

Concise report

High risk of coronary artery aneurysm in Kawasaki disease

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Abstract

Objective. Kawasaki disease (KD) is a vasculitis of unknown aetiology with a high risk of coronary aneurysms if untreated. Timely treatment with intravenous immunoglobulin decreases the risk for coronary artery aneurysms (CAA). In this study, we set out to elucidate the factors associated with the risk of developing CAA.

Methods. Records of all KD-diagnosed children in Skåne between 2004 and 2014 were collected and clinical and demographic data were compiled. KD is defined according to the revised American Heart Association diagnostic criteria and classified as either complete KD (cKD) or incomplete KD (iKD).

Results. KD was diagnosed in 77 children and CAA was found in 31% ($n=24$). Children with CAA were younger compared with children without (median; 20 vs 34 months) and intravenous immunoglobulin treatment within 10 days was less likely to be received (75% vs 91%). In children presenting with iKD, 47% developed CAA compared with 21% in cKD patients. Using multivariate analysis, an association between the risk of CAA with low age in children with iKD was observed.

Conclusion. The risk of CAA development is disturbingly high in young children with iKD. This highlights the importance of rapid intense treatment and vigilance in infants, who are the most difficult to diagnose, in order to reduce the frequency of CAA.

Key words: Kawasaki disease, coronary artery aneurysms, treatment, population-based study

Rheumatology key messages

- Aneurysm is associated with incomplete Kawasaki disease and low age.
- This unexceptional high risk of aneurysms is not seen in children with complete Kawasaki disease.
- Early detection and treatment are essential when suspecting KD in young children with incomplete symptomatology.

Introduction

Kawasaki disease (KD) is an acute vasculitis of unknown aetiology that predominantly affects medium sized arteries. KD may present in two different forms

depending on fulfilment or non-fulfilment of diagnostic criteria: complete KD (cKD) or incomplete KD (iKD). In Japan, the incidence is 309/100 000 children per year [1], whereas in studies from Sweden, UK and USA the incidence is about 5–8/100 000 [2–4]. This genetic predisposition remains even after moving into a new geographic area, suggesting that the risk for KD is strongly correlated to genetic heritage [5].

The most serious complication of KD is coronary artery aneurysms (CAA). KD is the most common cause of acquired heart disease among children within developed countries [6] and a risk factor for myocardial infarction in early adulthood [7].

Known risk factors associated with the development of CAA are, amongst others, low age and delay of treatment [8]. Indeed, early treatment with IVIGs with or without additional corticosteroid therapy has been shown to

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TABLE 1 Patient data of children with Kawasaki disease

	All cases	CAA negative	CAA positive	cKD	iKD
Patients, <i>n</i>	77	53	24	47	30
Age at onset, median (IQR), months	28 (11.5–53.5)	34 (18.5–61.5)	20 (10–38.75)	33 (19–62)	20.5 (9–50.75)
Male, %	55.8	56.6	54.2	55.3	56.7
Developed CAA, <i>n</i> (%)	24 (31)	n/a	n/a	10 (21.3)	14 (46.7)
Z-score, <i>n</i> (%)					
2.5–<5	12 (15.6)			6 (12.8)	6 (20)
5–<10	8 (10.4)			3 (6.4)	5 (16.7)
≥10	4 (5.2)			1 (2.1)	3 (10)
Pericardial effusion, <i>n</i> (%)	18 (23.4)			9 (19.1)	9 (30)
Valve regurgitation, <i>n</i> (%)	28 (36.4)			16 (34.0)	13 (43.3)
Treatment					
Treated with IVIG, <i>n</i> (%)	74 (96.1)	51 (96.2)	23 (95.8)	46 (97.9)	28 (93.3)
Treatment with IVIG ≤10 days of symptoms <i>n</i> (%)	66 (85.7)	48 (90.6)	18 (75)	43 (91.5)	23 (76.7)
Repeated treatment with IVIG, <i>n</i> (%)	12 (15.6)	3 (5.7)	9 (37.5)	8 (17)	4 (13.3)
Glucocorticosteroids, <i>n</i> (%)	3 (3.9)	1 (1.9)	2 (8.3)	0	3 (10)
Days from onset to treatment with IVIG, median (IQR), days	7 (5–9)	7 (5–8)	7.5 (6–10.75)	7 (5–8)	7 (5–10.25)

reduce the risk of CAA from 15–25% to about 4% in Japanese populations where incidence of KD is high [4, 9, 10]. However, we and others outside East Asia have previously shown that in populations with a low incidence of KD, the risk of developing CAA is much higher [2, 11–15].

