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Dissecting Kawasaki disease: a state-of-the-art review

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Abstract Kawasaki disease (KD) is a pediatric vasculitis with coronary artery aneurysms (CAA) as its main complication. The diagnosis is based on the presence of persistent fever and clinical features including exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosae and extremities. Although the etiology remains unknown, the current consensus is that it is likely caused by an (infectious) trigger initiating an abnormal immune response in genetically predisposed children. Treatment consists of high dose intravenous immunoglobulin (IVIG) and is directed at preventing the development of CAA. Unfortunately, 10–20% of all patients fail to respond to IVIG and these children

need additional anti-inflammatory treatment. Coronary artery lesions are diagnosed by echocardiography in the acute and subacute phases. Both absolute arterial diameters and z-scores, adjusted for height and weight, are used as criteria for CAA. Close monitoring of CAA is important as ischemic symptoms or myocardial infarction due to thrombosis or stenosis can occur. These complications are most likely to arise in the largest, so-called giant CAA. Apart from the presence of CAA, it is unclear whether KD causes an increased cardiovascular risk due to the vasculitis itself.

Conclusion: Many aspects of KD remain unknown, although there is growing knowledge on the etiology,

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treatment, and development and classification of CAA. Since children with previous KD are entering adulthood, long-term follow-up is increasingly important.

What is known:

- *Kawasaki disease (KD) is a pediatric vasculitis with coronary artery damage as its main complication.*
- *Although KD approaches its 50th birthday since its first description, many aspects of the disease remain poorly understood.*

What is new:

- *In recent years, multiple genetic candidate pathways involved in KD have been identified, with recently promising information about the ITPKC pathway.*
- *As increasing numbers of KD patients are reaching adulthood, increasing information is available about the long-term consequences of coronary artery damage and broader cardiovascular risk.*

Keywords Kawasaki disease · Coronary artery aneurysms · Intravenous immunoglobulins · Genetics

Abbreviations

ABCC4	ATP-binding cassette, subfamily C, member 4
AHA	American Heart Association
ANGPT	Angiotensin
CAA	Coronary artery aneurysms
CABG	Coronary artery bypass grafting
CIMT	Carotid intima-media thickness
cMRI	Cardiac MRI
DC	Dendritic cells
GWAS	Genome-wide association study
HRQOL	Health-related quality of life
ITPKC	Inositol-triphosphate 3-kinase
IVIG	Intravenous immunoglobulins
JSC	Japanese Circulation Society
KD	Kawasaki disease
NFAT	Nuclear factor of activated T cells
PCA	Percutaneous coronary intervention
SNP	Single nucleotide polymorphism
SPE	Streptococcal pyrogenic exotoxin
TGF- β	Transcription growth factor beta
TIE-2	Angiotensin receptor
TSST-1	Toxic shock syndrome toxin-1
VEGF	Vascular endothelial growth factor

Introduction

Mucocutaneous lymph node syndrome is an acute vasculitis first described by Dr. Tomisaku Kawasaki in 1967 [60]. This condition, now known as “Kawasaki disease (KD),” is increasingly recognized in Western countries but has a greatly increased incidence in Japan and Asia. The main complication

is coronary artery damage or coronary artery aneurysms (CAA) and KD is the leading cause of pediatric acquired heart disease in asset-rich countries.

Epidemiology

Kawasaki disease is commonest in infants and young children. The incidence varies markedly between ethnic groups. The incidence of KD in recent European studies is 5–10 per 100,000 children under the age of 5 years [45, 55, 105, 120]. A considerably higher incidence is reported in Asian countries [14, 44]. The highest incidence is found in Japan; the most recent nationwide survey reported an incidence of 265/100,000 children under the age of 5 in 2012, and suggested that the incidence of KD is still rising [78]. Most patients are 6 months to 5 years old, although cases in older children and adults also occur [36]. The male/female ratio is approximately 1.5 to 1 [120].

Diagnosis

The diagnosis of KD is based on the presence of clinical features of persistent fever in combination with a polymorphous exanthema, cervical lymphadenopathy, non-purulent conjunctival injection, changes of the lips and oral cavity (including strawberry tongue, cracked lips, redness of the mucosae), and changes in extremities (swelling and redness of the palms, desquamation in the subacute phase) [83]. In the most recent American Heart Association (AHA) guidelines, persistent fever is classified as ≥ 5 days, but in the presence of four or more symptoms, the diagnosis can be made with only 4 days of fever [83, 99]. “Complete” KD is defined as fever and ≥ 4 out of the 5 symptoms. It is important to appreciate that criteria may present successively instead of simultaneously. The AHA has created an algorithm to increase the possibility of “incomplete” KD in case ≤ 3 criteria are present. This algorithm includes CA abnormalities on echocardiography and/or laboratory abnormalities [83]. There is no diagnostic test for KD, and the diagnosis may be delayed or overlooked. To improve diagnosis, multiple new biomarkers have been studied, but none has so far proved specific for KD [96]. Classification tools have been developed to aid in the differentiation between KD and other febrile illness, although the utility as a point-of-care diagnostic test remains unproven [46, 74].

Etiopathogenesis

Although the etiology of KD is unknown, the current consensus is that it is likely caused by an (infectious) trigger initiating an abnormal immune response in genetically predisposed

children. An infectious etiology is suspected due to the symptomatology of KD resembling common childhood infections, once-in-a-lifetime occurrence at young age (although second manifestations do occur), spatial and temporal clustering, and the clear seasonal pattern in high-incidence countries [57, 78].

