



# Kawasaki disease in siblings in close temporal proximity to each other—what are the implications?

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## Abstract

Kawasaki disease (KD) is the commonest medium vessel vasculitis in children. The etiology of KD remains an enigma despite extensive research. Infections are considered to be one of the triggers for KD, especially in genetically susceptible hosts. KD occurring within a short time interval among siblings is an important clinical observation supporting this hypothesis. In addition, siblings of children with KD are at a higher risk of developing the disease as compared with other children. Screening for KD in febrile siblings, therefore, seems prudent. This would help initiate timely therapy and prevent complications. We briefly review 16 English language reports of KD in siblings diagnosed within 1 month of each other to highlight its etiological and therapeutic implications.

## Key Points

- KD should be suspected in febrile children who have a sibling recently diagnosed with KD.
- Etiological studies should also focus on siblings who develop KD in close temporal proximity.

**Keywords** Etiology · Infection · Kawasaki disease · Screening · Siblings

## Introduction

Kawasaki disease (KD) is one of the commonest childhood vasculitides and usually occurs in children below 5. Recognition of the characteristic signs and symptoms is crucial as the diagnosis remains essentially clinical. However, in cases with incomplete KD, certain laboratory parameters and echocardiographic assessment of coronary arteries may facilitate the diagnosis [1]. KD has lately generated enormous interest among physicians, scientists, and even the lay public

due to its association with the novel coronavirus pandemic (SARS-CoV-2/COVID-19) [2]. This is reflected in the increasing number of publications that are emerging from around the globe linking KD to an infectious trigger. As a unique coincidence, Dr. Tomisaku Kawasaki, the legendary Japanese pediatrician after whom the disease is eponymously named, passed away recently [3].

Despite intense research efforts spanning over many decades, the exact etiology remains unknown. The etiological hypotheses include a KD-specific RNA virus, superantigen-mediated illness, and tropospheric winds transporting infectious or toxic agents. Environmental triggers, especially infections, are believed to trigger the disease in genetically susceptible individuals [4]. An important clinical observation that supports this hypothesis is the occurrence of KD in siblings who have disease onset in close temporal proximity to each other. Another clinical observation favoring this hypothesis is the older sibling often presenting with KD first—probably a reflection of greater likelihood of exposure to an infectious trigger. Despite an increased risk of developing KD, siblings of index cases may not be diagnosed due to atypical or incomplete presentations. Incomplete or “atypical” KD patients seem to be at a higher risk of developing coronary artery abnormalities (CAAs) which may be partly due to delays in diagnosis [5].

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In this manuscript, we have reviewed the published literature on siblings with KD who developed the disease in close temporal proximity to each other. This may help in answering the long-standing question regarding the exact etiology of KD.

## Search strategy

There have been only a few case reports and retrospective studies that have described the occurrence of KD in siblings within a short time period. Two authors (AZB, DB) independently performed a literature search using PubMed/Medline and Google scholar databases. The keywords included in the search were “Kawasaki disease” and “sibling,” “Kawasaki disease” and “twin,” and “Kawasaki disease” and “family.” The term “Mucocutaneous lymph node syndrome” was also used in place of “Kawasaki disease” for literature search and used in combination with sibling, twin, and family for performing a detailed literature search. All articles describing KD in siblings (irrespective of the time frame) were selected for full-text reading. English language articles describing the occurrence of KD in siblings within a month of each other were selected for our non-systematic review (Table 1). English language reports describing cases published in other languages were also included in the review. References of retrieved articles were also cross-checked. Reports where interval between the onset of KD in sibling pairs was not specified were excluded from this review. We were unable to retrieve the abstract and full text of one article reporting simultaneous KD in a twin pair (Table 1, S. No. 17) [22].

## Clinical presentation of Kawasaki disease

Kawasaki disease presents with a unique symptom complex of fever accompanied by (a) non-exudative conjunctival injection, (b) polymorphous rash, (c) unilateral cervical lymphadenopathy, (d) changes in lips or oral mucosa, and (e) extremity changes [23]. This characteristic symptom complex is included in the American Heart Association (AHA) clinical criteria for diagnosis of KD, with “complete” or “typical” KD patients fulfilling at least 4 of the abovementioned clinical features in addition to fever. Patients presenting with fever and only 2 or 3 classical manifestations are labeled as “incomplete” KD. Despite being so-called “incomplete” KD, coronary artery involvement may, in fact, be higher in these patients [24]. Unless detected early and treated promptly, the long-term consequences in patients with incomplete KD can be grave [25]. Incomplete KD was recognized even in the first published manuscript on KD [26].

