European Journal of Pediatrics (2021) 180:271–275
https://doi.org/10.1007/s00431-020-03712-6

SHORT COMMUNICATION

Long-term follow-up of coronary artery lesions in children in Kawasaki syndrome

Ilaria Maccora[1] · Giovanni Battista Calabri[2] · Silvia Favilli[2] · Alice Brambilla[2] · Sandra Trapani[3] · Edoardo Marrani[1] · Gabriele Simonini[4]

Received: 31 January 2020 / Revised: 27 May 2020 / Accepted: 2 June 2020 / Published online: 15 June 2020

Abstract

To describe clinical and epidemiological characteristics of a Kawasaki syndrome cohort. In a monocentric, retrospective, observational study, between February 1982 and August 2018, we enrolled 361 children, aged 1 month to 24.4 years. Coronary artery lesions were detected in 20.2% of patients: 16% had coronary ectasia, and 4.15% had coronary aneurisms. A significant difference regarding age at disease onset ($p = 0.025$), fever duration ($p < 0.0001$), CRP ($p = 0.001$) and day of first IVIG administration ($p < 0.0001$) was detected among group. A significant correlation between coronary artery lesions and disease onset < 6 months ($p = 0.009$), second IVIG dose ($p < 0.001$) and male gender ($p = 0.038$) has been detected. Median long-term follow-up was 10.2 years (1–36 years). At the last available follow-up, patients without coronary involvement and coronary ectasia had normal cardiological tests, conversely, in patients with aneurisms, 8/13 showed persistent aneurisms at echocardiography, one ECG repolarization alterations, and one ST depression at the peak of effort during ergometric test.

Conclusion: Children with lower age, longer fever, higher level of CRP and retard in IVIG administration are at higher risk to develop coronary artery lesions. Our long-term follow-up analysis confirms, over 36 years of observation, the benign course of Kawasaki syndrome even in coronary artery lesion patients, if timely treated.

What is already known about this topic?

- *Stopping cardiologic assessment in no risk patients results economically advantageous, timesaving and able to reduce emotional discomfort in children and their families.*
- *Age at disease onset, fever duration, CRP level, and day of first IVIG administration are possible risk factors for coronary artery lesions*

What is New?

- *During 36 years of observation in real life, our study shows the benign course of Kawasaki syndrome without coronary artery lesions after 6–8 weeks from the disease onset.*
- *Age < 6 months at disease onset is strongly related with coronary artery lesion development.*

Keywords Kawasaki · Vasculitis · Paediatric vasculitis · Coronary artery aneurism · Childhood

Communicated by Nicole Ritz

✉ Ilaria Maccora
ilamaccora@gmail.com

Giovanni Battista Calabri
giovanni.calabri@meyer.it

Silvia Favilli
silvia.favilli@meyer.it

Alice Brambilla
alice.brambilla@unifi.it

Sandra Trapani
sandra.trapani@unifi.it

Edoardo Marrani
edoardo.marrani@gmail.com

Gabriele Simonini
gabriele.simonini@unifi.it

[1] Pediatric Rheumatology Unit, School of Human Health Science, A. Meyer Children's University Hospital, University of Florence, Florence, Italy

[2] Cardiology Unit, A. Meyer Children's University Hospital, Florence, Italy

[3] Department of Paediatrics, A. Meyer Children's University Hospital, University of Florence, Florence, Italy

[4] Rheumatology Unit, A. Meyer Children's University Hospital, University of Florence, Florence, Italy

Abbreviations

CAL	Coronary artery lesion
CAn	Coronary aneurism
CE	Coronary ectasia
CRP	C-reactive protein
ECG	Electrocardiogram
IVIG	Intravenous immunoglobulins
KS	Kawasaki syndrome
SD	Standard deviation

