Updates in Kawasaki Disease (KD) and Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19

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Source: Ghosh P, Katkar GD, Shimizu C, Kim J, Khandelwal S, Tremoulet AH, Kanegaye JT. Pediatric Emergency Medicine Kawasaki Disease Research Group. An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. Nat Commun. 2022 May 16; 13(1):2687. DOI: 10.1038/s 41,467-022- 30,357-w. PMID: 355,77777; PMCID: PMC 911,0726.

Multisystem inflammatory syndrome in children (MIS-C) is an illness that emerged amidst the COVID-19 pandemic but shares many clinical features with the pre-pandemic syndrome of Kawasaki disease (KD). In this study, the researchers compare the two syndromes using a computational toolbox of two gene signatures that were developed in the context of SARS-CoV-2 infection, that is, the viral pandemic (ViP) and severe-ViP signatures and a 13-transcript signature previously demonstrated to be diagnostic for KD, and validated their findings in whole blood RNA sequences, serum cytokines, and formalin-fixed heart tissues.

Results show that KD and MIS-C are on the same continuum of the host immune response as COVID-19. Both the pediatric syndromes converge upon an IL15/IL15RA-centric cytokine storm, suggestive of shared proximal pathways of immunopathogenesis; however, they diverge in other laboratory parameters and cardiac phenotypes.

Source: Fabi M, Filice E, Andreozzi L, Mattesini BE, Rizzello A, Palleri D, Dajti E, Zagari RM, Lanari M. Combination of Fecal Calprotectin and Initial Coronary Dimensions to Predict Coronary Artery Lesions Persistence in Kawasaki Disease. Sci Rep. 2022 May 23; 12(1):8640. DOI: 10.1038/s 41,598-022- 12,702-7. PMID: 356,06405; PMCID: PMC 912,7106.

The researchers prospectively study to determine if fecal calprotectin (FC) could be useful in predicting the development or persistence of coronary artery lesions (CALs) in 26 children (76.9% boys; median age 34.5 months) with KD.

The combination of FC > 250 microg/g and z-score >2 during the acute phase was associated with the persistence of CALs ($p = 0.022$). A z-score >2 alone during the acute phase was not related to CALs during the subacute stage ($p > 0.05$). A neutrophil percentage of 70% and WBC > 15,000/mmc during the acute phase significantly correlated with the presence of CALs during the subacute phase ($p = 0.008$). C-reactive protein (CRP) > 13 mg/dL at KD onset was significantly associated with the presence of CALs during the acute ($p = 0.017$) and subacute phase ($p = 0.001$). *According to this study, a combination of FC > 250 microg/g and a z-score >2 during the acute phase of KD may be used as a predictor of CALs persistence. It can be useful, especially in children with an initial CRP < 13 mg/dL.*

Source: Sacco K, Castagnoli R, Vakkilainen S, Liu C, Delmonte OM, Oguz C, Kaplan IM, Alehashemi S, Burbelo PD, Bhuyan F, de Jesus AA. Immunopathological Signatures in Multisystem Inflammatory Syndrome in Children and PediatricCOVID-19. Nature Medicine. 2022 Feb 17:1-3. DOI:10.1038/s 41,591-022- 01,724-3.

In this longitudinal multi-institutional study, the authors applied multiomics (analysis of soluble biomarkers, proteomics, single-cell gene expression, and immune repertoire analysis) to profile children with COVID-19 ($n = 110$) and MIS-C ($n = 76$), along with pediatric healthy controls (pHCs; $n = 76$). pCOVID-19 was characterized by robust type I interferon (IFN) responses, whereas prominent type II IFN-dependent and NF–κB–dependent signatures, matrisome activation, and increased levels of circulating spike protein were detected in MIS-C, with no correlation with SARS-CoV-2 PCR status around the time of admission. Transient expansion of TRBV11–2 T cell clonotypes in MIS-C was associated with signatures of inflammation and T cell activation. The association of MIS-C with the combination of HLA A*02, B*35, and C*04 alleles suggests genetic susceptibility. MIS-C B cells showed a higher mutation load than pCOVID-19 and pHC. These results identify distinct immunopathological signatures in pCOVID-19 and MIS-C that might help better define the pathophysiology of these disorders and guide therapy.

Source: Gurlevik SL, Ozsurekci Y, Sağ E, Derin Oygar P, Kesici S, Akca ÜK, Cuceoglu MK, Basaran O, Göncü S, Karakaya J, Cengiz AB. The Difference of the Inflammatory Milieu in MIS-C and Severe COVID-19. Pediatric research. 2022 Mar 29:1-0. DOI: 10.1038/s 41,390-022-02,029-4.

This study defines a pattern of distinctive immune responses in children with MIS-C and in patients with severe/critical COVID-19. *The results suggest that IL-1 and IFN-γ pathways play an important role in the pathophysiology of MIS-C.* Most cytokines and chemokines related to the IL-1 family and IFN-γ pathway (including IL-18 and MIG/CXCL9) and IL-17A were significantly higher in the MIS-C group when compared to the severe/critical COVID-19 group and healthy controls (HCs). *IP-10/CXCL10 and IL-10 were higher in both MIS-C patients and severe/critical COVID-19 compared to HCs.*

One of the limitations of the study is the relatively small cohort of patients with severe/critical COVID-19. Another limitation is the fact that 90% of the severe/critical COVID-19 group had a comorbid disease and the researchers were unaware of how the underlying

diseases affected the pathogenesis so further investigation was needed. Lastly, serum cytokines and chemokines concentrations were measured only at admission and serial measurements with certain time periods might better clarify their role in disease outcome.

