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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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ABSTRACT

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.

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

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Table 1
List of reported simultaneous family cases with Kawasaki disease

Case	Pedigree	sex	age y	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		
IIa	index	m	4		fever, redness of the eyes, red cracked lips, strawberry tongue, erythema, swollen red palms and soles, cervical lymphadenopathy. Recovered	HAdV (+)	Fukuda S. Pediatr Rheumatol Online J. May 16;15(1):39 (2017)
IIb	monozygotic twin	m	4	4d	fever, redness of eyes, red cracked lips, strawberry tongue, cervical lymphadenopathy. Recovered	HAdV (+)	
IIIa	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)
IIIb	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	N/A	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	N/A	
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		
VIIIa	index	f	2		fever, rash, cracked lips, redness of eyes, swollen red palms. Recovered	symptoms of a common cold (+)	Hara K. Shonika Rinsho. 36: 1249-1252 (1983)
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 (+) Measles epidemic (2 weeks ago)	Izumida N. Shonika Rinsho. 36: 1279-1282 (1983)
Xb	sibling	f	1	7d	N/A. dead	symptoms of a common cold (+) Measles epidemic (2 weeks ago)	
Xc	sibling	f	0	6d	N/A. Recovered	Measles epidemic (2 weeks ago)	
XIa	index	f	4		N/A. Recovered		
XIb	sibling	m	1	1d	N/A. Recovered		
XIIa	index	f	0		N/A. Recovered	Sibling: cough symptoms of a common cold (+)	
XIIb	twin	f	0	0d	N/A. Recovered	Sibling: cough symptoms of a common cold (+)	

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

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Ethical approval

Approval was not required.

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