

Five Years of Kawasaki Disease in the Netherlands

A National Surveillance Study

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Background: The aim of this study was to evaluate the incidence, disease presentation, treatment and cardiac outcome of Kawasaki disease (KD) in The Netherlands.

Methods: The national Dutch Pediatric Surveillance Unit was used to prospectively register new KD cases from 2008 through 2012. Questionnaires were sent to pediatricians to obtain clinical information.

Results: Nationwide 341 cases were reported during the 5-year study period, of which 319 questionnaires (93.0%) were returned. The mean incidence of KD was estimated to be 5.8/100,000 children <5 years of age. The median age at disease onset was 2.4 years (range 0.1–14.6 years) and 79.2% of cases were <5 years of age. The male-to-female ratio was 1.5 to 1. Incomplete KD was diagnosed in 22.3% of cases and these cases were significantly younger than complete cases [median: 1.1 (0.1–13.7) vs. 2.8 (0.2–14.6) years, $P < 0.001$]. In total, 308 patients (96.6%) received intravenous immunoglobulins (IVIG). Retreatment with IVIG was given in 71 (23.1%) and additional steroid treatment in 17 patients (5.5%). During the acute phase, coronary artery aneurysms developed in 43 cases (13.5%). Multivariate logistic regression analysis showed that male gender, delay of treatment (>10 days) and IVIG retreatment were independent risk factors for coronary artery aneurysms development.

Conclusions: This prospective study of KD in The Netherlands revealed a mean annual incidence of 5.8/100,000 children <5 years of age. Clinicians should consider the diagnosis of KD in young (male) children with persistent inexplicable fever to start IVIG treatment within 10 days to prevent development of coronary artery aneurysms.

Key Words: Kawasaki disease, coronary artery aneurysm, IVIG, cohort, incidence

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Kawasaki disease (KD) is an acute vasculitis that predominantly occurs in children <5 years of age. The disease was first described in 1967 in Japan by Tomisaku Kawasaki and has now been reported worldwide in all ethnic and racial groups.¹ The main complication of this rare disease is the development of coronary

artery aneurysms (CAA), which occurs in up to 25% of untreated patients and in 5–10% of patients adequately treated with high-dose intravenous immunoglobulins (IVIG) within 10 days after the disease onset. KD is the leading cause of acquired heart disease in developed countries. It is characterized by prolonged fever unresponsive to antibiotics in combination with a constellation of other features, including bilateral conjunctival injection, rash, erythema of the lips and oral mucosa, cervical lymphadenopathy and changes of the extremities.²

The etiology of the disease remains unknown, despite 4 decades of research. The leading hypothesis is that KD reflects an abnormal inflammatory response to 1 or more infectious triggers in genetically susceptible individuals. A genetic predisposition is supported by the striking difference in annual incidence between children of Asian (69–222 per 100,000 children <5 years of age) and European descent (4–15 per 100,000 children <5 years of age).^{3–7} The first case of KD in The Netherlands was reported in 1976.⁸ The aim of our study was to determine the incidence of KD in The Netherlands and to examine the demographic characteristics, treatment regimen and cardiac outcome in Dutch patients with KD.

MATERIALS AND METHODS

Surveillance System

The Dutch Pediatric Surveillance Unit (DPSU) is a national system for surveillance of rare and new diseases in infancy and childhood in The Netherlands. All clinically active pediatricians participate in the DPSU through the Dutch Pediatric Society. Pediatricians receive a monthly electronic card to register various disorders, which are under surveillance by the DPSU. For the period January 2008 to January 2013, KD was 1 of those diseases. Before the start of the registration, all pediatricians had obtained background information about the disease and instructions for registration of cases.

At the end of each month, cases were registered and subsequently the DPSU provided our KD study group with the names and contact addresses of the pediatricians who had reported 1 or more KD cases. The pediatricians received an online questionnaire for each reported case to collect clinical details on sex, age, ethnicity, clinical symptoms, laboratory results, treatment regimen and cardiac outcome. Personal details of the patients were limited to the initials and date of birth. This study was conducted according to the guidelines of our national and local ethics committee.