Source: Savorgnan F, *Acosta* S, Alali A, Moreira A, Annapragada A, Rusin CG, Flores S, Loomba RS, Moreira A. Social and Demographic Disparities in the Severity of Multisystem Inflammatory Syndrome in Children. Pediatr Infect Dis J. 2022 Jun 1; 41(6):e256-e258. DOI: 10.1097/INF. 000,000 000,0003511. Epub 2022 May 6. PMID: 355,37132; PMCID: PMC 908,3307.

Social constructs are known risk factors for MIS-C. The area deprivation index (ADI) is a validated metric, originally based on measures created by the US Health Resources and Services Administration, that ranks neighborhoods by socioeconomic disadvantage. Factors comprising the tool include housing quality, employment, education, and income.

The cohort included 206 patients based in Texas according to their residential postal codes. Despite severity levels, all patients survived hospitalization. The median age was 9.4 years. All patients were under 21 years of age. Overall, 45% (*n* = 92) of children were female and 42% (*n* = 86) were overweight. The predominant race/ethnicity was Hispanic (49%), followed by non-Hispanic Black (23%) and non-Hispanic White (20%). *Children with severe MIS-C were typically older, overweight, and with an elevated ADI.*

The median length of hospital stay was 6.7 days, while the median ADI was 5. Children with severe MIS-C were more likely to have exaggerated levels of brain natriuretic peptide, CRP, white blood cells, ferritin, procalcitonin, creatinine, blood urea nitrogen, international normalized ratio, protime, and reduced amounts of platelets. The median hospital stay for a child with severe MIS-C was 8.1 days compared with 5.6 days for cases with mild MIS-C. The administration of steroids coupled with immunomodulators (e.g., anakinra) was higher in children with severe MIS-C (98 vs 65%).

Source: Jennifer J. Y. Lee, Ethan Lin, Jessica Widdifield, Quenby Mahood, Brian W. McCrindle, Rae S. M. Yeung, Brian M. Feldman. The Long-term Cardiac and Noncardiac Prognosis of Kawasaki Disease: A Systematic Review. Pediatrics March 2022; 149 (3): e 202,1052567. DOI: 10.1542/peds.2021– 052,567.

It is uncertain if children with KD are at risk for noncardiac diseases and if children with KD but without coronary artery aneurysms (CAA) are at risk for long-term cardiac complications. The authors perform a systematic review to determine the long-term mortality and prognosis of children after KD.

Seventy-four studies were included. Thirty-six studies reported mortality, 55 reported a cardiac outcome, and 12 reported a noncardiac outcome. Survival ranged from 92 to 99% at 10 years, 85–99% at 20 years, and 88–94% at 30 years. The major adverse cardiovascular events (MACE)—free survival, mostly studied in those with CAA, varied from 66 to 91% at 10 years, 29–74% at 20 years, and 36–96% at 30 years. Seven of 10 studies reported an increased risk of early atherosclerosis. *All six included studies demonstrated an increased risk of allergic diseases*.

The systemic review may have missed associated chronic comorbidities because short-term studies were excluded. *The majority of outcomes were evaluated in East-Asian patients*, which may limit generalizability. Studies frequently excluded patients without CAA and did not compare outcomes to a comparison group.

The systematic review concludes >90% survival up to 30 years follow-up. MACE is observed in children with CAA but is not well studied in those without CAA.

Source: Abrams JY, Ae R, Maddox RA, Schonberger LB, Nakamura Y, Belay ED. First-line Corticosteroids for Kawasaki Disease: Pulse Versus Multiple Dose. Pediatrics International. 2022 Jan; 64(1):e 15,112. DOI:10.1111/ped. 15,112.

In KD, Corticosteroids added to initial standard intravenous immunoglobulin (IVIG) treatment may decrease the risk for severe coronary artery abnormalities (CAAs). Different corticosteroid regimens (single-day high dose pulse vs multiple lower doses) may contribute to the discrepant results of prior studies.

Using data from the 22nd, 23rd, and 24th Japanese nationwide KD surveys (2011–2016), the authors identified KD patients who did not have CAAs at first presentation and who were treated with either pulse or multiple-dose corticosteroids as part of their initial treatment. Occurrence of subsequent CAAs and treatment failure were compared between the treatment regimens and adjusted odds ratios were calculated controlling for sex, age group, illness day at first treatment, survey, and recurrent KD.

There were 782 KD patients who received pulse corticosteroid treatment and 4,817 who received multiple-dose treatment. *Patients receiving multiple-dose treatment were less likely to develop CAAs or treatment failure. Adjusted analyses showed similar protective effects of multiple-dose treatment against CAAs and treatment failure*.

Source: Wang Q, Morikawa Y, Akahoshi S, Miyata K, Sakakibara H, Matsushima T, Koyama Y, Obonai T, Kaneko T, Miura M. Follow-Up Duration of Echocardiography in Patients with Kawasaki Disease with No Initial Coronary Aneurysms. J Pediatr. 2022 May; 244:133–138.e1. DOI: 10.1016/j.jpeds.2021.11.022. Epub 2021 Nov 17. PMID: 347,98077.

In this single-center, retrospective, observational study, the authors review the results of follow-up echocardiography in children with KD enrolled in the Prospective Observational Study on Stratified Treatment with Immunoglobulin Plus Steroid Efficacy for KD from a children's hospital. The main enrollment criterion was the absence of coronary aneurysms, defined as a maximum *z*-score (Zmax) ≥2.5, in the proximal right coronary artery and the proximal left anterior descending artery within 9 days from treatment initiation. The primary outcome was Zmax on follow-up echocardiography at up to 5 years.