## Etiology of KD—a brief overview

Infections have come a long way as the probable cause eliciting an aberrant immune response leading to KD in genetically predisposed individuals. In-depth studies of autopsy specimens have implicated a specific RNA virus in causation of KD [27]. Several other infectious triggers that have been implicated include streptococci, staphylococci [28], *Yersinia* [29], and a number of viruses [30].

Epidemiological studies on KD have also revealed a striking association with the pattern of tropospheric winds, which have been hypothesized to transport *Candida* spp. and trigger KD through mechanisms that are not clearly understood [31–33]. In fact, *Candida albicans* water-soluble fraction has been shown to result in a KD-like illness in murine models [34].

Analysis of sibling pairs with KD is useful as it helps to reflect on these individual etiologies. The fact that the prevalence of KD is higher in some ethnic groups (e.g., Asians) led to the identification of genes attributed to increased susceptibility to the disease. Among these, single-nucleotide polymorphisms in CD40L, inositol 1, 4, 5-trisphosphate 3-kinase C (ITPKC), and several interleukin genes have been extensively studied [35]. Shimizu et al. also reported the association of transforming growth factor (TGF)-beta 2 (TGFB2), TGF-beta receptor 2 (TGFB2R2), and SMAD3 polymorphisms with KD and the development of coronary artery lesions [36]. A linkage study by Onouchi et al. identified 10 chromosomal loci in siblings with KD which had positive linkage signals. Among these, 12q24 region had the most significant association [37]. However, these results need to be replicated from other geographical regions.

## How common is KD in siblings?

The occurrence of KD in siblings was first reported by Tominaga et al. in 1977. They described 51 sibling cases, two-thirds of whom had an interval of  $\leq 1$  week between onset of disease [38, 39]. The first English language report of KD presenting simultaneously in siblings appeared in 1978 [6]. Detailed epidemiological studies conducted in Japan and Korea usually describe a sibling incidence rate of KD of about 2% and 0.2% respectively [10, 11, 40–42]. Though these studies reported siblings with KD, the exact interval between disease onsets has not been clearly reported, and thus, these studies were not included in the present review.

## Clinical features unique to KD in siblings

Irrespective of the time duration between disease onset, siblings appear to be at a significantly higher risk of developing

