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Difference between Kawasaki Disease and the Multisystem Inflammatory Syndrome in Children

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Abstract: Multisystem Inflammatory Syndrome in Children (MIS-C) is a disease associated with Severe Acute Respiratory Syndrome-Associated Coronavirus (SARS-CoV-2) infection and is characterized by multiple systemic involvement such as fever, cardiovascular damage, skin and mucosal changes, and digestive system symptoms. Its clinical characteristics are similar to Kawasaki disease (KD). According to the latest case reports and research progress, this paper introduces the differences between MIS-C and KD, in order to improve the ability of clinical pediatricians to identify MIS-C.

1. Introduction

In December 2019, the Coronavirus Disease 2019 caused by SARS-CoV-2, (COVID-19), was rapidly spread around the world. Several previous studies have shown that children have fewer cases, mild disease and high cure rate compared with adults [1-3]. However, in April 2020, most countries began to report a disease related to SARS-CoV-2 infection, which can cause childhood fever, cardiovascular damage, skin and mucosal changes, and digestive tract symptoms. The WHO named it as MIS-C in May 2020. The clinical presentation of KD and MIS-C patients were very similar, most MIS-C, and patients also met the diagnostic criteria for KD [4]. This causes trouble for the diagnosis and treatment of both diseases. Therefore, understanding the differences in the two diseases in epidemiology, diagnostic criteria, clinical manifestations, laboratory indicators and treatment is important for guiding clinicians in differential diagnosis and treatment.

2. Epidemiology

The statistical MIS-C pandemic mainly occurred about 4 weeks after the peak number of SARS-CoV-2 infection cases [5]. MIS-C has a clear bias towards race and age, which in both two large case series showed the highest proportion of black race and Hispanics, second by white race and lowest among Asians. Most patients had an onset age of 6 to 12 years, a median age of 8 years, and a male-female ratio was similar to gender [6,7]. The main incidence population of Kawasaki disease is Asian, especially in Japan, and it has an increasing trend in recent years. White incidence rates are low, while Blacks and Hispanics are extremely low. In terms of age of onset, 80% of children are between 6

months and 5 years, with peak onset between 2 and 3 years, but Kawasaki disease can occur at any age and cases have been reported in adults [8,9].

3. Diagnostic criteria

The diagnostic criteria for MISC published by the World Health Organization: (1) the child was <19 years; (2) fever 3 d; (3) at least two of the following criteria: ① rash, bilateral nonsuppurative conjunctivitis, or signs of skin and mucosal inflammation. ② Hypotension or shock. ③ Cardiac insufficiency, pericarditis, valvular inflammation, or coronary artery abnormalities. ④ disturbance of blood coagulation. ⑤ Acute gastrointestinal symptoms. (4) History of recent or current evidence of infection (PCR, antigen or positive serology) or exposure to COVID 19 virus.

The diagnostic criteria for MIS-C published by the Centers for Disease Control and Prevention: (1) age <21 years; (2) body temperature> 38.0℃ and duration> 24 h; (3) severe illness requiring hospitalization involving at least 2 organs (cardiovascular, respiratory, renal, nerve, blood, gastrointestinal, skin); (4) laboratory confirmation of SARS-CoV-2 infection, or a history of SARS-CoV-2 exposure within 4 weeks before the onset of symptoms.

Royal College of Paediatrics and Child Health criteria: (1) child temperature> 38. 5℃, single or multiple organ impairment; (2) exclusion of other causes; no positive SARS-CoV-2 infection or exposure [10].

Kawasaki disease usually depends on clinical diagnosis. According to the Diagnosis, Treatment and Long-term Management of Kawasaki Disease in 2017, the criteria for diagnosis of Kawasaki disease require 5 days, clinical features 4 / 5; or fever for 4 days, clinical criteria 4 (especially swollen hands and feet) can also be diagnosed; for clinically experienced doctors, only fever 3 D. A patient was classified as incomplete Kawasaki disease if they were febrile for 5 days, with 2 to 3 clinical features or echocardiographic abnormalities [11].