Among 386 patients, 106 (27.5%) received prednisolone with IVIG for first-line therapy, and 57 (14.8%) showed a poor response. Echocardiography at 1 month detected nine patients with a Zmax ≥2, including three (0.8%) with coronary aneurysms requiring additional antithrombotic treatment and observation. Of seven patients (1.8%) with normal echocardiographic findings at 1 month but a Zmax ≥2 later, 2 were lost to follow-up and five experienced spontaneous resolution, but none of the seven patients required any change in management.

The optimal duration of echocardiographic follow-up maybe 1 month in patients with no initial coronary aneurysms and a Zmax < 2 at 1 month. Coronary artery abnormalities observed after 1 month are rare and mostly benign in this category of patients.

Source: Takeuchi A, Namba T, Matsumoto N, Tamai K, Nakamura K, Nakamura M, Kageyama M, Kubo T, Tsukahara H, Yorifuji T. Preterm Birth and Kawasaki Disease: A Nationwide Japanese Population-based Study. Pediatr Res. 2021 Oct 8. DOI: 10.1038/s 41,390-021-01,780-4. Epub ahead of print. PMID: 346,25654.

The authors investigate whether preterm birth increased the morbidity of KD. They included 36,885 (34,880 term and 2005 preterm) children born in 2010 in Japan and examined the association between preterm birth and hospitalization due to KD using a large nationwide survey.

In log-linear regression models that were adjusted for children's characteristics (sex, singleton birth, and parity), parental characteristics (maternal age, maternal smoking, paternal smoking, maternal education, and paternal income), and residential area, preterm infants were more likely to be hospitalized due to KD. They examined whether breastfeeding status modified the potential adverse effects of preterm birth on health outcomes. *Preterm infants with partial breastfeeding or formula feeding had a significantly higher risk of hospitalization due to KD compared with term infants with exclusive breastfeeding.*

Preterm infants were at high risk for Kawasaki disease, and exclusive breastfeeding might prevent this disease among preterm infants.

Previous studies showed that preterm birth increased the risk for hospital admissions in infancy and childhood due to some acute diseases; however, the risk of preterm children developing KD remains unknown. *This Japanese large population-based study showed that preterm infants were at high risk for KD for the first time. Furthermore, this study suggested that exclusively breastfeeding might prevent KD among preterm infants.*

Source: Sagiv E, Slee A, Buffone A, Choueiter NF, Dahdah NS, Portman MA. Etanercept with IVIg for Acute Kawasaki Disease: A Long-term Follow-up on the EATAK Trial. Cardiol Young. 2022 May 12:1–6. DOI: 10.1017/S 104,795 112,2001470. Epub ahead of print. PMID: 355,45881.

The Etanercept as Adjunctive Treatment for Acute KD, a phase-3 clinical trial, showed that etanercept reduced the prevalence of IVIG resistance in acute KD. In patients who presented with coronary artery involvement, it reduced the maximal size and short-term progression of coronary artery dilation. Patients were followed for at least 1 year after the trial. The size of dilated arteries (z-score ≥ 2.5) was measured at each follow-up visit. The z-score and size change from baseline were evaluated at each visit and compared between patients who received etanercept versus placebo at the initial trial.

Forty patients who received etanercept (22) or placebo (18) in the Etanercept as Adjunctive Treatment for Acute KD trial were included. All patients showed a persistent decrease in coronary artery size measurement: 23.3 vs 5.9% at the 6-month visit, 24 vs 13.1% at the 1-year visit, and 20.8 vs 19.3% at the ≥2-year visit for etanercept or placebo, respectively, with similar results for a decrease in coronary artery z-scores. In a multivariate analysis, correcting for patients' growth, a greater size reduction for patients on the etanercept arm vs placebo was proved significant for the 6-month ($p = 0.005$) and the 1-year visits ($p = 0.019$) with a similar end outcome at the ≥2-year visit. In conclusion, *primary adjunctive therapy with etanercept for children with acute Kawasaki disease does not change the end outcome of coronary artery disease but may promote earlier resolution of artery dilation.*

Source: Takura T, Horiuchi S. Cost-effectiveness Analysis of Infliximab for the Treatment of Kawasaki Disease Refractory to the Initial Treatment: A Retrospective Cohort Study. J Cardiol. 2022 Mar 25:S0914–5087(22) 00,057–0. DOI: 10.1016/j.jjcc.2022.03.005. Epub ahead of print. PMID: 353,41683.

This study from Japan is aimed to compare the cost-effectiveness of Infliximab (IFX) and other therapeutic strategies for KD refractory to initial treatment, including IVIG, steroids, immunosuppressants, and plasma exchange therapy.

This multicenter, retrospective cohort study utilized data from the public medical insurance system of Japan. The target population included those who received treatment for KD. The Eligibility criteria were as follows: (1) initial onset of KD, (2) age <15 years at onset, and (3) administration of 3rd line treatment if the 1st line treatment was IVIG alone or 2nd line treatment if the 1st line treatment was a combination of IVIG and steroids, in accordance with Japanese guidelines (2012). Those with KD-related cardiovascular complications before admission and those with congenital cardiac disease were excluded. *The primary outcome was cost-effectiveness*, which was calculated based on the number of admission events per annum divided by medical expenses per *annum* (times/10,000 US dollars).

Among 1,267 patients with KD, 25 received IFX treatment; while 206 received another treatment after the disease was designated refractory to initial treatment. The frequency of steroid use during initial IVIG treatment (a predictor of severity) was higher in the non-IFX group than in the IFX group (70.4 vs 32.0%, $p < 0.001$) but became comparable after propensity-score matching. *Their analysis indicated that IFX was more cost-effective than other treatments* for patients with KD that is refractory to initial treatment.

