Rheumatol Int (2015) 35:1053–1058
DOI 10.1007/s00296-014-3186-9

Rheumatology INTERNATIONAL

SHORT COMMUNICATION - OBSERVATIONAL RESEARCH

Risk factors for coronary artery abnormalities in children with Kawasaki disease: a 10-year experience

Lorna Stemberger Maric · Ivica Knezovic · Neven Papic · Branko Mise · Srdan Roglic · Leo Markovinovic · Goran Tesovic

Received: 22 September 2014 / Accepted: 18 November 2014 / Published online: 28 November 2014

Abstract Kawasaki disease (KD) is an acute systemic vasculitis of childhood. Due to development of coronary artery aneurysms (CAA) it is considered the most common cause of acquired heart disease in children. The clinical and laboratory features of patients with complete and incomplete KD were compared in order to identify the possible predictors of CAA development. A cross-sectional study of children with KD treated at the University Hospital for Infectious Diseases, Zagreb, between January 2003 and December 2012 was conducted. A total of 111 KD patients were included; 70.3 % patients had complete KD. Patients with complete KD had more frequently rash, changes on extremities and mucous membranes, as well as higher serum bilirubin, aminotransferases, gamma-glutamyl transferase and lactate dehydrogenase levels. Patients with incomplete KD had longer duration of fever before the diagnosis (8 vs. 7 days) and delayed IVIG treatment (day 8 vs. 7). CAA was detected in seven children (6.3 %). Disease duration before hospitalization >6 days (OR 7.16, 95 % CI 1.51–100.35), age <6 months (OR 25.86, 95 % CI 1.68–398.35) and platelet count >771 after the 7th day of disease (OR 13.33, 95 % CI 2.19–80.87) were independently associated with CAA development. The diagnosis and treatment in incomplete KD can be delayed due to the absence of major criteria. Age, duration of symptoms prior hospitalization and platelet count were identified as independent predictors of CAA development.

Keywords Kawasaki disease · Incomplete Kawasaki disease · Coronary artery aneurysm · CAA · IVIG

L. S. Maric (✉) · I. Knezovic · B. Mise · S. Roglic · L. Markovinovic · G. Tesovic
Clinical Department for Pediatric Infectious Diseases, University Hospital for Infectious Zagreb, Mirogojska 8, 10 000 Zagreb, Croatia
e-mail: lorna_stemberger@yahoo.com

N. Papic
Department for Viral Hepatitis, Zagreb, University Hospital for Infectious Diseases, Zagreb, Croatia

B. Mise · G. Tesovic
School of Medicine, Unversity of Zagreb, Zagreb, Croatia

Introduction

Kawasaki disease (KD) is an acute systemic inflammatory disease and the leading cause of acquired heart disease among children in developed countries. Systemic vasculitis predominantly affects coronary arteries resulting in coronary artery aneurysm (CAA) development in up to 20 %, myocardial infarction in 5 % and sudden death in up to 1 % of previously healthy children [1, 2].

The diagnosis is based on clinical criteria established by the American Heart Association (AHA) in 2004 [3]. Complete KD is defined by fever longer than 5 days and the presence of ≥4 of the 5 principal clinical features (bilateral conjunctival injection, cervical lymphadenopathy, polymorphous skin rash, changes on the lips or oral mucosa, and changes in the distal extremities) [3]. The presentation of KD is incomplete/atypical in approximately 20 % of patients, thus representing a significant diagnostic challenge [4]. This is of particular relevance since the early anti-inflammatory treatment with intravenous immunoglobulin (IVIG) reduces the risk for CAA. 20 % of patients who develop CAA will develop coronary artery stenosis and may subsequently require invasive cardiac treatment [3].

The majority of clinical studies are reported from Asian countries. Due to the significant differences in genetic susceptibility and clinical manifestations, those are not

necessarily reflecting the clinical impact in European population. Here we provide the first description of clinical profiles of children diagnosed with KD, treated in a tertiary-care medical center in Croatia.

Patients and methods

Study design and population

A retrospective, cross-sectional study of KD patients admitted to the University Hospital for Infectious Diseases (UHID) in Zagreb, Croatia in the period from January 2003 to December 2012 was performed. We reviewed laboratory and clinical data of 117 patients with a clinical diagnosis of KD, according to AHA recommendations [3]. Six patients were excluded from the study due to incomplete medical records. The study was fully compliant with all provisions of the Declaration of Helsinki and was approved by the Hospital Ethics Committee.