4. Pathogenesis

MIS-C mainly appears as a cytokine storm of innate and adaptive immune cells, and the novel coronavirus may be a trigger factor or immune regulatory factor. Mechanism for shedding COVID 19 virus particles in infected tissue, resulting to a molecular simulation form, including antibodies or T cells to the infected cell expression of virus antigen recognition, virus superantigen fragment induced by the formation of immune complexes and excessive inflammatory reaction activation, lead to excessive inflammatory immune response. In MIS-C, an inflammatory reaction occurs when the immune system attempts to clear virus particles from the body. Activation of G amma interferon (IFN γ) can increase the human leukocyte antigens in tissues, leading to a more "sensitized" immune response. Activation of the I nterleukin 1 (IL 1) and IFN γ pathway leads to CD8+Cytotoxic T cell response, which migrates to the heart and other organs and destroys the virus-resident tissues. Stimulation of CD8＋The release of inflammatory response mediators from cytotoxic T cells can also lead to viral suppression and platelet activation in the bone marrow. KD is an acute systemic vasculitis reaction syndrome that mainly involves children under 5 years of age, often involving medium and small coronary vessels.

KD is usually a self-limiting disease, and prompt management is fundamental to the prevention of cardiac sequelae. The pathogenesis of KD is related to an excessive immune response to the environment or infection trigger in genetically susceptible children, or to an acute vasculitis of intermediate arteries (including coronary arteries) caused by prior viral infection. The formation of immune complexes in KD marks the proliferation of monocytes and macrophages, leading to increased neutrophilia. A severe inflammatory response caused by immune complexes triggers the

release of cytokines, leading to organ damage. The same signals generated by the immune complexes would also trigger a reactive thrombocytopenia and boost the platelet count. In addition to immune complex responses, I mmunoglobulin A (IgA) plays a role in KD, and increased IgA levels are associated with coronary artery involvement.

5. Clinical manifestations

5.1. Cardiovascular system

The major complication of Kawasaki disease is coronary aneurysms with an incidence of <10% [12,13]. In contrast, the incidence of coronary artery dilatation in MIS-C patients ranged from 14% to 36% [14]. Left ventricular systolic dysfunction (left ventricular ejection fraction <50%) is rare in Kawasaki disease, but in MIS-C, 18 to 87% of children exhibit ventricular dysfunction [15]. And Pouletty et al. [16] have found that 40% to 80% of MIS-C patients develop symptomatic myocarditis, about 50% of MIS-C patients with myocarditis require intensive care, and older children are at higher risk. Conversely, symptomatic myocarditis occurs in <5% in patients with Kawasaki disease [17]. Pericarditis, pericardial effusion, and valvulregurgitation also occur in patients with MIS-C. Patients with MIS-C may have ECG abnormalities, including PR interval extension, T wave, and ST segment changes. Severe MIS-C can cause hypotension and hemodynamic instability, causing cardiogenic shock. These patients need pressors, and Extracorporeal Membrane Oxygenation (ECMO) should be applied promptly in severe cases [18].

5.2. Digestive system symptoms

Digestive symptoms are the main clinical manifestation of MIS patients with MIS-C, and the digestive system is the second most affected system after the cardiovascular system[19]. Clinically, it often includes abdominal pain, vomiting, and diarrhea. When MIS-C patients develop digestive symptoms, CT or MRI more often indicate mesenteric lymphadenitis, hepatosplenomegaly, intestinal wall thickening, and intestinal inflammation. The pathophysiological mechanism of gastrointestinal involvement is that ACE 2 is a functional host receptor for SARS-CoV-2, which is mostly present in intestinal cells and can mediate inflammation, with an intensified inflammatory response during SARS-CoV-21 infection [20]. Sahn et al. [21] reported gastrointestinal involvement in 34 of 35 patients with MIS-C, with over 50% of abdominal CT imaging suggesting ileisitis and bowel wall thickening. In a survey of MIS-C patients, 80% had any gastrointestinal symptoms, 60% had abdominal pain, 58% had nausea or vomiting, and 49% had diarrhea [22].

Children with Kawasaki disease have relatively few digestive symptoms, which are atypical and often occur after clinical typical symptoms.

5.3. Skin and mucosal manifestations

The presence of redness at the BCG vaccination site is known as card scar red, which is considered an important positive sign of KD in a statement issued by the American Heart Society [11]. Rezai [23] classed the literature of red in KD patients, found that 49.87% of patients with KD. The cases of red scar in MIS-C have not been reported. The incidence of unseen in KD ranges from 68% to 98% [24], While there are few reports of perithyroid membrane peeling in MIS-C patients.

5.4. Respiratory system

The MIS-C respiratory system often presents with respiratory insufficiency and pleural effusion.

And through a study of 186 patients, Feldstein et al.[18] found that 109 patients (59%) had respiratory insufficiency or failure, 37 (20%) received invasive mechanical ventilation and 32 (17%) non noninvasive mechanical ventilation.