Source: Godfred-Cato S, Abrams JY, Balachandran N, Jaggi P, Jones K, Rostad CA, Lu AT, Fan L, Jabbar A, Anderson EJ, Kao CM, Hunstad DA, Rosenberg RB, Zafferani MJ, Ede KC, Ballan W, Laham FR, Beltran Y, Bryant B, Meng L, Hammett TA, Oster ME, Bamrah Morris S, Belay ED. Distinguishing Multisystem Inflammatory Syndrome in Children From COVID-19, Kawasaki Disease and Toxic Shock Syndrome. Pediatr Infect Dis J. 2022 Apr 1; 41(4):315–323. DOI: 10.1097/INF. 000,000 000,0003449. PMID: 350,93995; PMCID: PMC 891,9949.

Distinguishing MIS-C, KD, and toxic shock syndrome (TSS) can be challenging. Because clinical management of these conditions can vary, timely and accurate diagnosis is essential. Data were collected from patients <21 years of age hospitalized with MIS-C, COVID-19, KD, and TSS in four major health care institutions. Patient demographics and clinical and laboratory data were compared among the four conditions, and a diagnostic scoring tool was developed to assist in clinical diagnosis.

A total of 233 patients with MIS-C, 102 with COVID-19, 101 with KD, and 76 with TSS were included in the analysis. Patients with MIS-C had the highest prevalence of decreased cardiac function (38.6%), myocarditis (34.3%), pericardial effusion (38.2%), and mitral regurgitation (31.8%), and pleural effusion (34.8%) compared with patients with the other conditions. *Patients with MIS-C had increased peak levels of CRP and decreased platelets and lymphocyte nadir counts compared with patients with COVID-19 and KD and elevated levels of troponin, brain natriuretic peptide, and pro-brain natriuretic peptide compared with COVID-19.*

Compared with COVID-19, KD, and TSS, patients with MIS-C had a significantly higher prevalence of cardiac complications, elevated markers of inflammation and cardiac damage, thrombocytopenia, and lymphopenia.

Source: Wessels PA, Bingler MA. A comparison of Kawasaki Disease and Multisystem Inflammatory Syndrome in Children. Prog Pediatr Cardiol. 2022 Jun; 65: 101,516. DOI: 10.1016/j.ppedcard.2022. 101,516. Epub 2022 Mar 16. PMID: 353,13700; PMCID: PMC 892,5196.

Yet another well-conducted review tries to distinguish the difference between KD and MIS-C. Age of the patient can be helpful, with KD more typically seen in younger patients and MIS-C more frequently seen in adolescents and teens. The presence of recent COVID-19 infection, exposure to confirmed COVID-19 case or positive polymerase chain reaction (PCR), serology, or antigen testing is needed to make the diagnosis of MIS-C. Coronary artery dilation or aneurysms can be found in both diseases but tend to be more common in KD while elevated cardiac enzymes, ventricular dysfunction, and hemodynamic instability are more frequently associated with MIS-C. Similarly, gastrointestinal symptoms and hypercoagulability are seen more commonly in MIS-C. Elevated white blood cell count with eosinophilia and elevated platelets all point more toward the diagnosis of KD while patients with MIS-C more commonly develop thrombocytopenia. Elevated D-dimer and ferritin are more common in MIS-C.

Source: Daniels LB, Roberts S, Moreno E, Tremoulet AH, Gordon JB, Burns JC. Long-term Health Outcomes in Young Adults after Kawasaki Disease. Int J Cardiol Heart Vasc. 2022 May 4; 40: 101,039. DOI: 10.1016/j.ijcha.2022. 101,039. PMID: 355,73651; PMCID: PMC 909,6130.

The researchers compare the long-term health of adults with prior KD to controls and determined whether outcomes varied by coronary artery (CA) status. It is a prospective cohort study of 258 KD subjects (mean 19 ± 9 years since KD) and 148 age-similar controls who completed extensive health questionnaires. KD subjects were divided into two groups, Cohort 1 included 109 in-house subjects followed since KD diagnosis; Cohort 2 included 149 KD subjects diagnosed elsewhere. KD subjects and controls were of similar age at the time of questionnaire completion. Overall, 128 subjects (including 60 in Cohort 1) reported normal CAs during and after KD. Compared to controls, KD subjects with normal CAs reported several medical conditions with increased prevalence including migraine headaches, shortness of breath, and leg pain with walking, among others. When limited to Cohort 1, KD subjects were significantly more likely to report chest pain or palpitations compared to controls. The prevalence of depression was similar.

Despite always having normal CAs in the acute and subacute phases of KD, young adults with a history of KD with normal coronaries were more likely than controls to experience cardiovascular symptoms. These differences could be influenced by anxiety or depression, but the report of depression was similar between groups. Whether these health differences reflect a heightened awareness of symptoms among KD subjects, or underlying vascular pathology (i.e., vasospasm, microvascular dysfunction, other) merits further study.

Source: Lei WT, Chang LS, Zeng BY, Tu YK, Uehara R, Matsuoka YJ, Su KP, Lee PC, Cavalcante JL, Stubbs B, Lin PY, Wu YC, Hsu CW, Chen TY, Chen YW, Yeh PY, Sun CK, Tseng PT, Kao YH. Pharmacologic Interventions for Kawasaki Disease in Children: A Network Meta-analysis Of 56 Randomized Controlled Trials. EBioMedicine. 2022 Apr; 78: 103,946. DOI: 10.1016/j.ebiom.2022. 103,946. Epub 2022 Mar 17. PMID: 353,06339; PMCID: PMC 893,3672.

