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Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19: Insights from simultaneous familial Kawasaki Disease cases

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A R T I C L E   I N F O

Article history:
Received 13 May 2020
Received in revised form 4 June 2020
Accepted 5 June 2020

Keywords:
COVID-19
SARS-CoV-2
Multisystem Inflammatory Syndrome in Children (MIS-C)
Kawasaki Disease

A B S T R A C T

Recently, an increasing number of SARS-CoV-2 patients with COVID-19 syndrome, which overlaps with Kawasaki Disease (KD), have been reported, supporting the suggestion that infection is one of the triggers of KD. We summarized the reports of simultaneous familial KD cases to better understand the etiopathogenesis of both KD and Multisystem Inflammatory Syndrome in Children (MIS-C) related to COVID-19. Here we discuss the etiology of these syndromes from the point of view of infection and genetic susceptibility.

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In 1967, Dr. Kawasaki first described Kawasaki disease (KD) as an acute febrile, mucocutaneous lymph node syndrome with self-limited vasculitis primarily affecting infants and children, usually under five years of age. The etiopathogenesis of KD remains unclear but is discussed from the perspective of an interplay of two features: genetic susceptibility and infection. There have been reports of familial aggregation of the disease (Dergun et al., 2005; Uehara et al., 2004) and a higher prevalence in Northeast Asia, which indicate genetic susceptibility leading to KD. In fact, several common variants associated with KD susceptibility were identified in patients (Onouchi et al., 2016; Onouchi et al., 2012). On the other hand, several factors have been proposed as triggers for KD, including infection. KD in the extratropical latitudes of the Northern Hemisphere shows January through March seasonality, and community-wide outbreaks are occasionally reported. Also, children under six months of age, who have a passive transmission of maternal Igs rarely develop KD. These reports strongly indicate the involvement of infection in KD onset, and several viruses or antigens have been considered as the trigger of KD, although no consensus has been reached.

Recently, a surge of SARS-CoV-2 patients with COVID-19 syndrome overlapping with KD, called multisystem inflammatory syndrome in children (MIS-C), have been reported (Belhadjer et al., 2020; Toubiana et al., 2020; Verdoni et al., 2020). KD and MIS-C share several common symptoms, such as skin rash, lymphadenopathy, strawberry tongue, and an elevation of inflammatory biomarkers. However, MIS-C in COVID-19 has some unique features, including older onset (cases of children in their teens), the prevalence of abdominal symptoms, and more cases with left ventricular systolic dysfunction (Belhadjer et al., 2020). Therefore, understanding the etiology of KD may provide us with new information about the pathogenesis of MIS-C in COVID-19, as well as the converse. To this end, we have specifically evaluated simultaneous familial cases of KD, that suggest both infectious etiology of KD and genetic factors leading to host susceptibility.

Ichushi, a Japanese medical database, and PubMed were searched using the terms: Kawasaki disease, simultaneous, sibling, and the equivalent Japanese words. The list of concurrent familial case reports that were diagnosed within ten days is in Table 1. Besides the case reports in Table 1, an epidemiological study analyzed 216 families with 435 sibling cases, including three trios (Imada et al., 1984). The interval of onset between cases was less than seven days for half of the families in this report. These simultaneous familial cases support the hypothesis that some contagious pathogen triggers KD. At the same time, we found that these cases included more twins, trios, or even quadruplets than expected in the general population.