KD patients generally do not involve the respiratory system, and only a few patients show pharyngeal congestion and cough.

5.5. Nervous system

The neurological manifestations of MIS-C are headache, drowsiness, confusion, and irritability. Epilepsy, coma, meningitis, stroke and these severe neurological manifestations are relatively low incidence [25]. A study conducted in the USA showed that out of 616 MIS-C patients, 20% had neurological manifestations [26]. In addition, 20 of these patients (3%) developed serious, life-threatening neurological diseases, including severe encephalopathy, demyelinating lesions, stroke, and acute cerebral edema.

KD patients had no obvious neurological symptoms, a study of 1582 patients [27] showed that neurological involvement was observed in 5. 1% (80 / 1582) Kawasaki patients with headache (13 / 80, 16.3%), convulsions (14 / 80, 17.5%), drowsiness (40 / 80, 50.1%), extreme irritability (21 / 80, 26.3%), meningitis signs (15 / 80, 18.8%), fontanelle (7 / 80, 8.8%), and facial paralysis (1 / 80, 1.3%).

5.6. Blood system

The hypercoagulable state was present in both KD and MIS-C patients, but more frequently than in MIS-C. A hypercoagulable state causes complications, including deep vein thrombosis and pulmonary embolism. Children with MIS-C develop hypercoagulable with vascular thrombosis. Prolonged prothrombin time and international normalized ratio, increased activated partial thromboplastin time, D dimer levels and low antithrombin. These abnormalities can lead to disseminated intravascular thrombosis, venous and arterial thrombosis, and pulmonary embolism. Thus, many patients with MIS-C receive anticoagulation therapy, including aspirin and enoxaparin. High-dose aspirin combined with warfarin or enoxaparin is commonly used in the treatment of severe coronary aneurysms.

6. Inspection indicators

Inflammatory markers in MIS-C patients were significantly higher, mainly C-reactive protein, procalcitonin, ferritin, and neutrophils, mostly MIS-C, with at least four increased inflammatory markers, but decreased lymphocytes and platelets in MIS-C patients [18,28]. In KD patients, they showed increased leukocytes, mainly neutrophils, normal platelets in the early stage, and increased from 2 to 3 weeks. In MIS-C, CRP, AST, NT-pro-BNP, troponin, D-dimer, fibrinogen, ferritin, and creatinine levels were significantly increased in treated patients compared with patients with KD [29].

7. Treatment

7.1. I ntravenous immunoglobulin (IVIG)

IVIG should be the first-line treatment for MIS-C inpatients, assessing cardiac function and fluid status, if abnormal, IVIG infusion rate should be slowed down, and diuretics are needed according to the condition to avoid volume overload. A single dose of IVIG is 2 g / kg, and a lower dose of 1g / kg is usually recommended for MIS-C patients with no obvious symptoms of Kawasaki disease[5]. MIS-C patients usually have higher age and weight than Kawasaki disease and require a larger dose

of IVIG, but have a higher risk of IVIG complications (e.g. , hemolytic anemia and volume overload). Therefore, further evaluation of a second dose of IVIG is needed in patients with refractory MIS-C. The second dose of IVIG can be applied to children with Kawasaki disease with poor efficacy of the first dose of IVIG.

7.2. Aspirin

MIS-C patients without risk of active bleeding or bleeding received low-dose aspirin [3 to 5 mg / (kg ·d)] at a maximum dose of 81 mg / d until the platelet count normalized and was discontinued after confirming the coronary artery was normal at 4 weeks of diagnosis [30].

In the acute phase of Kawasaki disease, high-dose aspirin should be used for anti-inflammatory treatment, according to [30-50 mg / (kg ·d)], once every 6 to 8 h. After inflammation control, temperature stabilization, adjusted to small dose, that is, [3 ~5 mg / (kg ·d)], and this dose will continue until coronary lesions and inflammatory indicators return to normal [31].

7.3. Glucocorticosteroids

As an adjuvant therapy for patients with MIS-C, low and medium doses of glucocorticoids [1 to 2 mg (kg ·d)] should be combined with IVIG twice. Children who are not responsive to intravenous immunoglobulin or insensitive to low-medium dose corticosteroids may be given high-dose glucocorticoids [10 to 30 mg (kg ·d), maximum to 1 g]. After clinical recovery, the patient can be switched to an equal dose of oral prednisone at discharge, and then reduced until withdrawal within 3 to 4 weeks [32].