Infectious agents

Multiple viral infectious triggers have been suggested, including coxsackie virus, parainfluenzavirus, respiratory syncytial virus, human metapneumovirus, chikungunya, and cytomegalovirus. In fact, two recent studies showed that up to about half of all KD patients had one of more respiratory viruses detected by PCR, but their etiological role is unproven [13, 128]. Also, the possibility of a respiratory RNA virus has been suggested by ultrastructural studies of autopsy specimens [102, 103]. However, no virus has repeatedly been confirmed in KD studies.

Bacteria have also been suggested as the trigger of KD, with research mainly focusing on bacterial superantigens. Superantigens produced by several bacteria are able to stimulate a large percentage of T cells by binding to the V β region of T cell receptors and so stimulate the production of pro-inflammatory cytokines. One study looking at five superantigens (streptococcal pyrogenic exotoxin (SPE)-A, C, G, and J, and toxic shock syndrome toxin-1 (TSST-1)), found these in 70% of stool samples collected from acute KD patients as opposed to 27% in healthy controls visiting the same center for vaccinations [117]. Another study found significantly increased IgM antibodies against five superantigens (staphylococcal enterotoxin A, B, and C, TSST-1, and SPE-A) [80]. Nevertheless, the role of superantigens in KD remains unclear.

Immunological response

The encounter of a susceptible individual with the unknown agent probably leads to an (exaggerated) immune response involving innate and adaptive pathways. Multiple studies have been performed, both evaluating animal models and immune response in the peripheral blood as well as immune infiltration in the coronary arteries [52, 131].

The general paradigm of the immune response is an imbalance between pro-inflammatory and anti-inflammatory pathways. For example, regulatory T cells, a subset of T cells limiting inflammation, have been shown to be important in the vascular inflammation [37]. Also, the IL-1 signaling pathway is upregulated, with upregulated IL-1 pathway genes and increased IL-1 concentrations in peripheral blood of KD patients during the acute phase [50, 119]. Recently, it has become clear that inflammasomes, multiproteins that are part of the innate immune system, are induced by the *NLRP3* gene and promote the production of IL-1 β and IL-18, play a role in KD [2].

In the coronary arteries, immune infiltration of the arterial wall with neutrophils, CD8+ cytotoxic T cells, Ig-A producing plasma cells, and macrophages have been found, accompanied by pro-inflammatory cytokines which may vary in proportion and contribution over time [6].

Genetics

Genetics are considered to contribute to susceptibility to KD, and probably to CAA and response to treatment [91, 132]. A number of genome-wide association studies (GWAS) have been performed [7, 63, 69, 72, 92, 94, 126]. Apart from the GWAS, multiple studies have identified specific single nucleotide polymorphisms (SNPs) in several genes. Most of these candidate genes have an immune regulatory function. Table 1 shows some of the key pathways and SNPs associated with KD susceptibility, CAA development, and intravenous immunoglobulin (IVIG) resistance.

In the first GWAS that resulted in a significant correlation with susceptibility to KD, we identified the major activating IgG receptor Fc γ RIIa (CD32a) on immune cells and platelets, encoded by the *FCGR2A* gene at the *FCGR2/3* gene cluster at chromosome 1q23 [7]. Following this study, Japanese and Taiwanese studies also confirmed this genetic association while at the same time characterizing *CD40* and *BLK*, respectively, as being associated with KD, as confirmed for *BLK* in Caucasian KD patients in a subsequent meta-analysis [12, 72, 94]. *CD40* is a protein expressed on antigen-presenting cells, such as dendritic cells, macrophages, and B cells, and interacts with CD40L which is primarily expressed by activated T cells and platelets [49]. The function of *FAM167A* and *BLK* gene is yet to be investigated. The *BLK* gene encodes for tyrosine kinase, which is presumed to play a role in B cell signal transduction [100].

From alternative genetic studies (non-GWAS), other pathways were found to be involved, such as vascular endothelial growth factor (VEGF) and angiopoietin (ANGPT). ANGPT1 and angiopoietin receptor (TIE-2) promote cell survival and induce anti-inflammatory signals in contrast to ANGPT2 and TIE-2, which have a pro-inflammatory effect with VEGF acting as a co-factor. Also the transcription growth factor beta (TGF- β) pathway may play an important role. TGF- β is important in T cell activation and cardiovascular remodeling. One of the more recent and promising pathways involves the inositol-triphosphate 3-kinase (*ITPKC*) gene. ITPKC expression is part of a transmembrane signaling pathway with release of Ca²⁺ from intracellular storage [48]. Initially, nuclear factor of activated T cells (NFAT) was suggested to be involved in regulating the immune response in KD. The NFAT pathway is calcium-dependent, and when these cytosolic proteins become dephosphorylated, they translocate from the cytoplasm to the nucleus to initiate transcription of downstream

Table 1 Candidate genes and pathways associated with disease susceptibility, CAA development, and IVIG resistance