Although the current consensus recommends a standard treatment of high-dose IVIG with high–dose aspirin to manage KD, the use of different adjunctive therapies remains controversial. The aim of this current network meta-analysis (NMA) was to compare the efficacy and tolerability of different existing interventions for the initial and refractory stages of KD. The initial stage of KD was defined as the first stage to treat patients with KD; the refractory stage of KD represents KD patients who failed to respond to standard KD treatment. The cut-off points for IVIG were low (100–400 mg), medium (1 gm), and high (at least 2 gm).

- A total of 56 RCTs with 6486 participants were included. NMA demonstrated that the medium-dosage IVIG + aspirin + IFX compared to high-dosage IVIG + aspirin exhibited the shortest fever duration;
- Likewise, the medium-dosage IVIG + aspirin + IFX compared to high-dosage IVIG + aspirin exhibited the smallest incidence of CAL in the initial-stage KD.
- In the refractory-stage KD, the high-dosage IVIG + pulse steroid therapy compared to the high-dosage IVIG only had the best rate of decline of fever; likewise, the high-dosage IVIG + ciclosporin compared to the high-dosage IVIG only exhibited the smallest incidence of CAL.
- Infliximab (IFX) significantly improved resolution compared to the high-dosage IVIG-only group in refractory-stage KD.

In a nutshell, the NMA demonstrated that the combination therapy with the standard therapy of IVIG and aspirin might have an additional effect on shortening the duration of fever and lowering the CAL incidence rate in patients with acute KD. Moreover, the combination therapy with high-dose IVIG and pulse steroid therapy or cyclosporine therapy might have an additional effect on improving the rate of decline of fever and lowering the incidence rate of CAL in children with refractory KD. Because some of the findings of this NMA should be considered hypothesis-generating rather than confirmatory, further evidence from de novo randomized trials is needed to support their results.

Source: Chen DT, Chang JP, Cheng SW, Chang HC, Hsu JH, Chang HH, Chiu WC, Su KP. Kawasaki Disease in Childhood and Psychiatric Disorders: A Population-based Case-control Prospective Study in Taiwan. Brain Behav Immun. 2022 Feb; 100:105–111. DOI: 10.1016/j.bbi.2021.11.017. Epub 2021 Nov 28. PMID: 348,48339.

Although some researchers have investigated neurodevelopmental consequences following KD, the findings have been inconsistent. This study claims to be the first population-based study targeted at KD and common psychiatric disorders.

The authors aimed to investigate the association between KD and psychiatric disorders and hypothesized that standard anti-inflammatory treatment by IVIG may protect against the development of psychiatric disorders.

Patients (n = 282,513) with psychiatric disorders (the case group) during 1997–2013 were included, and the control group was matched with age, sex, income, and urbanization (1:1). The prevalence of KD was calculated in both groups and odd ratios (ORs) were estimated and 95% confidence intervals (CIs) in the subgroup analyses for KD in conditions of age, severity, and common psychiatric comorbidity.

The numbers of patients with KD were 460 in the cases and 380 in the controls, and the crude OR of KD was 1.21 times greater in the case than in the control groups. KD patients without IVIG treatment (n = 126) were higher in the cases than those in the controls (n = 54), with an OR of 2.33. Subgroup analyses showed that KD survivors were at significant risk for autism spectrum disorders (ASD) and attention deficit and hyperactivity disorders (ADHD), and a trend of increased risk for anxiety disorders.

The study concludes that patients with KD were more likely to have comorbid psychiatric disorders, including ASD and ADHD. Moreover, anti-inflammatory treatment with IVIG may have potential prophylactic effects on the development of psychiatric disorders.

Source: Raynor A, Vallée C, Belkarfa AL, Lunte K, Laney M, Belhadjer Z, Vicca S, Boutten A, Bonnet D, Nivet-Antoine V. Multisystem Inflammatory Syndrome in Children: Inputs of BNP, NT-proBNP and Galectin-3. Clin Chim Acta. 2022 Apr 1; 529:109–113. DOI: 10.1016/j.cca.2022.02.011. Epub 2022 Feb 18. PMID: 351,83528.

In MIS-C, cardiac involvement is found in almost 80–85% of patients, typically with cardiac dysfunction with or without cardiogenic shock. In this small but interesting study, three cardiac biomarkers, brain natriuretic peptide (BNP), N-terminal (NT)-pro hormone BNP (NT-proBNP), and Galectin-3 were compared for the first time in MIS-C in a unique cohort of hospitalized French children.

Fourteen children with MIS-C hospitalized were included. All had proven cardiac involvement assessed by transthoracic echocardiography. NT-proBNP, BNP, and Galectin-3 were measured at admission, discharge, and first follow-up clinic. At admission, Galectin-3 measurements were comprised within the reference interval, both in patients with and without cardiogenic shock, and did not vary between admission, discharge, and first follow-up clinic. Both median admission BNP and NT-proBNP were higher in children with cardiogenic shock than without. Median admission NT-proBNP was higher than its predictive positive value in heart failure in both groups of children, while median BNP was below its negative predictive value in children without cardiogenic shock but with cardiac dysfunction. Galectin-3 does not seem affected by MIS-C. NT-proBNP seems to increase more precociously than BNP possibly making it a more sensitive marker for screening of heart failure in MIS-C.