Data collection

The epidemiologic, clinical, and laboratory characteristics were evaluated. Echocardiographic examination was performed prior to IVIG treatment and at discharge. The echocardiographic diagnosis of CAA was made by measuring the greatest luminal diameter of the coronary artery and comparing the value to the value derived using age-matched controls [3]. Patients were treated with IVIG, 2 g/kg in a single infusion over 10–12 h along with aspirin (ASA) 80–100 mg/kg/day. Once fever was controlled for at least 48 h, the aspirin dose was reduced to 3–5 mg/kg per day.

Statistical analysis

Statistical analysis was performed by using the Prism (ver 5.0) statistical software (GraphPad Software, San Diego, CA) and MedCalc for Windows®, ver 11.5.1.0 (MedCalc Software, Mariakerke, Belgium). The demographic, clinical and laboratory data were evaluated and presented descriptively. The Fisher's exact test and Mann–Whitney *U* test were used to compare the groups, as appropriate. All tests were two-tailed; a $p < 0.05$ was considered statistically significant. Binary logistic regression analysis was used to assess the independent predictors of CAA development. All predictors were entered in a backward stepwise logistic regression model. Statistically non-significant predictors were progressively excluded based on a likelihood ratio test. The strength of association was expressed as odds ratio (OR) and its corresponding 95 % confidence interval (CI).

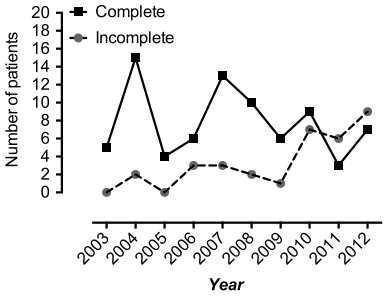

Fig. 1 Number of complete and incomplete KD cases hospitalized at the University Hospital for Infectious Diseases in Zagreb, Croatia per year

Results

During the 10-year period, data from 111 KD patients were eligible for analysis. The number of hospitalized patients varied during the studied period, as shown in Fig. 1. No seasonal trends were observed. However, we noticed a clear increasing trend of incomplete KD cases.

Patients' demographic and clinical characteristics

The study included 70 boys (63 %) and 41 girls (37 %); male to female ratio 1.7:1. Patients' age at the time of diagnosis ranged from 45 days to 14 years (median 27 months, IQR 12–50 months). No significant difference in age at presentation ($p = 0.9527$) was found between girls and boys. No child had a family history of KD. The majority of patients were admitted on the 5th day of disease (IQR 3–7). The diagnostic criteria for complete KD were fulfilled in 78 (70.3 %) patients, whereas 33 (29.7 %) were considered as incomplete cases. A comparative analysis of demographic and clinical characteristics of children with complete and incomplete KD is shown in Table 1.

Overall, 110 (99.1 %) patients had fever lasting ≥5 days; reaching its maximal values (median: 39.6 °C; IQR 39.1–40.0 °C) on the 5th day (4–6.5) of illness. In the incomplete KD group, 20 patients (60.6 %) fulfilled three and 13 (39.4 %) patients had two major diagnostic criteria. Regarding typical clinical findings, patients with complete form of disease had more often changes on the lips and in the oral cavity ($p = 0.0001$), changes on extremities ($p = 0.0207$) and exanthema ($p = 0.0192$). Importantly, fever duration prior to diagnosis was significantly longer in incomplete than in complete KD group (8, IQR 6–10 vs. 7, IQR 5–8 days, respectively, $p = 0.0049$).

Laboratory findings

The majority of patients had increased inflammatory markers. 108 patients (97.3 %) had elevated CRP and

Table 1 Clinical characteristics of children with complete and incomplete Kawasaki disease (KD), 2003–2012