Candidate pathway	Ethnicity	Reference	Included cases/controls	Susceptibility to KD (gene)	Susceptibility to CAA (gene)	Susceptibility to IVIG resistance (gene)
<i>ABCC4</i>	European descent (case-control), Australia, NL, USA, UK (family based)	Khor et al. [62]	26 pedigrees, case-control = 119/225, family based = 1093 cases, 1621 parents, 198 siblings	Yes (<i>ABCC4</i>)	x	x
<i>ANGPT</i>	Australia, US, UK (family based) and Dutch Caucasian (case-control)	Breunis et al. [5]	462 complete trios, case control: 123/171	Yes (<i>ANGPT1</i>)	Yes (<i>ANGPT2</i>)	x
Intergenic region <i>BLK-FAM167A</i>	Japanese	Onouchi et al. [94] (GWAS)	428/3379	Yes (<i>FAM167A-BLK</i>)	x	x
		Onouchi et al. [94] (Replication 1)	470/378	“	x	x
		Onouchi et al. [94] (Replication 2)	284/569	x	x	x
	(Han) Chinese	Yan et al. [130]	358/815	Yes (<i>FAM167A-BLK</i>)	No	x
	Taiwanese	Lee et al. [72] (GWAS)	622/1107 ^a	Yes (<i>BLK</i>)	x	x
		Lee et al. [72] (replication)	261/550	“	x	x
		Lou et al. [77]	428/493	Nominal association (<i>BLK</i>)	x	
	Korean	Chang et al. [12] (GWAS)	186/600 ^b	Yes (<i>BLK</i>)	x	x
		Chang et al. [12] (Replication)	288/498	“	x	x
	US (European, Asian, Hispanic, Mixed, African American, Native American, Samoan).	Onouchi et al. [94]	503 trios	Yes (<i>FAM167A-BLK</i>)	x	x
<i>CD40</i>	European	Chang et al. [12]	405/6252	Yes (<i>BLK</i>)	x	x
	Japanese	Onouchi et al. [93]	427/476	No (<i>CD40L</i>)	Yes (<i>CD40L</i>) ^c	x
		Onouchi et al. [94] (GWAS)	428/3379 ^d	Yes (<i>CD40</i>)	x	x
		Onouchi et al. [94] (replication 1)	470/378	“	x	x
		Onouchi et al. [94] (replication 2)	284/569	“	x	x
	Han Chinese	Kuo et al. [67]	428/493	Yes (<i>CD40</i>)	Yes (<i>CD40</i>) ^d	x
		Lou et al. [77]	381/569	Nominal association (<i>CD40</i>)	x	x
	Taiwanese	Lee et al. [72] (GWAS)	622/1107 ^a	Yes (<i>CD40</i>)	x	x
		Lee et al. [72] (replication)	261/550	“	x	x
	European	Shendre et al. [108]	112 complete trios	Yes (<i>CD40</i>)	x	x
<i>FCGR2/3</i>	Japanese	Taniuchi et al. [123]	65/566	Yes (<i>FCGR3a</i>)	Yes (<i>FCGR2a</i>)	x
		Onouchi et al. [94] (GWAS)	428/3379 ^e	Yes (<i>FCGR2a</i>)	x	x
		Onouchi et al. [94] (replication 1)	470/378	“	x	x
		Onouchi et al. [94] (replication 2)	284/569	“	x	x
				“	x	x

Table 1 (continued)

Candidate pathway	Ethnicity	Reference	Included cases/controls	Susceptibility to KD (gene)	Susceptibility to CAA (gene)	Susceptibility to IVIG resistance (gene)
ITPKC	(Han) Chinese	Duan et al. [32]	428/493	Yes (<i>FCGR2A</i>)	No	x
		Yan et al. [130]	358/815	Yes (<i>FCGR2A</i>)	No	No
		Khor et al. [61]	130/568	Yes (<i>FCGR2A</i>)	x	x
	Taiwanese	Khor et al. [61]	438/446	Yes (<i>FCGR2A</i>)	x	x
	Caucasian	Shrestha et al. [111]	176/369	x	x	Yes (<i>FCGR2B</i>)
		Shrestha et al. [110]	156 trios, 75 single parent-child	Yes (<i>FCGR2A</i>)	Yes (<i>FCGR2a/3B</i>) ^f	Yes (<i>FCGR3B</i>)
	European	Khor et al. [61] (GWAS)	405/625 ^g	Yes (<i>FCGR2A</i>)	x	x
	Japanese	Onouchi et al. [92] (Indep. set 1)	94 ^h	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>)	x
		Onouchi et al. [92] (Indep. set 2)	276/282	“	“	x
		Onouchi et al. [92] (Indep. set 3)	267/752	“	“	x
Chinese		Onouchi et al. [95]	546/947	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>) ⁱ	Yes (<i>ITPKC</i>) ^j
		Peng et al. [97]	223/318	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>)	No
		Khor et al. [61]	130/568	Yes (<i>ITPKC</i>)	x	x
		Chi et al. [18]	385 (of which 158 trios) /1158	No	No	x
Taiwanese		Lin et al. [73]	280/492	Yes (<i>ITPKC</i>)	No	x
		Kuo et al. [71]	341/1190	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>) ^j	No
		Above-mentioned studies combined	999/2781	Yes (<i>ITPKC</i>)	x	x
		Kuo et al. [68]	381/569	No ^k	Yes (<i>ITPKC</i>)	x
European		Khor et al. [61]	438/446	Yes (<i>ITPKC</i>)	x	x
		Khor et al. [61] (GWAS)	405/6252 (10)	Yes (<i>ITPKC</i>)	x	x
		Khor et al. [61] (Replication)	605 trios, 139 siblings ^l	“	x	x
		Onouchi et al. [92]	209 trios	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>)	Yes (<i>ITPKC</i>)
US		Cho et al. [20]	105/303	Yes (<i>SMAD5</i>)	No	x
		Peng et al. [98]	392/421	Yes (<i>TGFB2</i> , <i>SMAD3</i> , <i>ADAM17</i>)	Yes (<i>TGFB2</i>)	No
		Kuo et al. [70]	381/569	Yes (<i>SMAD3</i>)	No	No
		Choi et al. [21]	105/500	Yes (<i>TGFB2</i>)	Yes (<i>TGFB2</i>)	x
Japanese		Shimizu et al. [109] (cohort 1)	128/159	Yes	x	x
		Shimizu et al. [109] (cohort 2)	451 trios	(<i>TGFB2</i> , <i>TGFB2</i> , <i>SMAD3</i>) ^m	x	x
		Shimizu et al. [109] (cohort 3)	435	x	Yes ⁿ	x
		Shimizu et al. [109] (cohort 4)	237	x	Yes ⁿ	Yes (<i>TGFB2</i> , <i>SMAD3</i> , <i>SMAD5</i>)
TGF-β pathway						