**Table 1** Review of English language reports of KD in siblings

S. No.	Authors, year of publication [reference]	Country or region of origin	No. of pairs	Duration between disease onset; age of siblings (I, S)	Infectious trigger	Clinical features	Treatment and response
1.	Lyen et al. 1978 [6]	Jamaica	1	1 day I: 2 years S: 4.5 years	ND	S had a milder clinical course than I who developed pericarditis and hematuria. Echocardiography was normal.	Both children received supportive therapy only; improved.
2.	Elamin A, 1979 [7]	Zambia	1	1 month I: 7 years S: 1 year	ND	I had myocarditis, S had no cardiac involvement. Echocardiography was normal.	I received crystalline penicillin and prednisolone with anti-failure treatment, S treated with hydrocortisone. Both improved on treatment.
3.	Fink HW, 1984 [8]	USA	1	Same day I, S: 10 months	ND	Both twins had been operated for pyloric stenosis in the 2nd month of life.	ND
4.	Harada et al. 1986 [9]	Japan	23	Usually < 2 weeks	ND	These include 15 pairs of twins.	ND
5.	Yanagawa et al. 1988 [10]	Japan	At least 183	In all less than a week	ND	Nationwide Japanese survey 1985–1986. Number of siblings affected calculated from the data provided.	ND
6.	Fujita et al. 1989 [11]	Japan	20	Median: 4.5 days	ND	4 pairs of siblings developed KD on the same day, among which twin pairs 3 of 4. Coronary involvement in 22%. Significant illness in siblings.	ND
7.	Elamin A, 1993 [12]	Sudan	1	27 days I: 5 years S: 3 years	ND	Normal echocardiography in both siblings at 3 months of follow-up.	I treated with aspirin and phenoxymethyl penicillin; S treated with aspirin only; uneventful recovery in both.
8.	Anderson et al. 1995 [13]	Australia	1	1 week I: 12 years S: 10 years	Streptococcal infection in both. I developed impetigo on the face, cellulitis of the left external ear, and left suppurative lymphadenitis. Both had ↑ASO and anti-DNase B titers. However, throat swab showed <i>Haemophilus influenzae</i> .	Coronary arteries normal in both siblings.	Both received intravenous gammaglobulin and flucloxacillin; recovered uneventfully.
9.	Kaneko et al. 1995 [14]	Japan	1	4 days I, S: 1 year	No specific organism implicated.	Japanese dizygotic twins, no coronary artery involvement on follow-up at 1 month.	High-dose IVIg was given to both; recovered.
10.	Dergun et al. 2005 [15]	USA	2 pairs (including 1 pair of twins)	22 days and 7 days (in twin pair) respectively. Age of twins was 5.6 months. In other pair: I: 10 years, S: 2.5 years	ND	North American study. Both pairs did not have coronary involvement.	In the twin pair, I received 1 dose of IVIg, whereas S received 2 doses. In the other pair, I receive 1 dose of IVIg, and S did not receive IVIg.
11.	Türel et al. 2011 [16]	Turkey	1	4 days I, S: 7 months	ND	RCA and LCA dilatation in I. I had improving CAAs at 1 month of follow-up.	Rapid response to treatment with IVIg.
12.	Kottek A, 2011 [17]	USA	1	2 days I, S: 1.5 years	ND	Monozygotic twin pair from the USA. I had dilated coronary arteries; S had fever for 2 days only and fulfilled 2 of 5 AHA 2004 KD criteria. On evaluation ↑ ESR, CRP, and ALT; aortic root dilatation. Both had normal echocardiography at 1 year of follow-up. Review performed by Kottek et al. on monozygotic twins with KD: 3 English and 6 Japanese language reports. Incomplete KD was seen in 2 out of 5.	I treated with infliximab and IVIg, and S treated with IVIg alone.
			5	Within 10 days	ND		ND

Table 1 (continued)

S. No.	Authors, year of publication [reference]	Country or region of origin	No. of pairs	Duration between disease onset; age of siblings (I, S)	Infectious trigger	Clinical features	Treatment and response
13.	Zhang et al. 2013 [18]	China	1	Same time I, S: 71 days	ND	Chinese report on two monozygotic twins. Incomplete KD in both. Dilated RCA in both (elder twin on day 24 of illness, younger twin on day 20 of illness). Normal echocardiography on follow-up for both twins starting from 1 month of illness onset.	Both treated with IVIg.
14.	Fukuda et al. 2017 [19]	Japan	1	4 days I, S: 4 years	Adenoviral infection in both.	Japanese monozygotic twins. S was diagnosed as incomplete KD on admission; LCX dilated on day 10 of illness but resolved by 3 months. S was diagnosed first. I developed KDSS on day 8. S developed CAAs on day 26 (RCA, LCA). Coronary arteries normalized after 2 months of follow-up.	I treated with IVIg; however, S did not receive IVIg due to spontaneous defervescence of fever. S developed CAAs despite IVIg treatment. Additional treatment with 3 pulse doses of intravenous methylprednisolone was given followed by anakinra. I treated with steroids, inotropes, and diuretics. Both twins responded briskly to IVIg therapy.
15.	Maggio et al. 2019 [20]	Italy	1	Same time I: 7 years S: 9 months	Parvovirus infection		
16.	Namita et al. 2019 [21]	India	1	Same time I, S: 4 years	ND	Indian report on identical twins. Incomplete KD was seen in S who also had LCA dilatation.	
17.	Fink HW, 1985 [22]	USA	1	Simultaneous	ND	Identical twins. The full text could not be retrieved.	ND

S. No. serial number, I index child, S sibling, ND not documented, ASO anti-streptolysin O, DNase B deoxyribonuclease B, IVIg intravenous immunoglobulin, RCA right coronary artery, LCA left coronary artery, CAAs coronary artery abnormalities, AHA American Heart Association, ESR erythrocyte sedimentation rate, CRP C-reactive protein, ALT alanine aminotransferase, LCX left circumflex artery, KDSS KD shock syndrome, ↑ increase in