In this study we set out to investigate risk factors associated with CAA development in a population-based cohort of children with KD, diagnosed according to the 2017 AHA criteria [4].

Methods

Patients data and study design

The study area was Skåne, the southernmost region of Sweden, with the study period between 1 January 2004 and 31 December 2014. The study area, population, case identification, ascertainment of diagnosis and data collection were described previously [2].

Using the KD ICD-10 code (M30.3), 104 patients were identified. Of these patients, 90 were diagnosed during the study period and living within the study area. Use of the AHA algorithm (Supplementary Table S1, available at *Rheumatology* online) resulted in 77 patients that were considered to have KD [4]. Cardio Z software was used to calculate the Z-score (Dallaire and Dahdah [16]). CAA was defined as a Z-score ≥ 2.5 [8]. Importantly, when classifying the patients into cKD and iKD the result of the coronary ultrasounds were not included, and thus children presenting with iKD were considered to have iKD even if they had a CAA. This was done to minimize

the risk of classifying cases with iKD as cKD. Patient data and characteristics are described in Table 1 (for more detail see Supplementary Material, available at *Rheumatology* online). The study was approved by the Regional Ethical Review Board for southern Sweden (2010-517, 2015-153 and 301-2007) without the requirement to obtain informed consent from participants.

Statistical analyses

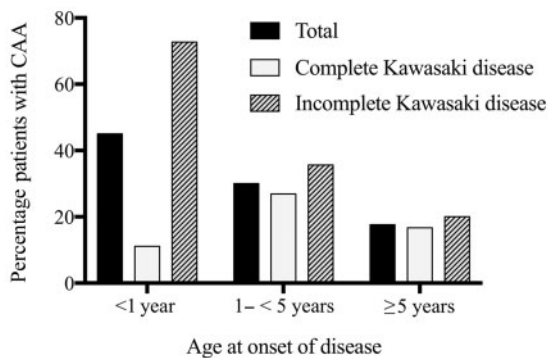
The follow-up time was defined as duration from time of KD diagnosis until the earliest of the following: death, moving outside the study area, reaching the age of 18 years or the end of study (31 December 2015). Differences in frequencies were tested with the χ^2 or Fisher's exact test and in medians with the Mann-Whitney *U* and Kruskal-Wallis test. Each covariate was assessed in a univariate model and then in a multivariate model (for details see Supplementary Methods, available at *Rheumatology* online). A *P*-value of <0.05 was considered significant.

Results

Frequency of CAA

Of the 77 children with KD, 24 (31%) developed CAA, with nine (11.7%) having CAA already at diagnosis and almost all (92%) developed their CAA within 6 weeks. Of the children that developed CAA, 50% had maximum Z-scores between 2.5 and <5, 33% had between 5 and <10, and four (17%) had higher than 10 (Table 1 and Supplementary Fig. S1, available at *Rheumatology*

Fig. 1 Coronary artery aneurysm in Kawasaki disease within different age groups



Percentage of CAA in all cases of KD and divided into complete KD and incomplete KD within the different age groups in Skåne between 2004 and 2014. CAA: coronary artery aneurysm; KD: Kawasaki disease.

online). CAA frequency was especially high in infants, where 45% developed CAA, compared with the 30% in children between 1 and 5 years and 17.6% in children 5 years and older (Fig. 1).

Differences in treatment between children presenting with or without CAA

Almost all children that developed CAA (95.8%) were treated with immunoglobulins but only 75% were treated within 10 days of symptom debut. In children without CAA, 96.2% received immunoglobulin therapy, of which 90.6% were treated within 10 days of symptom debut. Further treatment data are presented in Table 1.

Differences between children presenting with cKD vs iKD

In the cohort, 61% of children presented with cKD and 39% with iKD. In children with cKD, median age of onset was 33 months compared with 20.5 months in children with iKD (Table 1). In infants, 45% had cKD while 55% had iKD. However in children between 1 and 5 years, 65% had cKD and 35% had iKD, and in children 5 years and above, 70% had cKD and 30% iKD. In cKD-presenting children, only 21.3% were found to develop CAA, whilst among children with iKD, a larger 46.7% developed CAA ($P=0.025$) (Table 1).