Table 1 (continued)

Candidate pathway	Ethnicity	Reference	Included cases/controls	Susceptibility to KD (gene)	Susceptibility to CAA (gene)	Susceptibility to IVIG resistance (gene)
<i>VEGF</i>	Japanese	Kariyazono et al. [58]	103/144	x	Yes (<i>VEGF</i> , <i>KDR</i>)	x
	Taiwanese	Hsueh et al. [51]	93/96	Yes (<i>VEGF</i>)	x	x
	Australia, US, UK (family based), Dutch Caucasian (case-control)	Breunis et al. [5]	462 complete trios, case control: 123/171	Yes (<i>VEGFA</i>)	Yes (<i>VEGFR2</i>)	x
	Dutch Caucasian	Breunis et al. [4]	170/300	Yes (<i>VEGF</i>)	No	x

ABCC4 ATP-binding cassette, subfamily C, member 4, *ANGPT* angiotensin, *CAA* coronary artery aneurysm, *FCGR* Fc gamma receptor, *GWAS* genome-wide association study, *ITPKC* inositol-triphosphate kinase C, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease, *NL* Netherlands, *SNP* single nucleotide polymorphism, *TGF-β* transforming growth factor beta, *UK* United Kingdom, *US* United States, *VEGF* vascular endothelial growth factor

^a Numbers after quality control, starting numbers: 627/1118

^b Numbers after quality control, starting numbers: 222/600

^c Significant difference between male patients with CAA (*n* = 58) compared with male patients without CAA (*n* = 195) and with controls, not in female patients

^d rs4810485 has protective effects for CAL formation in KD patients

^e Numbers after quality control, starting numbers: 447/3397

^f Only significant taken in all ethnic groups (White and Asian combined)

^g Numbers after quality control, starting numbers: 576/7464 cases/controls

^h *ITPKC* SNP not genotyped in 564 controls of first cohort

ⁱ A two-locus model in combination with a SNP in *CASP3* was also significantly association with both CAA development and IVIG resistance

^j CAA of >4 mm or in children over 5 years of age, diameter of at least 1.5 times adjacent segment

^k Two SNPs found but significance disappeared after correction for multiple testing

^l Total included trios in study = 740 which 135 of non-European descent, combined analyses

^m Only one SNP remained significant after Bonferroni correction

ⁿ Different SNPs found in different cohorts but many of the SNPs colocalized to the first intron of each of the three genes (*TGFB2*, *TGFB2R2*, and *SMAD3*)

target genes including for cytokines such as IL-2, IL-10, and IFN γ . Stimulation of T lymphocytes accommodates the release of inositol-triphosphate (IP $_3$), which increases intracellular Ca $^{2+}$ through the endoplasmic reticulum (Fig. 1). *ITPKC* serves as a negative regulator of the Ca $^{2+}$ /NFAT pathway and—at the same time—is also believed to act as a key second messenger in T cell receptor signaling. This would make *ITPKC* responsible for a greater and more prolonged expansion of inflammation, thus creating an increased risk of KD and/or leading to disease severity [76]. Alphonse et al. suggested that the role of *ITPKC* is not T cell-mediated but more

monocyte/macrophage-dependent in its impact [2]. They showed that *ITPKC* influences *NLRP3* activation through intracellular calcium levels leading to an increased IL-1 β and IL-18 production. Khor et al. performed a global meta-analysis of SNP rs28493229 in *ITPKC* of all performed studies, including GWAS data, showing strong evidence for association with KD ($p = 8.28 \times 10^{-22}$) [61].

Other pathways and candidate genes have, sometimes inconsistently, been implicated including ATP-binding cassette, subfamily C, member 4 (*ABCC4*), interleukin-4, interleukin-10 and interleukin-18, chemokine receptors, tumor necrosis