Characteristic	Study population ($n = 111$)	Complete KD ($n = 78$)	Incomplete KD ($n = 33$)	p value[†]
Age, months (median, IQR)	27 (12–50)	27.5 (11.8–48.0)	26 (11.75–56.0)	0.9552
Boys (n, %)	70 (63.06)	49 (68.2)	21 (63.64)	1.0000
Major diagnostic criteria (n, %)				
Fever ≥5 days	110 (99.1)	77 (98.72)	33 (100)	1.0000
Conjunctival injection	98 (99.29)	72 (92.31)	26 (78.79)	0.0557
Lips and oral cavity changes	95 (88.29)	74 (94.87)	21 (63.64)	**0.0001**
Cervical lymphadenopathy	43 (38.74)	34 (43.59)	9 (27.27)	0.1368
Changes on extremities	79 (71.17)	61 (78.21)	18 (54.55)	**0.0207**
Rash[a]	98 (88.29)	73 (93.59)	25 (75.76)	**0.0192**
Additional diagnostic criteria (n, %)				
Gallbladder hydrops	21 (25.61)	14 (25.45)	7 (25.93)	1.0000
Aseptic meningitis	28 (25.22)	20 (25.64)	8 (24.24)	1.0000
Sterile pyuria	41 (36.94)	32 (41.03)	9 (27.27)	0.2009
BCG-reactivation	10 (9.01)	8 (10.26)	2 (6.06)	0.7203
Time of diagnosis, days (median, IQR)	7 (6–9)	7 (5–8)	8 (6–10)	**0.0049**

Bold values are statistically significant ($p < 0.05$)

[a] Macular 63.0 %, papular 32.9 %, morbilliform 2.8 %, scarlet-like 42.4 %, urticarial 5.5 %, erythematous 5.5 %, target-lesions 2.8 %, petechial 1.4 %, polymorphous 16.4 %

[†] Fisher's exact test and Mann–Whitney U test were used to compare the groups, as appropriate

Table 2 Laboratory findings in patients with complete versus incomplete Kawasaki disease (KD)

Laboratory parameter	Complete KD ($n = 78$)	Incomplete KD ($n = 33$)	p value
ESR, mm/h	60 (40.5–85.0)	70.0 (31.5–92.5)	0.8265
CRP, mg/L	81.5 (45.9–125.6)	71.3 (23.95–108.7)	0.1959
Fibrinogen, g/L	6.57 (5.00–8.31)	6.8 (5.45–8.35)	0.7344
ANC, $\times 10^9$/L	10.49 (6.96–14.19)	7.58 (5.74–9.54)	**0.0100**
Platelets (at admission), $\times 10^9$/L	407.0 (328.0–475.5)	350.0 (267.0–496.0)	0.1103
Platelets, $\times 10^9$/L (peak)	704.5 (521.5–855.8)	638.0 (496.8–834.8)	0.8275
Bilirubin, μmol/L	11.45 (8.00–28.88)	7.5 (5.6–9.5)	**0.0013**
AST, U/L	41.0 (26.50–107.5)	33.0 (23.0–69.0)	**0.0177**
ALT, U/L	85.0 (21.0–171.0)	24.0 (16.0–76.5)	**0.0015**
GGT, U/L	90.0 (25.5–163.3)	29.0 (15.0–79.5)	**0.0109**
LDH, U/L	287.5 (249.0–457.5)	257.0 (223.0–312.5)	0.0138
Pyuria, >5 neutrophils/mm^3	32 (41.03%)	9 (27.27%)	0.2009
Proteinuria, >0.5 g/L	30 (38.46%)	11 (33.33%)	0.6711
Abnormal ECG[a]	43 (55.13%)	14 (42.42%)	0.2990
Abnormal radiological findings[b]	7 (10.9%)	7 (25.9%)	0.1088

Bold values are statistically significant ($p < 0.05$)

[a] 44 patients had sinus tachycardia, 5 nonspecific atrial repolarization changes, 8 depolarization disturbances

[b] Chest X–ray was performed in 91 patients; of 14 patients with abnormal findings 2 had enlarged heart shadow, 9 had pulmonary infiltrates (3 alveolar, 3 interstitial and 3 peribronchial), 2 had hilovascular hyperemia, and 1 had pleural effusion)

105 (94.6 %) ESR values. At the time of admission, 54 (48.6 %) patients had thrombocytosis and three were thrombocytopenic (2.7 %). Importantly, 37 patients (of 89; 41.6 %) had thrombocytosis adjusted for age in the first week of disease. In the second week of illness, 80 patients (72.1 %) developed thrombocytosis (546 × 10^9/L, IQR 423–714 × 10^9/L).

A total of 65 patients (58 %) had abnormal values of ALT and 46 (41.4 %) of AST. Comparison between patients with complete and incomplete KD showed a statistically significant difference in bilirubin level, AST, ALT, GGT and LDH (Table 2).