Introduction

Kawasaki syndrome (KS) is an acute self-limited medium size vasculitis, principally affecting coronary arteries (CA) and children less than 5 years of age [1]. KS is one of the most common cause of acquired heart disease in children, and it is most frequent in Asian countries, particularly in Japan, where annual incidence of 308 cases per 100,000 children < 5 years of age has been detected [2, 3]. Conversely, in Europe the incidence ranged between 4.9 and 15.2 per 100,000 children <5 years of age [4]. It is characterized by persistent fever, exanthema, conjunctivitis, changes in the extremities, erythema of oral mucosa and lips and cervical lymphadenopathy along with coronary abnormalities [1]. Rarely, macrophage activation syndrome may complicate the clinical course of KS [5]. The aetiology is still unknown, even though many studies are still investigating the possible triggers of this vasculitis. Identification of risk factors for coronary artery lesions (CAL) in KS represents the current purpose of medical community to early detect patients needing a tailored therapy [1].

Objective

To describe epidemiological, clinical e laboratory characteristic of a mono-centric KS cohort, followed at Rheumatology and Cardiology Units between February 1982 and August 2018.

Materials and methods

This is a monocentric, retrospective, observational study involving patients with a diagnosis of KS between February 1982 and August 2018 at Rheumatology and Cardiology Unit of Anna Meyer Children's University Hospital. Complete and incomplete KD were defined according to the American Heart Association definition (1). In a customized database, clinical, laboratory and echocardiographic data have been extracted from medical records, stratifying subjects with no CAL, coronary ectasia (CE) and presence of coronary aneurisms (CAn) according to American Heart Association recommendation 2017 [1]. All patients included underwent to echocardiographic evaluation. Resistance to treatment was defined as persistence of fever 48 h by the end of IVIG infusion. Regardless CAL, patients underwent scheduled cardiologic follow-up until 6–8 weeks from the onset, thereafter at 6 months, 1 year and at 8 years, including ergometric test with tapis roulant (treadmill) according to Bruce protocol modified [6]. CAL patients received additional cardiac evaluation on clinical need. Patients with < 1-year follow-up were excluded from analysis regarding data of follow-up. Statistical analysis was performed using SPSS statistics version 25.0. Data are expressed as frequencies and total records, median, range or mean and standard deviation (SD). Data have been assessed by analysis of variance with Tukey, LSD and Bonferroni corrections, and r-Spearman and χ-square tests.

As per Anna Meyer Children's Hospital Ethical Committee, ethics board approval is not required for retrospective observational study.

Results

Between February 1982 and August 2018, 361 children have been diagnosed with KS, 47 patients between the 1982 and 1991 (follow-up range 1–36 years), 88 between the 1992 and 2001 (follow-up range 2–26 years), 141 between the 2002 and 2011 (follow-up range 1–16 years) and 85 between the 2012 and August 2018 (follow-up range 1 month −6 years). Among these, 219 patients were male (60.6%), with a male/female ratio of 1.5:1. They aged 1 month to 24.4 years, with a median age at disease onset of 2.1 years. Three hundred and twenty-five out of 361(90%) children developed the disease before 5 years, 94/361 (26%); before 1 year, 32/361 (8.9%); and before 6 months. All patients presented persistent fever (100%), 244 rash (91.4%), 229 conjunctivitis (85.8%), 224 mucositis (83.9%), 196 extremities abnormalities (73.4%) and 165 lymphadenopathies (61.8%). Patients younger than 6 months of age in the 68.75% (22/32) of case had an incomplete form of KS, versus the 46.64% (132/283) of patients aged 6 months-5 years, versus the 33.33% (15/45) of patients older than 5 years (χ2 9.46, p value 0.008). The median fever duration was 7 days (range 1–25 days). CAL was detected in 73/361 patients (20.2%): 58/361 had CE (16%), and 15/361 had CAn (4.15%).

In the different subgroups, we observed a median age at disease onset of 2 years and 1 month in No-CAL, 2 years and 5 months in CE, 5 months in CAn, a median duration of fever of 7 days in No-CAL, 8 days in CE, 11 in CAn, an average value of CRP of 6.81 mg/dl in No-CAL, 8.38 mg/dl mg/dl in CE, 14.15 mg/dl in CAn, a day of first dose of IVIG of 8th day in no-CAL, 7th day in CE and 11th in Can (see Table 1).