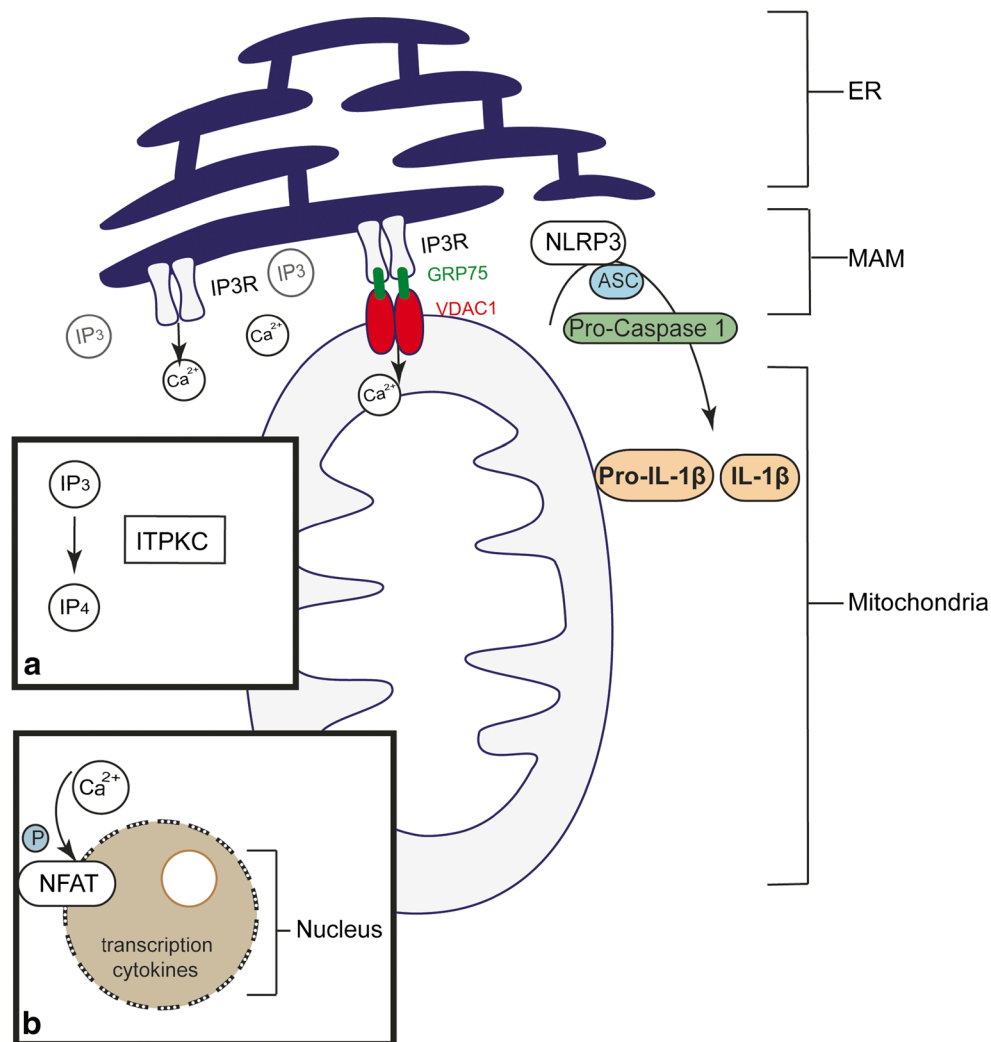


Fig. 1 The role of IP $_3$ and ITPKC in calcium signaling. (a) ITPKC phosphorylates IP $_3$ to IP $_4$ and modulates the abundance of IP $_3$ and influences the calcium signaling. (b) Nuclear factor of activated T cells (NFAT) are regulated by calcium signaling and enter the nucleus when dephosphorylated, there it activates cytokine transcription namely IL-2, IFN γ in T cells and Pro-IL1, IL-10, Pro-IL18 in macrophages. *Footnote:* Inositol triphosphate receptor (IP $_3$ R) forms a bridge between the endoplasmic reticulum (ER) and mitochondria creating a site of contact between the ER and mitochondria called the mitochondria-associated ER membrane (MAM). NLRP3 is an inflammasome that forms at or close to the MAM upon cellular activation and ER stress

and plays a pivotal role (by activating caspase-1) in the cleavage of pro-IL1b into IL1b and its subsequent secretion. The ER releases calcium into the cytosol and into mitochondria through (a.o.) the IP $_3$ R, which is a calcium channel, to which IP $_3$ as an agonist binds to induce calcium release. IP $_3$ R binds via glucose-regulated protein 75 (GRP75) with the mitochondrial voltage-dependent anion channel 1 (VDAC1) which may cause mitochondrial stress and leakage off reactive oxygen species (ROS), both important for inflammasome activation. Macrophages activate via their Toll-like receptors (TLRs) or G-protein coupled receptors several signaling pathways, that result in IP $_3$ formation, NF-kB activation, and/or ER stress.

factor- α and, even more variably, different regions of the human leukocyte antigen (*HLA*) region.

Treatment

The current treatment for KD is a high dose of 2 g/kg IVIG, given over 8–12 h [86]. The main goal of treatment is prevention of the development of CAA. Hypothesis on the mechanisms of efficacy of IVIG include immune modulation of T regulatory cells, neutralization of the etiologic agent, and reduction of cytokine production [8]. Treatment with IVIG significantly reduces the incidence of CAA [124]. IVIG is preferably given within the first 10 days after disease onset [83]. Apart from IVIG, high-dose aspirin is advised by the AHA, although evidence for further risk reduction for CAA is lacking [34, 124].

Adjunctive use of treatment

The majority of patients respond rapidly to IVIG, yet approximately 10–20% of all patients do not respond or have recurrent fever within 36–48 h after IVIG. These children have a higher risk of developing CAA [53]. In Japan, risk-scores have been developed to identify patients with a higher risk of IVIG resistance [35, 66, 106]. Unfortunately, these risk-scores do not perform adequately in Western, ethnically mixed, and in Chinese populations [24, 75, 104, 112, 115]. A possible method to decrease IVIG resistance is to intensify the initial treatment. A recent meta-analysis showed a beneficial effect of adding corticosteroids to the initial treatment with IVIG, yet this effect was only found in Japanese studies and not in two studies conducted in the USA [16]. Burns et al. showed that adding infliximab to initial IVIG treatment did not decrease treatment resistance but did decrease the number of days with fever and inflammation parameters 24 h after treatment [125].

