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An Outbreak of Kawasaki-like Disease in children during SARS-CoV- 2 Epidemic: No Surprise?

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Summary. *Background and aim:* Kawasaki disease is an acute systemic febrile illness of unknown aetiology, which usually affects children under 5 years of age. It is well known that Kawasaki disease is one of the most common causes of acquired heart diseases in children in the developed countries. Many studies, have suggested that heterogeneous infectious agents, such as common viruses, may trigger Kawasaki disease in young children with genetic background. Nowadays we are facing a pandemic caused by a Novel Coronavirus named SARS-CoV-2. Consequently, it could be possible that once exposed to this new coronavirus, some children, genetically predisposed, may mount an exaggerated inflammatory response which clinically manifests as Kawasaki Disease. *Methods:* from January to May 2020 a systematic search was performed on Pubmed for the following search terms: "COVID-19", "children", "SARS-CoV-2", "complications", "Kawasaki disease", "cytokine storm". *Results:* Usually, infants and children present milder symptoms of SARS-CoV-2 disease with a better outcome than adults. At variance, some children may be genetically disposed to a more robust inflammatory response to SARS-CoV-2, similar to Kawasaki disease. In fact, Kawasaki disease is the result of an abnormal immune response, in susceptible children, to an external trigger such as an infection. Thus, according to the pathogenesis of Kawasaki disease, paediatricians may expect an increase in cases of Kawasaki disease during the COVID-19 pandemic. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, children, Kawasaki disease, Kawasaki syndrome

Introduction

Kawasaki disease

Kawasaki disease (KD) is an acute vasculitis, which usually affects children under 5 years of age and leads to coronary artery aneurysms in approximately 25% of untreated cases. It has been reported worldwide and is the leading cause of acquired heart disease in children in developed countries. Table 1 and table 2 show the clinical criteria that are used to define KD.

In Europe, KD is reported in 5-15/100 000 children under 5 years of age annually. In the US 19 per 100 000 children younger than five years are hospitalized with KD annually. The incidence of KD in northeast Asian countries such as Japan, South Korea, China and Taiwan is 10–30 times higher than in the US or Europe (1).

Higher rates of KD in siblings of patients and twins suggest a genetic predisposition that may interact with a pathogenic agent in the environment (2). Evidence suggests that KD susceptibility and outcome, are influenced by several different genes and signalling pathways. In particular, family linkage studies have shown a relation between some genes, such as CASP3, HLA II, BLK, CD40 and the onset of the disease (3,4).

Actually, the cause of KD remains unknown. Current literature suggests that some pathogens (particularly virus with RNA) that infect the upper respiratory tract, may be a trigger for the development of the disease (5).

Table 1. Classic KD is diagnosed in the presence of fever for at least five days with at least four of the five principal features[1].

Diagnosis of Classic KD
• Erythema and cracking of lips, strawberry tongue and/or erythema of oral and pharyngeal mucosa
• Bilateral conjunctival injection
• Maculopapular rash
• Erythema and edema of the hands and feet and/or periungual desquamation
• Cervical lymphadenopathy (> 1,5 cm diameter), usually unilateral

Table 2. The diagnosis of incomplete KD should be considered in any infant or child with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings[1].

Suspected Incomplete KD
• Children with fever > 5 days and 2 or 3 compatible clinical criteria or infants with fever for 7 days without explanation
• CRP > 3 mg/dL and/or ESR > 40mm/hr
• 3 or more Laboratory Findings: - anemia for age - platelet count > 450,000 after the 7th day of fever - Albumin < 3.0 gr/dL - Elevated ALT level - WBC count of > 15.000/mm^3 - Urine > 10 WBC/hpf **Or** - Positive echocardiogram

Infections associated with Kawasaki disease

Infection has long been considered the main cause of KD.

The infectious evidence of Kawasaki disease includes:

- temporal clustering and seasonality,
- geographical and epidemic clustering,
- familial clustering,
- a high association between Kawasaki disease and infectious disease surveillance,
- age distribution, with highest incidence rates among children aged 6 months to 2-years who have low maternal antibodies (6).

Studies have reported that bacterial agents may be related to KD because of superantigens. Bacteria isolated from patients with KD include *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Mycoplasma pneumonia* (7-8).

Moreover, many studies have reported the role of viral infection in KD, including coronavirus (9), enterovirus (10), parainfluenza (11) and adenoviruses (12). In fact, according to a prospective study conducted by Chang et al., it was found that some infectious agents, that usually result in asymptomatic or mild infection, cause KD in a small group of genetically predisposed children. In their study, KD cases have significantly higher positive rates of PCR for various viruses including enterovirus, adenoviruses, rhinoviruses and pan-coronaviruses (6).

The mechanism that explains the relationship between KD and viral infection remains unclear but it is possible that large amounts of cytokines produced by viral-infected cells, such as IL-1, IL-6 and IL-18, may damage the vascular endothelium resulting in severe cases in Kawasaki Disease Shock Syndrome (KDSS).

KD and KDSS: role of infections

Kawasaki Disease Shock Syndrome (KDSS) has been defined by Kanegaye in 2009. This syndrome is characterized by shock and hypotension requiring critical care support in patients with acute KD. These patients seem to have higher incidences of coronary artery aneurism and IVIG resistance (13).