Table 1 Clinical and laboratory characteristic in the 3 different groups of 361 Kawasaki Syndrome children

	No-CAL	CE	CAn
N of patients	288	58	15
Median age at disease onset *Median (IQR)*	2 y 1 month (30.5)	2 years 5 months (36.75)	5 months (11.5)
Duration of fever (days), *Median (IQR)*	7 (3)	8 (4)	11 (5.75)
Average value of CRP (mg/dl) *Mean (SD)*	6.81 (7.05)	8.38 (8.01)	14.15 (10.62)
Day of first dose of IVIG *Mean (SD)*	8 (3)	7 (3)	11 (4.14)
Duration of follow-up *Median (IQR)*	48 (48)	60 (42)	19 (77)

No CAL, no coronary lesions; CE, coronary ectasia; CAn, coronary aneurisms

Among 169 patients with incomplete KS, children younger than 6 months developed CAL more frequently than children aged between 6 months and 5 years and children aged more than 5 years (7/22 vs 11/132 vs 3/15 (χ2 10.42, p value 0.005).

The different groups showed significant differences regarding age at disease onset ($F = 2.77$, $p = 0.025$), fever duration ($F = 16.32$, $p < 0.0001$), CRP ($F = 6.94$, $p = 0.001$) and day of first IVIG administration ($F = 7.963$ $p < 0.0001$) (Fig. 1).

A significant correlation between CAL and disease onset < 6 months ($\rho = 0.137$, $p = 0.009$), the need to administer second IVIG dose ($\rho = 0.305$, $p < 0.001$) and male gender ($\rho = -0.109$, $p = 0.038$) has been detected. No significative associations were evaluated among the presence/absence of CAL and conjunctivitis, cheilitis, rash, lymphadenopathies, hyponatremia and white blood count > 12.000 cell/mm3.

Until the 1986 (8 children), corticosteroids associated with high dose of aspirin was the main therapy. From the 1986 to 2005 (205 children), IVIGs, one or two doses, along with aspirin have been used, an additional third course of IVIG has been provided in 35 children, before receiving corticosteroids in case of persistent disease (10). From 2005 (148 children), after the failure of a second dose of IVIG, 36 patients received 3 boluses of corticosteroid. After 2012, Anakinra (2) and Infliximab (1) have been administered in severe/refractory forms not responding to steroid treatment.

Data of patients with at least one-year follow-up were available for 327 children. Median long-term follow-up was 10.2 years (range 1–36 years). At the last available follow-up, 261/327 no CAL patients and 53/327 CE patients had normal ECG, echocardiography and ergometric test (performed in 177/261 patients with no CAL and in 39/53 with CE). Conversely, among 13/327 CAn patients, 8/13 persistent CAn at echocardiography, one displayed ECG repolarization alterations. Nine out of 13 children underwent an ergometric test: one child showed ST depression at the peak of effort.

During this long-term follow-up, none of our patients developed additional systemic signs or features of others autoinflammatory diseases.

Discussion and conclusion

In this report, we have described the features of a cohort of KS in a tertiary Italian centre. Compared with literature data [7], we observed a lower age at disease onset: 90% patients developed KS before 5 years. However, the percentage of CAL (20.2%) is consistent with European data [4]. Furthermore, the subgroup with CAL showed a lower age at disease onset probably due to unusual/incomplete presentation and paucity of clinical signs, as previously reported. It is unclear if the increase risk of CAL is the consequence of the delayed diagnosis or to the age of the children [8].

Our long-term follow-up in a large, monocentric cohort reports possible CAL risk factors such as age at disease onset, fever duration, CRP level and day of first IVIG administration according to current data [9]. These parameters are part of different scores developed to predict CAL and IVIG resistance, but unfortunately there is no agreement about their applicability across populations with different genetic background [10]. Our study confirms, over 36 years of observation in real life, the benign course of KS without CAL after 6–8 weeks from the disease onset [1, 11, 12]. Additionally, it reports, in long-term follow-up, the favourable outcome of children with CAn: 40% no longer presented CAL and, significantly, only 7.69% showed abnormal function tests.