Rescue treatment following IVIG non-response

Children who do not respond to IVIG require additional anti-inflammatory treatment. A second dose of IVIG is commonly advised, particularly in patients who have partially responded. Furthermore, corticosteroids are still commonly advised. The above-mentioned meta-analyses showed no significant benefit for either of these approaches when used as rescue treatment [16]. In 2012, we published the first case report successfully using the IL-1 antagonist anakinra for refractory KD [22]. Since then, additional clinical trials have been instigated to investigate both efficacy and safety of this IL-1 inhibitor [9]. Other secondary treatment possibilities are infliximab (TNF- α inhibitor), cyclosporine (calcineurin inhibitor), and statins, yet efficacy remains to be investigated [10].

Additional treatment

After normalization of temperature, the AHA advises ongoing aspirin in a low dose until no evidence of CA dilation are present at by 4 to 6 weeks after the acute illness [83]. If CAA are present and persisting around that time, aspirin is continued as anti-thrombotic therapy. In case of large (around a z -score ≥ 10) or complex abnormalities, additional anticoagulation therapy should be administered to prevent clotting due to turbulence in these pro-coagulatory large coronary artery lesions [83, 87].

Coronary artery aneurysms

Multiple criteria have been used for diagnosis of CAA. The criteria of the Japanese Circulation Society (JSC) state that an aneurysm is an artery of >3 mm in a child under the age of 5 and an artery of >4 mm in a child ≥ 5 years or when an arterial segment is 1.5 times its adjacent segment [31]. A giant CAA is classified as ≥ 8 mm or >4 times its adjacent segment [42]. Conversely, over the past years, it has become clear that z -scores, diameters adjusted for basal-surface-area, may be better indication of abnormality [25]. Multiple z -score classifications exist [23, 79, 82, 90]. Unfortunately, the z -scores using different classifications can vary, mainly at larger dimensions [101]. The threshold for abnormality is a z -score ≥ 2.5 , although a z -score between 2 and 2.5 can be classified as a dilation [83]. A small-sized CAA has a z -score of 2.5–5, a medium-sized CAA of 5–10, and a giant CAA of ≥ 10 [79].

Risk factors for CAA have been inconsistently reported but include a male gender, a young age (<1 year), an incomplete disease presentation, IVIG resistance, and the duration of fever [43, 64, 113, 114].

Imaging of CAA

Multiple imaging techniques exist for the follow-up of patients after KD and in particular children with CAA. Echocardiography is a non-invasive method to image the coronary arteries, used in the acute phase of KD as well as during follow-up. With this non-invasive method, it is possible to evaluate the anatomy of the coronary arteries, myocardial function, and valve abnormalities. Nevertheless, it is impossible to visualize the distal coronary arteries with echocardiography. The gold standard for coronary anatomy is a conventional angiography, though this technique is invasive and exposes the patient to radiation. The role of cardiac MRI (cMRI) has been established over the past years [81, 122]. Using this modality, evaluation of the anatomy as well as cardiac function is possible. The disadvantage of cMRI is the need for anesthesia in younger children. CT angiography is an alternative. Although conventional CT angiography carries a high

burden of radiation exposure, the new low-radiation dose CT scanning machines are becoming more widely available, which decreases the radiation burden significantly showing good resolution capacity in a small study [33]. In Fig. 2, a MRI and CT image of a normal and a giant CAA are depicted.