https://doi.org/10.1016/j.ijid.2020.06.014
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| Case | Pedigree | sex | age | Interval from index onset | Symptom, Outcome | Feature | Reference |
|------|----------|-----|-----|---------------------------|-----------------|---------|-----------|
| Ia   | Index    | m   | 5   |                           | fever, rash, redness of eyes, cracked lips, strawberry tongue, erythema, swollen red palms and soles. Recovered |         | Namita U. J Family Med Prim Care. Apr;8 (4):1481-1482 (2019) |
| Ib   | monozygotic twin | m | 5 | 0d | fever, rash, sore throat, skin peeling, cracked lips, strawberry tongue. Recovered |         | Fukuda S. Pediatr Rheumatol Online J May 16;15(1):39 (2017) |
| Ia   | index    | m   | 4   |                           | fever, redness of the eyes, red cracked lips, strawberry tongue, erythema, swollen red palms and soles, cervical lymphadenopathy. Recovered | HAdV (+) |         |
| Iib  | monozygotic twin | m | 4 | 4d | fever, redness of eyes, red cracked lips, strawberry tongue, cervical lymphadenopathy. Recovered | HAdV (+) |         |
| Ila  | index    | m   | 2   |                           | fever, rash, redness of eyes, red lips, swollen red palms and soles, lymphadenopathy, joint pain. Recovered |         | Takeyama A. Shonika Rinsho. 62: 2439-2443 (2009) |
| Iib  | sibling  | f   | 1   | 5d | fever, rash, redness of eyes, red lips, swollen red palms and soles, lymphadenopathy. Recovered |         |         |
| IVa  | index    | f   | 1   |                           | fever, redness of eyes, red lips, strawberry tongue, lymphadenopathy, rash. Recovered | MR vaccination erythema at the Bacillus Calmette-Guerin (BCG) inoculation site | Ide T. Progress in MEDICINE. VOL. 27: 1535-1539 (2007) |
| IVb  | monozygotic twin | f | 1 | 1d | fever, red lips, strawberry tongue, lymphadenopathy, rash. Recovered | MR vaccination |         |
| Va   | index    | N/A | 0   |                           | N/A. Recovered |         | Dergun M. Arch Pediatr Adolesc Med; 159 (9):876-881 (2005) |
| Vb   | 1 of fraternal quadruplets of index | N/A | 0 | 7d | N/A. Recovered |         |         |
| VIa  | index    | f   | 5   |                           | fever, strawberry tongue, rash, lymphadenopathy, redness of eyes, swollen red palms and soles. Recovered |         | Ito T. Shonika Rinsho. 56: 1117-1119 (2003) |
| VIb  | sibling  | f   | 8   | 8d | fever, strawberry tongue, rash, lymphadenopathy, redness of eyes, swollen red palms and soles. Recovered |         |         |
| VIc  | mother   | f   | 39  | 10d | fever, joint pain, headache, strawberry tongue, rash, redness of eyes, swollen red palms and soles. Recovered |         |         |
| VIIa | index    | m   | 3   |                           | N/A |         | Sumita M. Shonika Rinsho. 48: 79-84 (1995) |
| VIIb | sibling  | m   | 0   | 8d | N/A |         | symptoms of a common cold (+) | Hara K. Shonika Rinsho. 36: 1249-1252 (1983) |
| VIIa | index    | f   | 2   |                           | fever, rash, cracked lips, redness of eyes, swollen red palms. Recovered | symptoms of a common cold (+) |         |
| VIIIb| monozygotic twin | f | 2 | 3d | fever, rash, cracked lips, lymphadenopathy, redness of eyes. Recovered | symptoms of a common cold (+) |         |
| IXa  | index    | m   | 1   |                           | fever, rash, strawberry tongue, cracked lips, lymphadenopathy, redness of eyes. Recovered |         |         |
| IXb  | sibling  | f   | 0   | 2d | fever, rash, redness of eyes, red lips. Recovered |         |         |
| Xa   | index    | m   | 3   |                           | N/A. Recovered |         | symptoms of a common cold (+) | Izumida N. Shonika Rinsho. 36: 1279-1282 (1983) |
| Xb   | sibling  | f   | 1   | 7d | N/A. dead |         | symptoms of a common cold (+) |         |
| Xc   | sibling  | f   | 0   | 6d | N/A. Recovered |         |         |
| Xa   | index    | f   | 4   |                           | N/A. Recovered |         |         |
| Xlb  | sibling  | m   | 1   | 1d | N/A. Recovered |         |         |
| Xlla | index    | f   | 0   |                           | N/A. Recovered |         |         |
| Xllb | twin     | f   | 0   | 0d | N/A. Recovered |         |         |
population, suggesting heritability. Some symptoms of COVID-19 are also possibly heritable (Williams et al., 2020). These results indicate the interplay between infection and host immunity affected by genetic factors in symptoms and disease severity of COVID-19.

One of the interesting findings is one case that showed erythema at the Bacillus Calmette-Guerin (BCG) inoculation site (Case IVa). The negative correlation between BCG vaccine and mortality from COVID-19 has been reported (O’Neill and Netea, 2020). Another focus is the implication of the involvement of measles (Cases IVa, IVb, Xa, Xb, and Xc). It is reported that the MMR vaccine may provide protection against COVID-19 (Franklin et al., 2020). These findings suggest the possibility that immune responses driven by BCG or MMR vaccination might react against SARS-CoV-2, leading to quick clearance of the virus; or, the exposure to these pathogens triggers a common cascade in immunity and sometimes induces the excess inflammation observed in severe cases like MIS-C and KD. These findings suggest the possible crosstalk among BCG, measles, and SARS-CoV-2 and may inform discussions about the immune response associated with SARS-CoV-2 leading to MIS-C.

Multisystem inflammatory syndrome in COVID-19 and candidate triggers for KD are not restricted to children. However, several unique symptoms of these syndromes— skin rash, lymphadenopathy, strawberry tongue etc.— show prevalence in children, suggesting that aging modifies the immune environment and its responses in our bodies.

It has been reported that the symptoms in children with COVID-19 are generally less severe compared to adults. On the other hand, the cases of MIS-C infected with SARS-CoV-2 indicate that a small percentage of patients mount a strong SARS-CoV-2-related inflammatory response resulting in multisystem inflammatory syndrome. The genetic susceptibility resulting in KD and MIS-C, and host factors affected by aging remain to be determined, but it will be worthwhile to evaluate potential similarities and differences. On a clinical level, given the critical mortality in KD due to coronary artery dilation and aneurysm formation, MIS-C patients should be closely followed for these symptoms. Further investigations elucidating the factors that impact the severity of COVID-19-related syndromes in children will be critical for developing appropriate and prompt treatment strategies.

Conflict of interest statement
None.

Funding sources
None.

Ethical approval
Approval was not required.

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