Treatment response

A total of 108 patients (97.3 %) were treated with IVIG. The median day of IVIG administration was the 7th day (IQR 6–9) of disease for patients with complete KD and the 8th (IQR 7–10) for those with incomplete KD, representing significant one-day delay ($p = 0.0157$). ASA was given to

Table 3 Multivariable analysis of epidemiological, clinical and laboratory findings of patients with KD as risk factors for the development CAA

Variable[a]	Adjusted odds ratio	95 % confidence interval	*p* value
Duration of symptoms before admission >6 days	7.16	1.51–100.35	0.0143
Age ≤6 months	25.86	1.58–398.35	0.0197
Thrombocytosis after 1st week ≥771 × 10^9	13.33	2.19–80.87	0.0049

[a] Statistically non-significant predictors such as male sex, serum sodium <136, admission platelets >568, CRP >81, and presence of major clinical criteria were progressively excluded from the model. The area under the ROC-curve in the fully adjusted binary logistic regression model was 0.897, which indicates a good discriminatory accuracy

all children (100 %). In seven children (6.3 %) fever did not resolve after the 1st IVIG, so the second dose was administered. After the second dose, fever resolved in all seven non-reactors. During the one-year follow up period, no mortality or recurrence were observed.

Cardiovascular complications and coronary aneurysm development

Cardiovascular complications were reported in 16 children (14.4 %); CAA in seven children (6.3 %; three in incomplete and four in complete group); pericarditis in 6 (5.4 %), myocarditis in 5 (4.5 %); congestive heart failure in 4 (3.6 %) and valvular regurgitation in 3 (2.7 %) patients. The prevalence of CAA was higher in incomplete ($n = 3$, 9.1 %) than complete form of KD ($n = 4$, 5.1 %).

Other significant findings reported were hydrops of the gallbladder in 21 cases (18.9 %) and aseptic meningitis in 28 cases (25.2 %). Nine children were admitted to the intensive care unit: five due to sepsis-like illness, three had cardiac failure and one was pancytopenic.

Identification of factors associated with CAA development

In multivariate analysis, none of the clinical signs were associated with CAA development. To explore continuous variables in the multivariable model, we dichotomized them at the following values: age <6 months, duration of fever before hospitalization <6 days, admission platelets >568, thrombocytes in the 2nd week ≥771 or serum sodium <136. In the final multivariable model, duration of fever before hospital admission >6 days, age ≤6 months and thrombocytosis ≥711 in the second week of disease were independently associated with CAA development (Table 3).

Disease presentation in young infants

Since infants ≤6 months represented 57.1 % of patients with CAA, we compared their characteristics with those of patients >6 months of age. There was no difference in disease form, duration of symptoms or degree of fever observed. Only 30.7 % of young infants had rash, compared with 90 % in older children ($p = 0.0075$). Interestingly, young infants had higher degree of thrombocytosis at admission (450 × 10^9/L vs. 379 × 10^9/L, $p = 0053$), in the 2nd week (709 × 10^9/L vs. 535 × 10^9/L, $p = 0.0012$) and peak thrombocyte count (860 × 10^9/L vs. 630 × 10^9/L, $p = 0.0004$), as compared to older counterparts. Furthermore, they were less likely to have elevated AST (7.7 vs. 45.9 %, $p = 0.0137$) and ALT (15.4 vs. 64.3 %, $p = 0.0016$) levels for their age.

Discussion

In the last decades, an increase in the prevalence of KD has been observed [5]. In Croatia there is no centralized reporting system for KD patients. Since our hospital serves as a referral center for all pediatric cases with presumptive infective etiology, the majority of KD cases are treated there. In the studied period, no significant changes in the number of KD cases were observed. While similar trends were published by authors from the Northern European countries, the incidence rates continuously rise in Asia, USA and the Western Europe [5, 6]. While seasonal fluctuations with high numbers in winter and low numbers in late summer and fall were reported in the Northern Hemisphere, in Croatia KD occurred equally throughout the whole year [7].

We noticed an increasing trend of diagnosing incomplete KD cases, which is higher than the 10–18 % reported in earlier studies [8–10]. This likely reflects both improved ascertainment after revision of diagnostic guidelines and a real increase in disease burden [8]. In Croatia, age and gender distribution mirrors that of other European populations. Importantly, children in European cohorts are significantly older than in Asia, but younger than those reported from Australia or USA, thus highlighting geographical differences in disease presentation [5, 6, 8, 10, 11].

Regarding clinical and laboratory risk factors for the development of CAA in patients with KD, we found that higher values of platelet count, age ≤6 months and hospital admission >6 days were significantly related to CAA. Previous studies show inconsistency in identification of

risk factors. Nevertheless, longer duration of fever prior to treatment, low serum albumin, age <1 year or >5 years and IVIG resistance are frequently reported as predictors of cardiovascular sequelae [12–16].