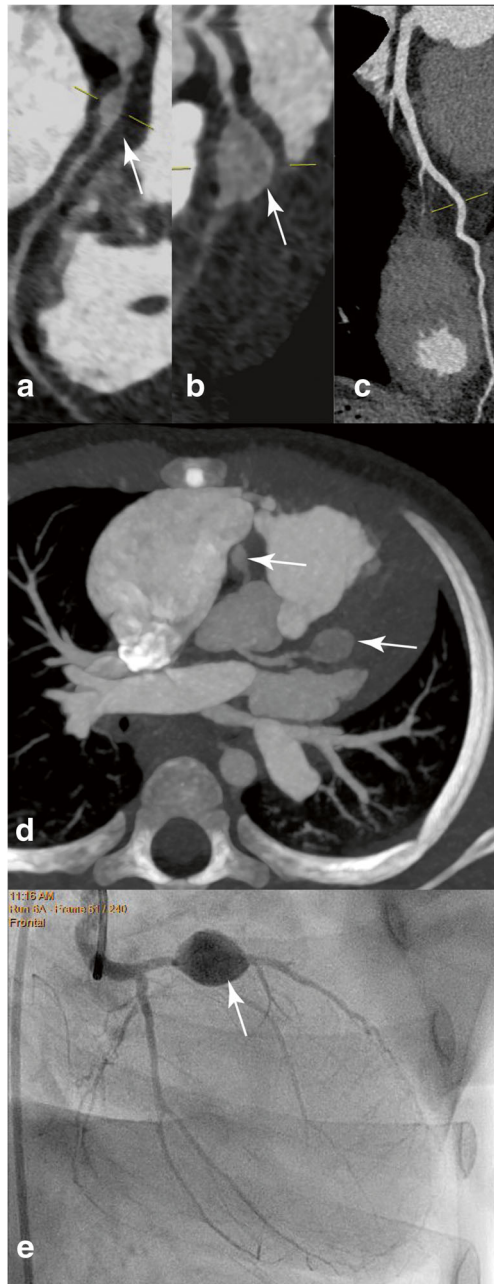


Fig. 2 Imaging techniques used for Kawasaki disease. **a, b, d, e** display coronaries of the same patient with different imaging techniques. **a** Curved multi-planar reformat of the coronary computed tomography angiography (cCTA) scan shows an aneurysm of the right coronary artery. **b** A giant aneurysm of the left anterior descending artery. **c** A normal left anterior descending artery. **d** Thin slab maximum intensity projection of the aneurysmatic proximal right coronary artery and left anterior descending artery. **e** A clearly depicted giant aneurysm of the left anterior descending artery, visualized with coronary angiography

The AHA and JCS have both published guidelines on the follow-up of patients after KD [42, 83]. Recently, we proposed a pathway to follow-up patients after KD based on the worst-ever z-score [28]. This pathway includes a cMRI (with or without adenosine stress testing according to the CAA status) during adolescence for all patients to visualize the complete coronary tree and a more intensive follow-up for patients with CAA (Fig. 3).

Natural history of CAA

Many CAA regress to a normal-sized lumen, mainly within the first 5 years. The likelihood of regression seems to be highly dependent on the original CAA size [19, 38]. While the lumen diameter may return to normal, it has become apparent that the vascular wall is often still damaged. Studies have shown persistent impaired dilation upon increased cardiac demand [39]. Also, changes in the coronary artery wall structure are seen, such as intimal hyperplasia [30, 54]. The remodeling of the coronary wall can cause potentially life-threatening situations as was shown by a case series of three adult patients who were released from follow-up care after normalization of the lumen but presented with chronic heart failure, unstable angina, and acute myocardial infarction [41].

Consequences of CAA

(Giant) CAA may have serious long-term consequences. Apart from thrombosis within the CAA and perfusion abnormalities after the CAA, there is an increased risk of stenosis just proximal or distal to the CAA [59].

In a large study of 245 Japanese patients with giant CAA (≥ 8 mm), Tsuda et al. found 10-, 20-, and 30-year event-free survival rates of 64, 48, and 36%, respectively [127]. Fifteen patients died during follow-up. In another study of 76 Asian patients with giant CAA (≥ 8 mm), 10-, 20-, and 30-year survival rates of 95, 88, and 88% were reported [116]. In a recent study by Friedman et al., 21 major adverse cardiac events (MACE) took place in 90 patients with giant CAA at diagnosis (z-score ≥ 10) [38]. This indicates that patients with giant CAA are at considerable risk for MACE and risk continues to exist years after the acute phase of KD.

The risk for patients with small-medium-sized CAA is less clear. In a study by Chih et al., only 1/51 patients with medium-sized CAA (>4 –8 mm) experienced ischemia during a median follow-up time of 47 months, although an additional 8 patients had stenosis and 4 patients developed calcification [19]. No patients with small-sized (localized dilatation with ≤ 4 mm diameter) CAA experienced MI. In the study by Friedman et al., no patients with small- (z-score 2.5–5) or medium-sized CAA (z-score 5–10) experienced any MACE. However, longer term studies will be needed to establish the