Glucocorticoids are the first-line treatment for KD children with complicated coronary aneurysm or peripheral hemangioma. Recommended dose: The dosage of Prednisone is 1 to 2 mg/(kg ·d), taken in the morning, with the total dose <60 mg/d. The dosage of Methylprednisolone is 1 to 2 mg /(kg d), administered intravenously, with 1 to 2 times daily. After the patient's body temperature and CRP are normal, the dosage for 15 days is 1 to 2 mg/(kg ·d), and the dosage for 5 days is 0.5 to 1 mg/(kg ·d) or 0.25 to 0.5 mg/(kg/d)]. In the treatment of Kawasaki disease shock syndrome, the recommended dose: methylprednisolone [10-30 mg (kg ·d)], using 1-3 d, each intravenous infusion time was 2 to 3 h; KD with primary treatment of macrophage activation syndrome recommended dose: methylprednisolone [10-30 mg (kg ·d)], continuous application for 3 d, each intravenous infusion time was 2-3 h. Sequential prednisone was administered orally [1 to 2 mg (kg ·d)] until complete control of macrophage activation syndrome secondary to Kawasaki disease [33].

7.4. Other treatments

For severe children, the preferred mAb for MIS-C was the IL-6 receptor antagonist tocilizumab, with a first dose of 4 to 8 mg / kg dissolved in 100 ml of saline. If the symptoms are not significantly relieved and the inflammatory index is not significantly reduced after the first dose, 1 dose can be added 12 h after the first dose, and a maximum of 2 doses can be accumulated[34].

The IL-1 receptor antagonist anabysin in children with IVIG resistant KD starts at [2mg (kg ·d)], [4mg (kg ·d)], with body temperature measured every 24h, and 2mg (kg ·d) at a maximum dose of [8mg (kg ·d)] [35].

8. Conclusion

Currently, the diagnosis and treatment of KD has formed a unified treatment plan, and no consensus on the diagnostic criteria of MIS-C, the focus is whether to have positive SARS CoV-2

infection or a history of SARS-CoV-2 contact as the diagnostic point. In the affected population, MIS-C is more in Hispanics and African Americans, while KD disease is better in East Asian populations, especially in Japanese children. In terms of clinical manifestations, both can accumulate multiple organ damage, and the clinical manifestations are very similar, but the probability of pathogenesis of different organs is very different. The drugs are similar in their treatment, but the details of the dose require the attention of clinicians. At present, although the severe situation in China has eased, the sequelae of MIS-C children still need long-term follow-up. In addition, the diagnosis and treatment plan of MIS-C should be unified to form a consensus to facilitate the early identification and treatment of MIS-C by pediatricians.

References

[1] Ladhani S N, Amin-Chowdhury Z, Davies H G, et al. COVID-19 in children: analysis of the first pandemic peak in England[J]. Arch Dis Child, 2020, 105(12):1180-1185.

[2] Bialek S, Gierke R, Hughes M, et al. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020[J]. MMWR Morb Mortal Wkly Rep, 2020, 69(14):422-426.

[3] Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy[J]. New England Journal of Medicine, 2020, 383(2):187-190.

[4] Wessels P A, Bingler M A. A comparison of Kawasaki Disease and multisystem inflammatory syndrome in children[J]. Prog Pediatr Cardiol, 2022, 65:101516.

[5] Törün S H, Çiftdoğan D Y, Kara A. Multisystem inflammatory syndrome in children[J]. Turkish journal of medical sciences, 2021, 51(7):3273-3283.

[6] Holstein B. Multisystem inflammatory syndrome in children[J]. The Journal for Nurse Practitioners, 2021, 17(8):941-945.

[7] Patel J M. Multisystem inflammatory syndrome in children (MIS-C)[J]. Current Allergy and Asthma Reports, 2022, 22(5):53-60.

[8] Marsaud C, Kon é-Paut I. Maladie de Kawasaki[J]. Journal de P édiatrie et de Pu ériculture, 2018, 31(5):225-234.

[9] Gehrmann A, Morwood K, Gillis D, et al. A case of adult-onset Kawasaki disease[J]. Med J Aust, 2018, 208(6):250-251.

[10] Lee M, Liu Y, Tsai C, et al. Similarities and differences between COVID-19-related multisystem inflammatory syndrome in children and Kawasaki disease [J]. Frontiers in Pediatrics, 2021, 9:640118.

[11] McCrindle B W, Rowley A H, Newburger J W, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association[J]. Circulation, 2017, 135(17):e927-e999.