In the cKD child group, no major differences in the frequency of CAA depending on age group were observed. However, iKD infants were by far the most affected group, with 73% developing CAA in comparison with infants with cKD (11%) and CAA frequency declining with age in children with iKD (Fig. 1).

The cKD group showed that 91.5% were diagnosed and treated with IVIG within the first 10 days after onset of symptoms, in comparison with only 76.7% in the iKD group (Table 1).

Association between risk factors and CAA

To assess different factors associated with CAA, a univariate logistic regression was first fitted with age, sex, treatment delay, or iKD/cKD respectively (Supplementary Table S2, available at *Rheumatology* online). Multivariate analysis showed a trend for lower age and iKD to be associated with CAA, although the association was not significant (Supplementary Table S3, Model 1a, available at *Rheumatology* online). As the outcome (i.e. CAA) was common in the cohort, a risk regression was also fitted to verify the results [17] (Supplementary Table S3, Model 1b, available at *Rheumatology* online).

As iKD and cKD clinically present differently and previous studies have analysed cKD independently, we divided the group into two cohorts, iKD and cKD. In the iKD group a significant association between age and CAA was shown, whereas no such association was observed between age and CAA in cKD patients (Supplementary Table S3, Model 2a and 3a, available at *Rheumatology* online). Again, as a sensitivity analysis, risk regressions were fitted to confirm the results (Supplementary Table S3, Model 2b and 3b, available at *Rheumatology* online).

Discussion

An alarming high frequency of CAA (31%) was found during our population-based study of KD using revised AHA criteria. CAA incidence proved much higher than previously described [4], although recent studies from UK, Germany and Russia have shown similar numbers [12–14]. Children presenting with iKD had an increased risk of CAA development (46.7%) in comparison with children with cKD (21.3%). Additionally, there was a significant association with CAA and low age in children with iKD. In our study, 73% of infants with iKD developed CAA, which is disturbingly high. Our data suggest, although do not prove, that CAA development risk is associated with low age and iKD, maybe in combination with treatment delay or other unknown factors. Our study has direct clinical implications, as younger children with atypical presentation, who have the highest risk of developing CAA and requirement of rapid treatment, are the most difficult to diagnose.

Although our cohort is small and results should be interpreted with care, we speculate that the data may reflect that iKD and cKD differ not only in clinical presentation, but also in IVIG resistance or CAA risk, regardless of treatment. However, this needs to be addressed in future studies with larger cohorts of patients. Furthermore, additional treatments with concomitant corticosteroids, ciclosporin or IL-1 blockade may reduce the frequency of CAA development [9]. However, we could not investigate if the lack of more aggressive treatments was associated with high risk of CAA, but the speculation arose that it may, in part, play a role in the high frequency of CAA.

It is important to address that our cohort is limited in sample size, and thus events per variable are few, and risk factors may co-vary, and hence all estimates and *P*-values should be interpreted with caution and any association must be validated by future studies in larger cohorts.

In recent years, *Z*-scores have become widely used to calculate coronary artery width. In our retrospective data, most cardiologists performing echocardiographs did not routinely use *Z*-scores and a standardized protocol to define CAA. In this study, we re-evaluated all echocardiographs and calculated *Z*-scores, making this an important study limitation. Nevertheless, we demonstrated that large and giant aneurysms (i.e. a *Z*-score ≥ 5 and very likely to be detected regardless of method) were more prevalent in our population (15.6%) than in both the UK (6.9%) and Japan (1.28%) [12, 18]. These larger aneurysms have been shown to be a risk factor for future cardiac events (such as stenosis, thrombosis and myocardial infarction) and it is of paramount importance that they be prevented [19, 20]. As such, KD is the most common cause of acquired heart disease in children within western populations and may result in long-term cardiac sequelae during adulthood [4, 21].

In conclusion, we demonstrate an extremely high frequency of CAA in young children with KD. However, the association between risk of CAA and age was only significant in children presenting with iKD. In addition, the high frequency of CAA could not be explained by treatment delay in the whole KD population. We therefore conclude that early detection and treatment are essential when suspecting KD in young children with incomplete symptomatology. Furthermore, based on our results, we speculate that cKD and iKD may be two different entities that may need distinct therapeutic processes. We feel our study highlights the need for further research into the treatment of KD in a European/American setting, as results from Asian studies likely cannot be extrapolated to a western setting.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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