KD [11]. Siblings may have incomplete KD or atypical KD [17] which may go unnoticed, and these children may go on to develop coronary artery abnormalities despite normal initial echocardiography [18, 19, 21]. There are several reports of incomplete KD in siblings (Table 1). Fever of any duration in siblings of KD, especially presenting within a short time interval after the index case, should alert the treating physician to a possibility of KD. These children should be actively screened for KD by a targeted history and detailed physical examination including subtle clinical pointers like perianal peeling, BCG site reactivation, and chromonychia. Other investigations that are helpful in these circumstances include assays of N-terminal pro-brain natriuretic peptide (NT-proBNP) assay and a detailed echocardiography. This would ensure timely treatment and decrease the risk of developing CAAs. In addition, these children need to be carefully followed up as CAAs may not be evident on initial echocardiography (Table 1). Data on coronary artery status were available for 13 sibling pairs only. Index patients developed CAAs in 3 pairs (3/13, 23%), and the sibling developed CAAs in 4 pairs (4/13, 31%). Additionally, only aortic root dilatation developed in the sibling in one pair (1/13, 8%).

## KD in siblings—guide to etiology?

In addition to implications in disease management mentioned above, the study of KD in siblings provides a valuable opportunity to analyze the etiology of KD. This is because the siblings are likely to have similar genetic backgrounds and exposure to environmental risk factors. Analysis of tropospheric winds transporting infectious or toxic agents in relation to the occurrence of KD reveals a probable incubation period of 6–48 h, thereby reflecting a host response to the antigen or toxin rather than an infection per se [32]. In such circumstances, KD would probably occur simultaneously in siblings. Such instances have also been reported in the literature. It has been noted that the older sibling often presents first with KD and there is a time lag in disease onset in siblings with KD. This could be a result of the older sibling getting infected at school/daycare and passing on the putative infectious agent to the younger sibling at home. The time lag would then be explained by the incubation period seen in infectious diseases. Many patients with “infection triggered” KD have a proven infection. This holds true even for sibling pairs (Table 1). Some of these “infection triggered” KD cases may be mediated through superantigens or heat shock proteins rather than through the infectious agent directly [28]. Of more than 200 sibling pairs reviewed, a specific infectious trigger was documented in only 3 pairs which included streptococcus, adenovirus, and parvovirus. In one pair, throat swab showed growth of *Haemophilus influenzae*. However, its role in directly triggering the disease was conjectural. When siblings of a patient

with KD develop a febrile illness in close temporal proximity, the attending pediatrician should be alert to the possibility of an infection that may also trigger KD [13].

## Conclusion

KD needs to be suspected strongly in febrile siblings of children recently diagnosed to have KD. Studies on the etiopathogenesis of KD need to put a greater emphasis on sibling pairs who develop KD in close temporal proximity to each other. Detailed genome-wide association studies need to be conducted in such situations. Recently, KD has been reported in association with novel coronavirus (SARS-CoV-2/COVID-19) infection in children [43]. It may be prudent to look for signs of KD in siblings of patients with COVID-19 who develop a febrile illness.

**Authors' contribution** AZB: Inception of idea, writing of initial draft of manuscript, editing and revision of manuscript at all stages of its production, and review of literature.

DB: Writing of initial draft of the manuscript, contributed to editing of manuscript, and review of literature.

VP: Editing of manuscript and critical revision of the manuscript at all stages of production and final approval.

SS: Contributed to editing of manuscript, revision of the manuscript and its final approval.

**Data availability** Relevant data included in Table 1.

## Compliance with ethical standards

**Disclosures** None.

**Ethical approval and informed consent** As this manuscript pertains only to a review, specific ethics approval is not mandated.

**Abbreviations** ↑, increase in; *AHA*, American Heart Association; *ALT*, alanine aminotransferase; *ASO*, anti-streptolysin O; *CAAs*, coronary artery abnormalities; *CRP*, C-reactive protein; *DNase B*, deoxyribonuclease B; *ESR*, erythrocyte sedimentation rate; *ITPKC*, inositol 1, 4, 5-trisphosphate 3-kinase C; *IVIg*, intravenous immunoglobulin; *KD*, Kawasaki disease; *KDSS*, KD shock syndrome; *LCA*, left coronary artery; *LCX*, left circumflex artery; *ND*, not documented; *RCA*, right coronary artery; *S. No.*, serial number; *TGF*, transforming growth factor; *TGFB2*, transforming growth factor-beta 2; *TGFBR2*, TGF-beta receptor 2

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