During the acute phase of KD, the immune system is activated with an increase of pro-inflammatory cytokines. Inflammatory cytokines may cause local and systemic damage. KD patients with IL-6 above 66.7 pg/ml, IL-10 above 20.85 pg/ml and IFN-γ above 8.35 pg/ml may have a higher risk to evolve into KDSS (14).

Pathogenesis of KDSS or other organ involvement in KD is unknown, but inflammatory mediators that are involved in the host immune reaction after an infection, may be associated with KDSS.

COVID-19 and KD

On December 2019, a cluster of pneumonia cases of unknown aetiology has been reported in Wuhan,

China. Scientists, collecting samples of patients, have discovered a novel coronavirus (called SARS-CoV-2) as the causative agent of this outbreak. As of 14 July 2020, 12 964 809 cases and 570 288 deaths have been reported worldwide (15).

Several countries affected by COVID-19 pandemic recently have reported cases of children that have been hospitalised due to an inflammatory multisystem syndrome characterized by signs and symptoms of Kawasaki disease (KD) and KDSS with cardiac involvement. A temporal association with SARS-CoV-2 infection has been supposed because some of the children that have been tested for SARS-CoV-2 infection were positive by polymerase chain reaction (PCR) or serology (16).

Particularly, Italy has reported an unusually high number of children with signs and symptoms of KD in paediatric intensive care. According to Verdoni et al., a high number of Kawasaki-like disease cases have been reported in Bergamo, with a monthly incidence that has been at least 30 times greater than the monthly incidence of the previous 5 years (17).

Discussion

Recently, several children with a novel multisystem inflammatory disease similar to toxic shock syndrome (TSS) and atypical Kawasaki disease (KD) with proven SARS-CoV-2 infection have been observed in the UK. Whittaker et al. has described the features of 58 children who have been admitted in eight UK Hospitals for 'Paediatric inflammatory multisystem syndrome temporarily associated to SARS-CoV-2 infection' between 23 March and 16 May 2020. The 78% of the patients have evidence of prior or current SARS-CoV-2 infection. Twenty-nine children, developed shock, often associated with clinical, echocardiographic and laboratory evidence of myocardial injury; seven children fulfilled the American Heart Association diagnostic criteria for KD (18). Likewise, an increased frequency of KD has been reported in Italy (17).

According to the Italian experience in Bergamo, the clinical and biochemical characteristics of the 10 children admitted to the ER during the COVID-19 pandemic, differ from the previous cohort of patients. In fact, from a clinical perspective, they were older, had meningeal signs, and signs of cardiovascular involvement and respiratory as well as gastrointestinal involvement. From a biochemical perspective, they had thrombocytopenia, leukopenia with marked lymphopenia and increased ferritin, signs of macrophage activation syndrome (MAS). Moreover, children had a more severe disease course, with resistance to intravenous immunoglobulin and need of steroids. The monthly incidence of these KD-like cases has been at least 30 times greater than that observed for KD in the same region across the previous 5 years (17).

The SARS-CoV-2 pro-inflammatory syndrome has already been reported in adults who present a wide range of signs and symptoms characterized by fever, lymphopenia, increased in transaminases, D-dimer, ferritin, and lactate dehydrogenase called "cytokine storm" (19).

Moreover, the epidemiology of KD supports the idea that infections may causes KD in a group of genetically predisposed children. KD seasonality and well-documented Japanese epidemics with wave-like spread support an infectious trigger (20).

According to Rowley and al., the prevalence of cytotoxic T cell, the upregulation of interferon pathway genes and the presence of CD8 T cells in the inflammatory infiltrate in the coronary arteries of children who have died of KD are suggestive of a viral aetiology (21).

It is also known that many viruses have been previously associated with Kawasaki Disease including Influenza (22), Rhinovirus (23) , Enterovirus (23), Adenovirus (22), Retrovirus (24), Herpes Virus (25), RSV (26), Varicella (27), Epstein-Barr (28), measles (29), other coronaviruses (30) and dengue (31).

Actually, the innate immunity is the first line of defence against infectious agents, but it is also accompanied by inflammatory reaction. KD could be associated with a dysregulation of the innate immune response. In fact, many microbes may stimulate immune cells through the interaction with specific receptors that may trigger innate immune response with the production of inflammatory cytokines. However, while a large number of microorganisms may cause KD, the prevalence of KD in children is potentially limited, suggesting that the genetic pattern may influence the

disease susceptibility. Molecular data show that many genes with KD-associated polymorphisms are responsible for the modulation of inflammatory responses. Thus, the pathogenesis of KD may be explained by a dysregulation of the immune response to infectious stimuli (32). Consequently, KD may be considered a stereotyped way of reaction of the patient to different aetiological factors. According to a recent paper by Ravelli et al., the occurrence of a Kawasaki-like disease in association with SARS-CoV-2 infection suggests that KD is not a disease, but rather a syndrome, whose main features depend on the type of the characteristics of the infectious agent as well as on the immune response of the patient (33).

Conclusion

The pathogenesis of KD seems to be explained by the interaction between an environmental trigger, such as an infection, and the development of an exuberant immune response in a susceptible patient. This would explain why an increase in the number of cases of KD should be expected during a pandemic outbreak. Moreover, according to recent studies, SARS-CoV-2 has a particular tropism for vases with a production of many inflammatory mediators that would also explain the effusive systemic response, confirming the double relevance of both the genetic predisposition in the immune response and the characteristics of the pathogens in the pathogenesis of Kawasaki disease (or syndrome).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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