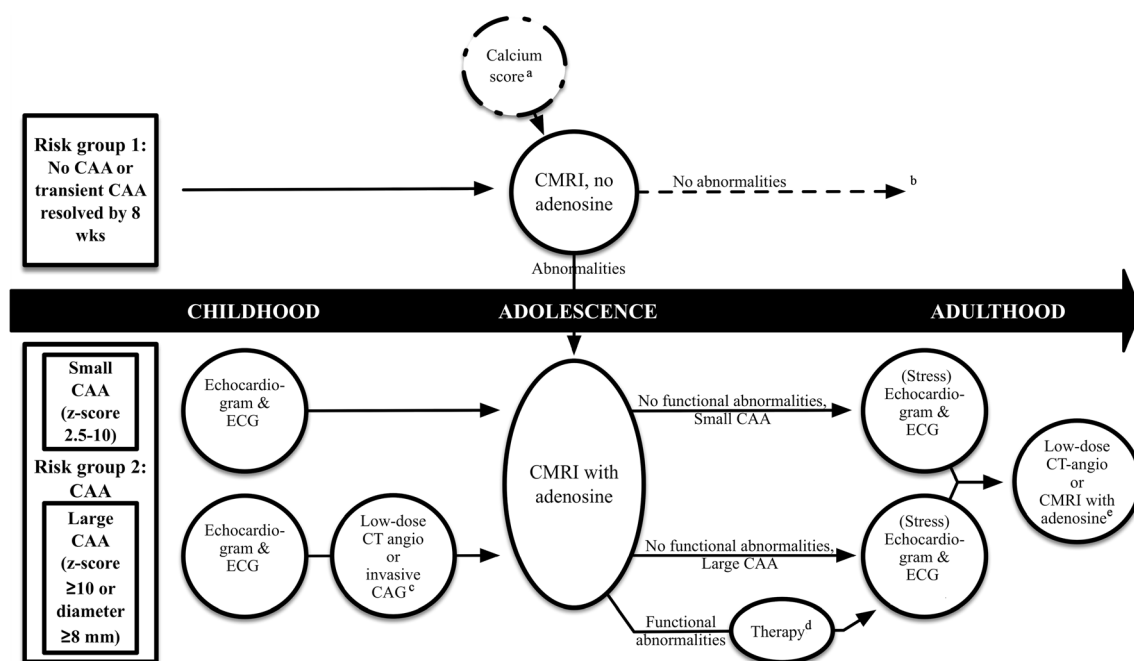


Fig. 3 Flow diagram of the monitoring of Kawasaki disease using different imaging modalities. Footnote: Originally published in: Insights into imaging: Dietz SM, Tacke CEA, Kuipers IM, Wiegman A, de Winter RJ, Burns RC, Gordon RB, Groenink M, Kuijpers TW, Cardiovascular imaging in children and adults following Kawasaki disease, Insights into Imaging, 2015;6:697 (adapted version). ^aWhen information is lacking about coronary arterial aneurysms (CAA) status, calcium score may be

indicated as a screening method. If positive, a CMRI with adenosine should be performed. ^bLong-term follow-up (cardiovascular counseling) of risk group 1 may be dictated by national health care policies and future studies. ^cAccording to the availability and experience of a center with (low-dose) CT angiography. ^dWhich of the different revascularization options improves prognosis best is unclear to date. ^eAdditional tests to evaluate for progression to stenotic lesions

long-term event rate in patients with small- or medium-sized CAA.

In patients with persisting CAA, calcifications are likely to develop as shown by a recent study looking at CT calcium scoring [56]. The data suggested this only occurs from approximately 10 years onwards following KD.

If thrombosis, stenosis, or abnormal blood flow in the CAA leads to a cardiac event or signs of ischemia, KD patients may need cardiac intervention. Thrombolytic treatment has been reported to be effective in treating fresh thrombus within giant CAA and in emergency management of ischemia due to thrombus [47].

Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can be used to revascularize the artery when stenotic lesions are present. CABG is used more often in multi-vessel disease. Percutaneous transluminal angioplasty may be complicated by the need of high balloon pressures in patients who have already developed calcification [1]. Two studies evaluating the difference between these two methods found that reinterventions were significantly higher in the PCI group [29, 84].

Available data are scarce on risk during pregnancy for women after KD. In a case series including 10 women who delivered 21 babies, none of the women experienced cardiovascular complications during pregnancy, including 4 women

with CAA, MI, and CABG in the past [40]. In a following comprehensive review, 56 women with 81 deliveries were described and cardiovascular complications were reported in 7 cases, including 2 MIs during pregnancy [40].

Longer term studies will be needed to define the long term risk of CAA. However, the significant proportion of patients developing thrombosis within giant CAA, or suffering ischemic events due to stenosis, suggests that all patients with significant aneurysms following KD need life time follow-up and are at risk of cardiac complications long term.

General cardiovascular risk

Apart from the increased cardiovascular risk due to persisting or regressed CAA, it is uncertain whether the vasculitis itself causes an increased cardiovascular or atherosclerotic risk at a later age. As most patients have not been followed long enough to evaluate the long-term natural course of the disease, multiple studies have focused on the use of surrogate markers for cardiovascular disease such as flow-mediated dilation, stiffness index, and carotid intima-media thickness (cIMT) [17, 89, 107]. Two reviews showed that most of these studies are small, lacking quality and there was significantly heterogeneity between studies [15, 27]. Nevertheless, results

suggested that surrogate markers were increased in CAA-positive but not in CAA-negative patients. In a follow-up study evaluating cIMT, we found that patients with giant CAA have a trend towards an increased cIMT at a later age, whereas in children without any coronary artery enlargement, their cIMT was initially increased but normalized to control values over time [26]. The results suggest that long-term effects of KD are not caused by atherosclerosis, as one would expect the differences in cIMT to increase compared with control measurements. This is in concordance with a postmortem study in which multiple growth factors were seen in the smooth muscle cells and intima layer of the coronary arteries, but no fatty streaks as seen atherosclerosis, distinguishing “KD vasculopathy” from atherosclerosis [118].

Quality of life and behavior

Multiple studies have investigated the cognitive and behavioral outcome after KD. Baker et al. studied 110 KD children, and found similar psychosocial and physical summary scores as an US population sample using a parent-completed questionnaire [3]. Only patients with giant CAA had a lower mean physical score. Parents did however report lower health perception. King et al. studied 38 KD patients and found no effect on cognitive or academic performance, but parents rated their children as having more internalizing and attentional behavior problems than controls [65]. Carlton-Conway et al. found that 40% of their patients showed internalizing scores in the clinical range as reported by parents, which was significantly more than their hospital controls who stayed in the hospital for a short period and had undergone cardiac catheterization [11]. Nishad et al. found no difference in social adaption, cognitive function, and behavioral function in 20 children [88]. Muta et al. studied 250 adolescents and young adults, including 19 patients with giant CAA and found significantly higher health-related quality of life (HRQOL) scores compared to national norms [85]. Two studies from our center showed significantly lower scores on several HRQOL scales in children under 5, when reported by their parents. However, self-report by the older KD children did not show any significant difference with controls. Moreover, parental perceptions of child vulnerability were significantly increased when compared to reference groups of Dutch parents [121, 129].

Conclusion

Although many aspects of KD are still unknown, there is increasing knowledge on the origin and treatment of KD as well as the development and classification of CAA. Since children with previous KD are entering adulthood, long-term

follow-up, with appropriate imaging modalities and awareness of the long-term effects, is increasingly important.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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