $F_c\gamma R$ expression can have significant implications on response to IVIg leading to complications like development of coronary artery aneurysms (CAAs) and myocardial dysfunction.

The current study was designed to understand functionally relevant genetic variants in the *FCGR2/3* locus and characterize the surface expression of $F_c\gamma Rs$ ($F_c\gamma RI$, $F_c\gamma RII$, $F_c\gamma RIII$) on various immune cell types in Indian patients with KD.

Material and Methods:

Treatment naïve children with KD and post treatment with IVIg were enrolled. They were classified as IVIg responders or IVIg resistant KD based on persistence of fever at 36 hrs of completion of IVIg infusion. In addition, healthy controls were also enrolled. Clinical and laboratory profile of patients were obtained from hospital records. Single Nucleotide Polymorphisms (SNPs) and Copy Number Variations (CNVs) were done using Multiplex Ligation-dependent Probe Amplification (MLPA) assay. Characterization of surface expression of $F_c\gamma Rs$ was done using flow cytometry.

Results:

45 patients with KD were enrolled. 21 treatment naïve samples were available while 26 post treatment samples were collected. Deletion in Copy Number Regions (CNRs) : (CNR1) (FCGR2C, HSPA7, FCGR3B); CNR2 (FCGR2A, HSPA6, FCGR3A, FCGR2C) and CNR4 (FCGR2C, HSPA7, FCGR3B, FCGR2B) were found in 10 patients. Functional SNPs [rs201218628; rs1801274; rs1050501] were also found in these patients. We further compared surface $F_c\gamma$ receptor [FcγRI (CD64), FcγRII (CD32, FcγRIII (CD16)] expression on various immune cells in patients with treatment naïve KD and post IVIg treatment KD.

Percentage expression of FcγRI (CD64) on neutrophils was significantly higher ($p=0.01$) in treatment naïve (pre IVIg) samples compared to healthy controls. Percentage expression of FcγRIIIB on neutrophils and NK cells [CD16B and CD16A] was significantly decreased ($p=0.01$) in treatment naïve samples compared to healthy control. Patients with CNVs and SNPs had corroborative changes in surface expression of the receptors. A patient with acute KD has CNVs in CNR1 and CNR2 region also had reduced expression of these receptors on flow cytometry.

Conclusions: Patients with KD have CNVs/SNPs in FcγRs and these variations in surface receptors of $F_c\gamma$ could be identified in pre as well as post IVIg condition. These changes may have therapeutic implications as well as can help stratify the response to IVIg.