Source: Nygaard U, Holm M, Hartling UB, Glenthøj J, Schmidt LS, Nordly SB, Matthesen AT, von Linstow ML, Espenhain L. Incidence and Clinical Phenotype of Multisystem Inflammatory Syndrome in Children After Infection with the SARS-CoV-2 Delta Variant by Vaccination Status: A Danish Nationwide Prospective Cohort Study. Lancet Child Adolesc Health. 2022 May 5:S2352–4642(22) 00,100–6. DOI: 10.1016/S2352–4642(22) 00,100–6. Epub ahead of print. PMID: 355,26537; PMCID: PMC 907,2929.

Multisystem inflammatory syndrome in children incidence is likely to depend on multiple factors, including the variant of the preceding SARS-CoV-2 infections and probably/possibly vaccine effectiveness. The researchers aimed to estimate the incidence of MIS-C, and describe the clinical phenotype, following the delta variant of SARS-CoV-2 (B.1.617.2 and sublineages) according to vaccination status. They aimed to compare the incidence and clinical phenotype of MIS-C from their own cohort during the pre-Delta era. This prospective, population-based cohort study included patients aged 0–17 years hospitalized with MIS-C in Denmark during a period dominated by the delta variant. They identified MIS-C cases from all 18 pediatric departments. Aggregated number of SARS-CoV-2 infections by vaccination status was obtained from the surveillance registries. The incidence of MIS-C was calculated using the estimated number of infected individuals by vaccination status. They calculated the incidence of MIS-C per 1,000,000 vaccinated and unvaccinated person-years and estimated vaccine effectiveness as a 1–incidence rate ratio using Poisson regression. Incidence and phenotype of MIS-C were compared with MIS-C cases from the first year of the pandemic.

A total of 51 MIS-C cases were identified among unvaccinated individuals and one in a fully vaccinated adolescent. The incidence of MIS-C was one in 3400 unvaccinated individuals with the delta variant and one in 9900 vaccinated individuals with breakthrough infection. The estimated vaccine effectiveness against MIS-C after the delta variant was 94% in individuals aged 5–17 years. *The clinical phenotype during the delta wave was comparable to the pre-delta era.*

They found the incidence and phenotype of MIS-C in unvaccinated children during the delta wave to be similar to the incidence during the first year of the pandemic. They found vaccine effectiveness to be high against MIS-C, which they suggest was due to protection from infection and, possibly, a decreased incidence of MIS-C after breakthrough infection. *Knowledge of the incidence of MIS-C after different SARS-CoV-2 variants and the effect of vaccination might contribute to the elucidation of the extent to which MIS-C is a vaccine-preventable disease.*

Source: Sokunbi O, Akinbolagbe Y, Akintan P, Oyeleke G, Kusimo O, Owowo U, Olonade E, Ojo O, Ikhazobor E, Amund O, Ogbuokiri E. Clinical Presentation and Short-term Outcomes of Multisystemic Inflammatory Syndrome in Children in Lagos, Nigeria Duringthe COVID-19 Pandemic: A case series. eClinicalMedicine. 2022 Jul 1; 49: 101,475. DOI: 10.1016/j.eclinm.2022. 101,475

MIS-C has increasingly been documented in a significant proportion of children of Black descent. There has been a noticeable discrepancy in the presentation and outcomes of COVID-19 infection in sub-Saharan Africa compared to the rest of the world. In this retrospective study, the authors document the demography, clinical, laboratory findings, therapeutic management, and short-term

outcomes of pediatric patients with MIS-C diagnosed during the COVID-19 pandemic in Lagos, Nigeria. Data on clinical presentation, laboratory investigations, therapy as well as outcomes at 2 weeks, 6 weeks, 3 months, and 6 months were analyzed.

- A total of 28 children and adolescents with a median age of 7.5 years were diagnosed with MIS-C. MIS-C was suspected in 24 patients at initial clinical evaluation and mucocutaneous, gastrointestinal, and cardiovascular manifestations were identified in 75.0, 71.4, and 89.3% of patients, respectively. Acute kidney injury and aseptic meningitis were noted in 32.1 and 17.9% of patients, respectively. Cardiac manifestations at presentation included coronary dilatation and pericardial effusion in 46.4% each, ventricular dysfunction (32.1%), atrioventricular valve regurgitation (25.0%), prolonged QTc interval (40.0%) and first-degree atrioventricular block (16.0%). Therapy included aspirin in 89.3%, steroids in 75.0%, and IVIG infusion in 60.7%. All patients survived and were discharged after a mean of 11.14 days. The frequency of coronary dilatation had reduced from 46.4 to 7.1% by 3 months follow-up and prolonged QTc interval persisted until the 6-week follow-up in 4.5% of patients. Echocardiogram and electrocardiogram findings were normal in all patients assessed at 6 months follow-up.

In this study, cardiovascular manifestations occurred in several children with MIS-C and improved by 6 months follow-up.

Source: Abuhammour W, Yavuz L, Jain R, Abu Hammour K, Al-Hammouri GF, El Naofal M, Halabi N, Yaslam S, Ramaswamy S, Taylor A, Wafadari D, Alsarhan A, Khansaheb H, Deesi ZO, Varghese RM, Uddin M, Al Suwaidi H, Al-Hammadi S, Alkhaja A, AlDabal LM, Loney T, Nowotny N, Al Khayat A, Alsheikh-Ali A, Abou Tayoun A. Genetic and Clinical Characteristics of Patients in the Middle East With Multisystem Inflammatory Syndrome in Children. JAMA Netw Open. 2022 May 2; 5(5):e 221,4985. DOI: 10.1001/jamanetworkopen.2022. 14,985. PMID: 356,39375.