Nonetheless the potential interpretation bias due to be a monocentric, retrospective chart review, these data outlines the benign course of KS over time, in no CAL subjects as well as in children with CAn.

According to recent guidelines, stopping cardiologic assessment in no risk patients might result timesaving and able to reduce emotional discomfort in children and their families as evaluated by de Ferranti and colleagues in their recent study (12). Our long-term data confirms the benign course of KS and should prompts physicians in tailoring diagnostic and therapeutic efforts in selected KS children.

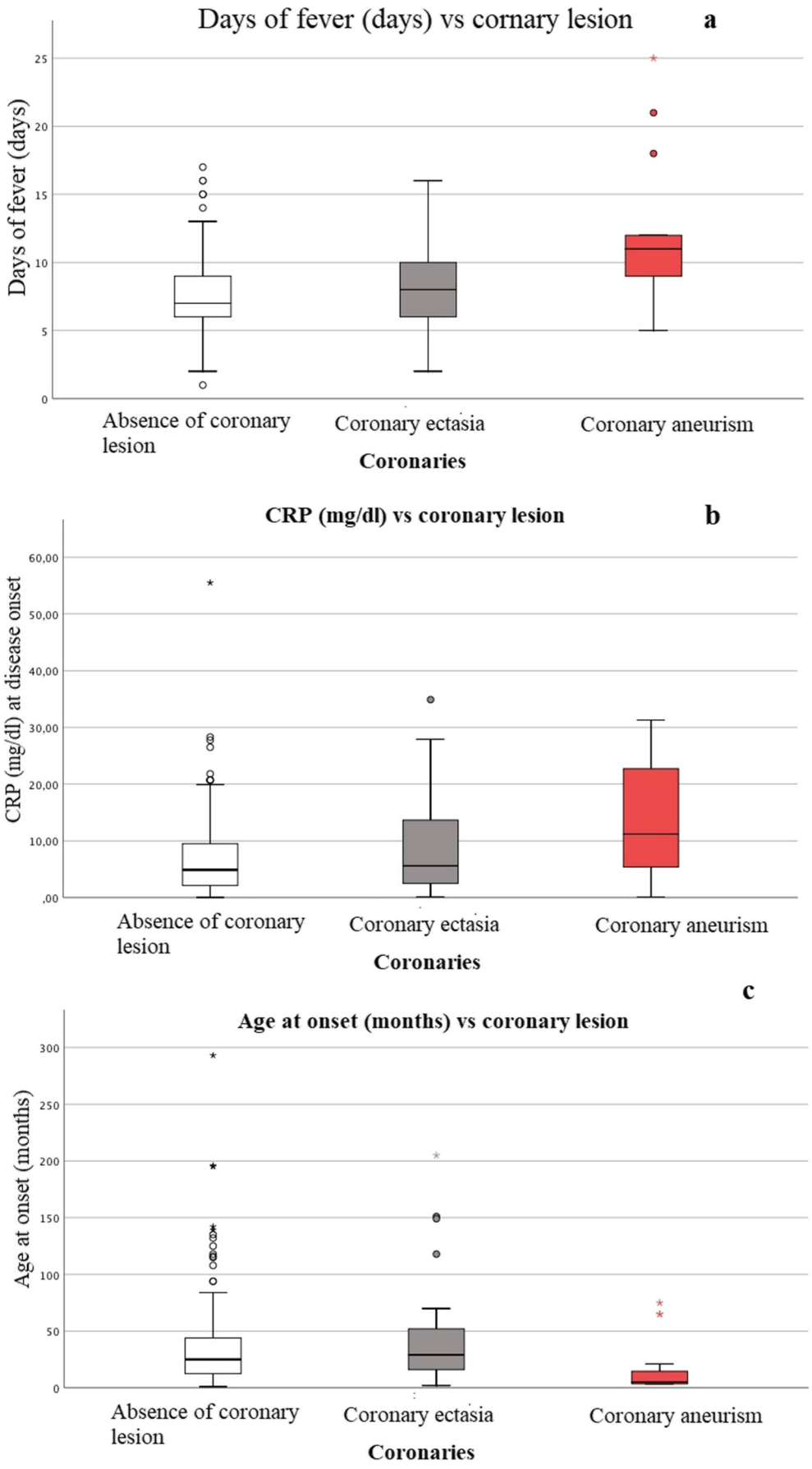

Fig. 1 Figure reports significant differences regarding **a** days of fever, **b** CRP values and **c** age at disease onset in Kawasaki syndrome children without coronary artery lesions, coronary ectasia and coronary aneurisms. In detail, section **a** highlights longer duration of fever in patients with coronary aneurism ($p < 0.0001$), section **b** highlights lower values of CRP in patients without coronary artery lesion (p 0.001), section **c** highlights younger age in the group of coronary aneurism (p 0.025). no-CAL, non-Coronary artery lesion; CE, coronary ectasia and CAn, presence of coronary aneurism

Authors' contributions Ilaria Maccora contributed to the study design, data analysis and writing of first draft and approved of the final version of the manuscript. Giovanni Battista Calabri contributed to the study design, data collection and approved the final version of the manuscript. Alice Brambilla contributed to the study design, dat collection and approved the final version of the manuscript. Silvia Favilli contributed to the study design, dat collection and approved the final version of the manuscript. Sandra Trapani contributed to the study design, data analysis and approved the final version of the manuscript. Edoardo Marrani contributed to the study design, data analysis and approved the final version of the manuscript. Gabriele Simonini contributed to the study design, data analysis and approved the final version of the manuscript.

Compliance with ethical standards

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