[12] Jhaveri S, Ahluwalia N, Kaushik S, et al. Longitudinal echocardiographic assessment of coronary arteries and left ventricular function following multisystem inflammatory syndrome in children[J]. The Journal of pediatrics, 2021, 228:290-293.

[13] Gaitonde M, Ziebell D, Kelleman M S, et al. COVID-19-related multisystem inflammatory syndrome in children affects left ventricular function and global strain compared with Kawasaki disease[J]. Journal of the American Society of Echocardiography, 2020, 33(10):1285-1287.

[14] Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study[J]. BMJ, 2020, 369:m2094.

[15] Alsaied T, Tremoulet A H, Burns J C, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children[J]. Circulation, 2021, 143(1):78-88.

[16] Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort[J]. Annals of the rheumatic diseases, 2020, 79(8):999-1006.

[17] Pilania R K, Jindal A K, Bhattarai D, et al. Cardiovascular involvement in Kawasaki disease is much more than mere coronary arteritis[J]. Frontiers in Pediatrics, 2020, 8:526969.

[18] Feldstein L R, Rose E B, Horwitz S M, et al. Multisystem inflammatory syndrome in US children and adolescents[J]. New England Journal of Medicine, 2020, 383(4):334-346.

[19] Feldstein L R, Tenforde M W, Friedman K G, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19[J]. Jama, 2021, 325(11):1074-1087.

[20] Agarwal A, Chen A, Ravindran N, et al. Gastrointestinal and liver manifestations of COVID-19[J]. Journal of Clinical and Experimental Hepatology, 2020, 10(3):263-265.

[21] Sahn B, Eze O P, Edelman M C, et al. Features of intestinal disease associated with COVID-related multisystem inflammatory syndrome in children[J]. Journal of pediatric gastroenterology and nutrition, 2021, 72(3):384.
[22] Dufort E M, Koumans E H, Chow E J, et al. Multisystem inflammatory syndrome in children in New York State[J]. New England Journal of Medicine, 2020, 383(4):347-358.
[23] Rezai M S, Shahmohammadi S. Erythema at BCG inoculation site in Kawasaki disease patients[J]. Materia Socio-medica, 2014, 26(4):256.
[24] Wang S, Best B M, Burns J C. Periungual desquamation in patients with Kawasaki disease[J]. Pediatr Infect Dis J, 2009, 28(6):538-539.
[25] Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children [J]. JAMA neurology, 2020, 77(11):1440-1445.
[26] LaRovere K L, Riggs B J, Poussaint T Y, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome[J]. JAMA neurology, 2021, 78(5):536-547.
[27] Liu X, Zhou K, Hua Y, et al. Neurological involvement in Kawasaki disease: a retrospective study[J]. Pediatric Rheumatology, 2020, 18(1):1-8.
[28] Zou H, Lu J, Liu J, et al. Characteristics of pediatric multi-system inflammatory syndrome (PMIS) associated with COVID-19: a meta-analysis and insights into pathogenesis[J]. International Journal of Infectious Diseases, 2021, 102:319-326.
[29] Tong T, Yao X, Lin Z, et al. Similarities and differences between MIS-C and KD: a systematic review and meta-analysis [J]. Pediatric Rheumatology, 2022, 20(1):1-13.
[30] Henderson L A, Canna S W, Friedman K G, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS –CoV -2 and hyperinflammation in pediatric COVID -19: version 3[J]. Arthritis & Rheumatology, 2022, 74(4):e1-e20.
[31] Wang Yong, Peng Qian and diagnosis of Kawasaki disease [J]. Modern Clinical Medicine, 2021, 47 (06): 468-471.
[32] Hançerli T S, Yilmaz Ç D, Kara A. Multisystem inflammatory syndrome in children[J]. Turk J Med Sci, 2021, 51(SI-1):3273-3283.
[33] Du Zhongdong, Zhang Weihua Zhang, Yang Xiaodong, and other pediatric expert consensus of glucocorticoids in the treatment of Kawasaki disease [J]. Chinese Journal of Contemporary Pediatrics, 2022, 24 (03): 225-231.
[34] Zhang S, Li L, Shen A, et al. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia[J]. Clinical drug investigation, 2020, 40:511-518.
[35] Koné-Paut I, Tellier S, Belot A, et al. Phase II Open Label Study of Anakinra in Intravenous Immunoglobulin-Resistant Kawasaki Disease[J]. Arthritis Rheumatol, 2021, 73(1):151-161.