This prospective, multicenter cohort study attempts to assess the genetic and clinical characteristics of patients with MIS-C of primarily Arab and Asian origin. Forty-five patients with MIS-C and a matched control group of 25 healthy children with a confirmed SARS-CoV-2 infection status were recruited. Whole exome sequencing in all 70 participants was performed to identify rare, likely deleterious variants in patients with MIS-C and to correlate genetic findings with the clinical course of illness.

A total of 45 patients with MIS-C; mean [SD] age, 6.7 [3.6] years and 25 controls (17 [68.0%] male; 24 [96.0%] of Middle Eastern origin; mean [SD] age 7.4 [4.0] years) participated in the study. Key inflammatory markers were significantly dysregulated in all patients with MIS-C. Rare, likely deleterious heterozygous variants in immune-related genes, including TLR3, TLR6, IL22RA2, IFNB1, and IFNA6, were identified in 19 patients, of whom seven had multiple variants. There was higher enrichment of genetic variants in patients relative to controls. Patients with those variants tended to have earlier disease onset (seven patients with genetic findings vs two without genetic findings were younger than 3 years at onset) and resistance to treatment (eight patients with genetic findings vs three patients without genetic findings received two doses of IVIG).

The results of this cohort study suggest that rare, likely deleterious genetic variants may contribute to MIS-C disease. This finding paves the way for additional studies with larger, diverse populations to fully characterize the genetic contribution to this new disease entity.

Source: Villacis-Nunez DS, Jones K, Jabbar A, Fan L, Moore W, Peter AS, Henderson M, Xiang Y, Kelleman MS, Sherry W, Chandrakasan S, Oster ME, Jaggi P, Prahalad S. Short-term Outcomes of Corticosteroid Monotherapy in Multisystem Inflammatory Syndrome in Children. JAMA Pediatr. 2022 Jun 1; 176(6):576–584. DOI: 10.1001/jamapediatrics.2022.0292. PMID: 353,44042; PMCID: PMC 896,1405.

To compare short-term patient outcomes based on initial treatment with corticosteroids, IVIG, or both to compare short-term patient outcomes based on initial treatments with corticosteroids, IVIG, or both. The primary outcome was a failure of initial therapy, defined as therapy escalation due to fever or worsening or lack of improvement of laboratory, cardiac, or noncardiac clinical factors after 24 hours (ICU patients) or 48 hours (non-ICU patients) from the time of therapy initiation, per clinician assessment. Secondary outcomes included the presence of complications, cardiovascular outcomes, fever duration, length of hospital and ICU stays, corticosteroid use duration, and need for readmission.

Among 228 eligible patients, 215 patients were included in the univariate analysis; the median age was 8 years, and 135 (62.8%) were boys. There were 69 patients in the corticosteroids group, 31 patients in the IVIG group, and 115 patients in the IVIG plus corticosteroids group. Patients in the corticosteroids group had a milder disease at presentation. After propensity score weighting including 179 patients (68 in the corticosteroids group and 111 in the IVIG plus corticosteroids group), rates of initial treatment failure were similar between groups.

Among patients whose initial treatment failed, treatment failure in the IVIG plus corticosteroids group was more likely to be based on laboratory parameters and less likely to be based on cardiovascular markers, per clinician assessment. Patients in the IVIG plus corticosteroids group had a longer median inpatient stay and longer median corticosteroid course duration compared with the corticosteroids group. Forty-nine patients (71% of 69 in the corticosteroids group) recovered after receiving corticosteroid monotherapy for 10 days or less.

The study concludes that corticosteroid monotherapy is a reasonable management option for a subset of patients with MIS-C, particularly those with mild disease.

Source: Davies P, du Pré P, Lillie J, Kanthimathinathan HK. One-Year Outcomes of Critical Care Patients Post-COVID-19 Multisystem Inflammatory Syndrome in Children. JAMA Pediatr. 2021 Dec 1; 175(12):1281–1283. DOI: 10.1001/jamapediatrics.2021.2993. PMID: 344,59875; PMCID: PMC 840,6209.

Data were available from 68 of 76 patients (89%) of the initial surviving cohort. There were no deaths, and two patients (3%) had critical care readmission. Both readmissions were unrelated to complications of PIMS-TS or immunomodulatory therapy. The median length of hospital stay was 10 days and none needed respiratory support postdischarge.

It is possible that for many patients whose blood test results did not normalize, lack of repeated tests, rather than failure to normalize, may be contributory. Only two of 65 test results (3%) for CRP, two of 59 test results (3%) for D-dimer, and 1 of 60 test results (2%) for

troponin were abnormal when tested more than 50 days postadmission. All results for blood tests performed for levels of lymphocytes, neutrophils, platelets, creatinine, ferritin, and alanine transaminase more than 50 days postadmission were normal. Although resolution to normality for D-dimer, ferritin, and troponin was demonstrated in fewer patients, fewer patients had serial monitoring of these parameters.

Of those patients who presented with aneurysms, 14 of 19 had a resolution, and of those who presented with subjectively "bright" coronary arteries, 9 of 10 had resolution and one patient progressed to having unresolved CAA (albeit the latest follow-up echocardiography was 86 days postadmission). All patients who presented with impaired function without aneurysm recovered by day 74.