In our study, we did not find longer duration of fever as a predictor of CAA. This is probably due to the difference in the timing of IVIG administration. 86 % of studied patients received IVIG ≤10th day of disease, the time period in which IVIG administration significantly reduces the risk of CAA [3, 17]. Our practice is to administer IVIG to all patients, even if the interval is >10 days. However, the IVIG non-responder rate was significantly lower (6.8 %) than previously reported (10–25 %) [3, 18, 19].

Although thrombocytosis is a well-known laboratory marker of KD, the association with CAA development was not consistently reported; while the majority of studies showed no association, some recognized both thrombocytopenia and marked thrombocytosis as CAA predictors [20, 21]. Although the exact mechanism of thrombocytosis remains unknown, it is suggested that acute inflammatory response through elevated thrombopoietin levels drives thrombocytopoesis [22]. Here we suggested that platelets ≥771 in the 2nd week might serve as an additional predictor of CAA development.

Although infants ≤6 months represented the majority of patients with CAA in our study, this was not related with incomplete presentation, late diagnosis or treatment, elevated laboratory markers of inflammation, bilirubin, albumin or sodium levels, as previously reported [23, 24]. Instead, young infants had more pronounced thrombocytosis, which might reflect higher degree of inflammatory response [22].

Contradictory results regarding the development of CAA in incomplete KD have been reported. Incomplete KD is considered to be associated with higher risk of developing CAA due to the diagnosis and treatment delay [24, 25]. In the present study we did not find any difference in CAA incidence between complete and incomplete KD, despite the one-day delay in IVIG administration. Those groups seem to differ just in the number of signs and symptoms and have similar laboratory findings, except aminotranspherase levels.

The main limitations of this study include its retrospective design of data collection and a limited number of patients with CAA, as compared to Japanese and American studies. Therefore, a detailed subgroup analysis was not possible and cause–effect relationships could not have been determined. Nevertheless, in this study we analyzed a relatively large cohort of KD patients in Europe and provided the first report of KD in Croatia.

In conclusion, our findings highlight the absence of a uniform pattern of disease presentation and the need for better biomarkers to predict CAA development. Special consideration should be given to early recognition, especially in children <6 months and in patients with thrombocytosis that might suggest a more severe course of the disease.

Acknowledgments The authors thank Mrs. Arijana Pavelić for her help in the preparation of the manuscript.

Conflict of interest All the authors hereby declare that they have no conflicts of interest.

References

1. Freeman AF, Shulman ST (2006) Kawasaki disease: summary of the American Heart Association guidelines. Am Fam Physician 74(7):1141–1148
2. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R (1996) Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 94(6):1379–1385
3. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA, Committee on Rheumatic Fever E, Kawasaki Disease CoCDitYAHA (2004) Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. American Heart Association. Pediatrics 114(6):1708–1733. doi:10.1542/peds.2004-2182
4. Giannouli G, Tzoumaka-Bakoula C, Kopsidas I, Papadogeorgou P, Chrousos GP, Michos A (2013) Epidemiology and risk factors for coronary artery abnormalities in children with complete and incomplete Kawasaki disease during a 10-year period. Pediatr Cardiol 34(6):1476–1481. doi:10.1007/s00246-013-0673-9
5. Uehara R, Belay ED (2012) Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol 22(2):79–85
6. Salo E, Griffiths EP, Farstad T, Schiller B, Nakamura Y, Yashiro M, Uehara R, Best BM, Burns JC (2012) Incidence of Kawasaki disease in northern European countries. Pediatr Int 54(6):770–772. doi:10.1111/j.1442-200X.2012.03692.x
7. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodo X, Uehara R, Burgner D, Bainto E, Pierce D, Tyree M, Cayan D, Kawasaki Disease Global Climate C (2013) Seasonality of Kawasaki disease: a global perspective. PloS One 8(9):e74529. doi:10.1371/journal.pone.0074529
8. Ghelani SJ, Sable C, Wiedermann BL, Spurney CF (2012) Increased incidence of incomplete Kawasaki disease at a pediatric hospital after publication of the 2004 American Heart Association guidelines. Pediatr Cardiol 33(7):1097–1103. doi:10.1007/s00246-012-0232-9
9. Gorczyca D, Postepski J, Olesinska E, Lubieniecka M, Lachor-Motyka I, Opoka-Winiarska V, Gruenpeter A (2014) The clinical profile of Kawasaki disease of children from three Polish centers: a retrospective study. Rheumatol Int 34(6):875–880. doi:10.1007/s00296-013-2836-7
10. Lin YT, Manlhiot C, Ching JC, Han RK, Nield LE, Dillenburg R, Pepelassis D, Lai LS, Smythe JF, Chahal N, Yeung RS, McCrindle BW (2010) Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. Pediatr Int 52(5):699–706. doi:10.1111/j.1442-200X.2010.03092.x