Ethical approval As per Anna Meyer Children's Hospital Ethical Committee, ethics board approval is not required for retrospective observational study.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention (2017) Diagnosis, treatment, and long-term management of Kawasaki Disease: a scientific statement for health professionals from the American Heart Association. Circulation. 135:e927–e999
2. Burns JC, Glodé MP (2004) Kawasaki syndrome. Lancet 364:533–544
3. Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, Kojo T, Aoyama Y, Kotani K, Yanagawa H (2018) Epidemiological observations of Kawasaki disease in Japan, 2013-2014. Pediatr Int 60:581–587
4. Uehara R, Belay ED (2012) Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol 22:79–85
5. Jin P, Luo Y, Liu X, Xu J, Liu C (2019) Kawasaki disease complicated with macrophage activation syndrome: case reports and literature review. Front Pediatr 7:423
6. Bruce RA, Pearson R, Lovejoy FW, Yu PNG, Brothers GB (1949) Variability of respiratory and circulatory performance during standardized exercise. J Clin Invest 28(6 Pt 2):1431–1438
7. Nakamura Y (2018) Kawasaki disease: epidemiology and the lessons from it. Int J Rheum Dis 21:16–19
8. Mastrangelo G, Cimaz R, Calabri GB, Simonini G, Lasagni D, Resti M, Trapani S (2019) Kawasaki disease in infants less than one year of age: an Italian cohort from a single center. BMC Pediatr 19:321
9. Hua W, Ma F, Wang Y, Fu S, Wang W, Xie C, Zhang Y, Gong F (2019) A new scoring system to predict Kawasaki disease with coronary artery lesions. Clin Rheumatol 38:1099–1107
10. Jakob A, von Kries R, Horstmann J, Hufnagel M, Stiller B, Berner R, Schachinger E, Meyer K, Obermeier V (2018) Failure to predict high-risk Kawasaki disease patients in a population-based study cohort in Germany. Pediatr Infect Dis J 37:850–855
11. Maccora I, Calabri GB, Simonini G (2019) Is echocardiography critical in patients with Kawasaki disease with a z score less than 2 to 6 weeks from onset? JAMA Pediatr 173:700
12. de Ferranti SD, Gauvreau K, Friedman KG, Tang A, Baker AL, Fulton DR, Tremoulet AH, Burns JC, Newburger JW (2018) Association of initially normal coronary arteries with normal findings on follow-up echocardiography in patients with Kawasaki disease. JAMA Pediatr 172:e183310