All six patients (9%) with ongoing echocardiographic abnormalities had aneurysmal changes, with the latest echocardiograms between days 86 and 336 postadmission. At presentation, these six patients had a median (interquartile range [IQR]) C–reactive protein level of 22.1 mg/dL (6.6–36.9 mg/dL), compared with 25.8 mg/dL (18.2–32.3 mg/dL) (to convert to milligrams per liter, multiply by 10) for those without aneurysmal changes at follow–up, a lymphocyte count of 1100/μL (600–3300/μL) vs 900/μL (500–1400/μL) (to convert to × 109/L, multiply by 0.001), and platelet count of 217 × 103/μL (128–368 × 103/μL) vs 151 × 103/μL (85–198 × 103/μL) (to convert to × 109/L, multiply by 1). Surprisingly, median troponin levels were significantly lower in the group with aneurysm (0.06 ng/mL [0.02–0.418 ng/mL] vs 0.157 ng/mL [0.033–0.81 ng/mL] [to convert to micrograms per liter, multiply by 1]; $p = 0.02$). All six received IVIG, compared with 46 of 62 of the other patients; 5 of 6 received steroids vs 46 of 62, and 1 of 6 received a biological agent vs 13 of 62. According to the case reports, 5 of the 6 were Afro-Caribbean boys and 1 was a White girl, with an age range of 0–13 years (median, 8.75 years).

Source: Pfeifer J, Thurner B, Kessel C, Fadle N, Kheiroddin P, Regitz E, Hoffmann MC, Kos IA, Preuss KD, Fischer Y, Roemer K, Lohse S, Heyne K, Detemple MC, Fedlmeier M, Juenger H, Sauer H, Meyer S, Rohrer T, Wittkowski H, Becker SL, Masjosthusmann K, Bals R, Gerling S, Smola S, Bewarder M, Birk E, Keren A, Böhm M, Jakob A, Abdul-Khaliq H, Anton J, Kabesch M, Pino-Ramirez RM, Foell D, Thurner L. Autoantibodies Against Interleukin-1 Receptor Antagonist in Multisystem Inflammatory Syndrome in Children: A Multicentre, Retrospective, Cohort Study. Lancet Rheumatol. 2022 May;4(5):e329-e337. doi: 10.1016/S2665-9913(22)00,064-9. Epub 2022 Mar 29. PMID: 353,68387; PMCID: PMC896,3770.

Recently, neutralizing autoantibodies against inflammatory receptor antagonists progranulin and interleukin-1 receptor antagonist (IL-1Ra) were found in adult patients with critical COVID-19. The aim of the study was to investigate the role of any such autoantibodies in MIS-C.

As controls, the authors included children with KD, children with inactive systemic juvenile idiopathic arthritis, and children with suspected growth retardation (noninflammatory control); (all aged ≤18 years). Serum samples from the CoKiBa trial were used as two further control groups, from healthy children (negative for SARS-CoV-2 antibodies) and children with previous mild or asymptomatic COVID-19 (aged ≤17 years). MIS-C and control samples were analyzed for autoantibodies against IL-1Ra and progranulin, and for IL-1Ra concentrations.

Autoantibodies against IL-1Ra could be detected in 13 (62%) of 21 patients with MIS-C (11 girls and 10 boys), but not in children with KD ($n = 24$; nine girls and 15 boys), asymptomatic or mild COVID-19 ($n = 146$; 72 girls and 74 boys), inactive systemic juvenile idiopathic arthritis ($n = 10$; five girls and five boys), suspected growth retardation ($n = 33$; 13 girls and 20 boys), or in healthy controls ($n = 462$; 230 girls and 232 boys).

Anti-IL-1Ra antibodies in patients with MIS-C belonged exclusively to the IgG1 subclass, except in one patient who had additional IL-1Ra-specific IgM antibodies.

Autoantibodies against progranulin were only detected in one (5%) patient with MIS-C. In patients with MIS-C who were positive for anti-IL-1Ra antibodies, free plasma IL-1Ra concentrations were reduced, and immune complexes of IL-1Ra were detected.

Notably, an additional, hyperphosphorylated, transiently occurring atypical isoform of IL-1Ra was observed in all patients with MIS-C who were positive for anti-IL-1Ra antibodies. Anti-IL-1Ra antibodies impaired IL-1Ra function in reporter cell assays, resulting in amplified IL-1β signaling.

Source: Yousaf AR, Cortese MM, Taylor AW, Broder KR, Oster ME, Wong JM, Guh AY, McCormick DW, Kamidani S, Schlaudecker EP, Edwards KM, Creech CB, Staat MA, Belay ED, Marquez P, Su JR, Salzman MB, Thompson D, Campbell AP. MIS-C Investigation Authorship Group. Reported Cases of Multisystem Inflammatory Syndrome in Children Aged 12-20 Years in the USA Who Received a COVID-19 Vaccine, December, 2020, through August, 2021: A Surveillance Investigation. Lancet Child Adolesc Health. 2022 May;6(5):303-312. doi: 10.1016/S2352-4642(22)00,028-1. Epub 2022 Feb 23. PMID: 352,16660; PMCID: PMC886,4018.

In the USA, reporting of MIS-C after vaccination is required under COVID-19 vaccine emergency use authorizations. The authors aimed to investigate reports of individuals aged 12–20 years with MIS-C after COVID-19 vaccination.

- A total of 21 individuals with MIS-C after COVID-19 vaccination were identified. Of these 21 individuals, the median age was 16 years (range 12–20); 13 (62%) were male and eight (38%) were female. All 21 were hospitalized: 12 (57%) were admitted to an intensive care unit and all were discharged home. A total of 15 (71%) of 21 individuals had laboratory evidence of past or recent SARS-CoV-2 infections and six (29%) did not. As of 31st August 2021, 21,335,331 individuals aged 12–20 years had received one or more doses of a COVID-19 vaccine, making the overall reporting rate for MIS-C after vaccination 1.0 cases per million individuals receiving one or more doses in this age group. The reporting rate in only those without evidence of SARS-CoV-2 infection was 0.3 cases per million vaccinated individuals.

This study finding suggests that MIS-C after COVID-19 vaccination is rare.

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