11. Kim GB, Han JW, Park YW, Song MS, Hong YM, Cha SH, Kim DS, Park S (2014) Epidemiologic features of Kawasaki disease in South Korea: data from nationwide survey, 2009–2011. Pediatr Infect Dis J 33(1):24–27. doi:10.1097/INF.0000000000000010
12. Anderson MS, Todd JK, Glode MP (2005) Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. Pediatrics 115(4):e428–e433. doi:10.1542/peds.2004-1824
13. Kim T, Choi W, Woo CW, Choi B, Lee J, Lee K, Son C, Lee J (2007) Predictive risk factors for coronary artery abnormalities in Kawasaki disease. Eur J Pediatr 166(5):421–425. doi:10.1007/s00431-006-0251-8
14. Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RS (2012) Complete and incomplete Kawasaki disease: two sides of the same coin. Eur J Pediatr 171(4):657–662. doi:10.1007/s00431-011-1631-2
15. Nakamura Y, Yashiro M, Uehara R, Watanabe M, Tajimi M, Oki I, Ojima T, Sonobe T, Yanagawa H (2004) Use of laboratory data to identify risk factors of giant coronary aneurysms due to Kawasaki disease. Pediatr Int 46(1):33–38. doi:10.1111/j.1442-200X.2004.01840.x
16. Yellen ES, Gauvreau K, Takahashi M, Burns JC, Shulman S, Baker AL, Innocentini N, Zambetti C, Pancheri JM, Ostrow A, Frazer JR, Sundel RP, Fulton DR, Newburger JW (2010) Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. Pediatrics 125(2):e234–e241. doi:10.1542/peds.2009-0606
17. Patel A, Holman RC, Callinan LS, Sreenivasan N, Schonberger LB, Fischer TK, Belay ED (2013) Evaluation of clinical characteristics of Kawasaki syndrome and risk factors for coronary artery abnormalities among children in Denmark. Acta Paediatr 102(4):385–390. doi:10.1111/apa.12142
18. Son MB, Gauvreau K, Ma L, Baker AL, Sundel RP, Fulton DR, Newburger JW (2009) Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. Pediatrics 124(1):1–8. doi:10.1542/peds.2008-0730
19. Tacke CE, Breunis WB, Pereira RR, Breur JM, Kuipers IM, Kuijpers TW (2014) Five years of Kawasaki disease in the Netherlands: a national surveillance study. Pediatr Infect Dis J 33(8):793–797. doi:10.1097/INF.0000000000000271
20. Weng KP, Hsieh KS, Huang SH, Ou SF, Ma CY, Ho TY, Lai CR, Ger LP (2012) Clinical relevance of the risk factors for coronary artery lesions in Kawasaki disease. Kaohsiung J Med Sci 28(1):23–29. doi:10.1016/j.kjms.2011.09.002
21. Chen J, Liu Y, Liu W, Wu Z (2011) A meta-analysis of the biomarkers associated with coronary artery lesions secondary to Kawasaki disease in Chinese children. J Huazhong Univ Sci Technol Med Sci 31(5):705–711. doi:10.1007/s11596-011-0587-9
22. Ishiguro A, Ishikita T, Shimbo T, Matsubara K, Baba K, Hayashi Y, Naritaka S, Nakahata T (1998) Elevation of serum thrombopoietin precedes thrombocytosis in Kawasaki disease. Thromb Haemost 79(6):1096–1100
23. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH (2006) Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J 25(3):241–244. doi:10.1097/01.inf.0000202067.50975.90
24. Song D, Yeo Y, Ha K, Jang G, Lee J, Lee K, Son C, Lee J (2009) Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. Eur J Pediatr 168(11):1315–1321. doi:10.1007/s00431-009-0925-0
25. Ha KS, Jang G, Lee J, Lee K, Hong Y, Son C, Lee J (2013) Incomplete clinical manifestation as a risk factor for coronary artery abnormalities in Kawasaki disease: a meta-analysis. Eur J Pediatr 172(3):343–349. doi:10.1007/s00431-012-1891-5