Clinical Data Collection

All cases aged 0–18 years with a diagnosis of complete or incomplete KD were included in the study. Complete KD was defined by the presence of ≥5 days of fever and ≥4 of the 5 classic criteria for KD.⁹ These classic criteria included (1) bilateral non-exudative conjunctival injection; (2) oral mucosal changes, such as erythema of the lips or strawberry tong; (3) changes of the extremities, such as edema, erythema and desquamation; (4) polymorphous rash and (5) cervical lymphadenopathy. Incomplete KD cases were defined according to the guidelines of the American Heart Association as patients with ≥5 days of fever and <4 classic criteria, but who had

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CAAs upon echocardiography or a set of suspect laboratory criteria.² These laboratory criteria include C-reactive protein (CRP) $\geq 30\text{ mg/L}$, and ≥ 3 of the following supplemental laboratory criteria: albumin $<30\text{ g/L}$, anemia for age, elevation of alanine aminotransferase, platelets after day 7 $\geq 450 \times 10^9/\text{L}$, white blood cell count $\geq 15 \times 10^9/\text{L}$ and urine ≥ 10 white blood cells/high-power field (in the absence of a positive culture). Cases were excluded if they were duplicate reports or known errors of reporting, which included incorrect diagnosis or diagnosis outside the study period.

Results of 2-dimensional echocardiography during the acute phase and at least 8 weeks after the acute phase were collected. CAA were defined according to criteria established by the Japanese Ministry of Health in 1984, that is, a lumen diameter $>3\text{ mm}$ in children <5 years, $>4\text{ mm}$ in those >5 years or a diameter 1.5 times the size of an adjacent segment or an irregular lumen.¹⁰

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences version 20.0 for Windows. Data are expressed as mean \pm standard deviation (SD), median with range or number with percentage as appropriate. Descriptive statistics were performed on the demographic characteristics. Parametric and nonparametric comparative tests for continuous data and χ^2 test for categorical data were used to compare variables between groups. Multivariate logistic regression analysis was performed to analyze risk factors for CAA development. The odds ratio (OR) and 95% confidence intervals were reported. $P < 0.05$ was considered statistically significant. The annual incidence rates of KD in The Netherlands were calculated based on census data from Statistics Netherlands (Centraal Bureau voor Statistiek).

RESULTS

Report of Cases

During the 5-year study period from 2008 through 2012, the mean return rate of the electronic cards was 84%. In total, 384 KD cases were reported by the clinicians. Forty-three cases were excluded because of duplicated reports ($n = 38$) or known errors of reporting ($n = 5$). The median age at disease onset of the remaining 341 cases was 2.6 years (range 4 weeks to 14.6 years). Many patients (270/341 = 79.2%) were <5 years of age and 79 patients (23.2%) were <1 year of age at the onset of KD (Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/B810>, which shows the distribution of age at the onset of disease).

Incidence Rates

Based on the census data provided by Statistics Netherlands, the mean annual incidence of KD in The Netherlands was calculated (Table 1). From 2008 through 2012, the annual incidence was estimated to be 5.8 per 100,000 children under the age of 5 years and 8.7 per 100,000 children under the age of 1 year (Table 1). The annual number of reported cases under the age of 5 years varied

between 47 and 60 per year, corresponding to an annual incidence rate between 5.1 and 6.3 per 100,000 children. The annual incidence in the age group of <1 year showed more variation, with the lowest incidence in 2010 (5.4/100,000 children) and the highest incidence in 2008 (12.4/100,000 children).

The Netherlands is divided into 12 provinces. The incidence of KD per province for the 5-year study period is shown in Figure 1A. The incidence of KD was higher in the provinces with a higher density of population (Fig. 1B).

Seasonal Distribution of KD

The seasonal distribution is shown in Figure 2. The number of cases peaked in the winter months of December and January during the 5-year study period (Fig. 2A). During the 5-year period, the onset of KD occurred most frequently in winter (101 cases, 29.6%), followed by spring (85 cases, 24.9%), autumn (84 cases, 24.6%) and summer (71 cases, 20.8%).

Patient Characteristics

Questionnaires about the clinical characteristics were returned by the pediatricians for 319 of the 341 cases (response rate 93.5%). The characteristics of these patients are described in Table 2. There were 193 males (60.5%) and 126 females (39.5%), providing a gender ratio of 1.53 to 1. Ethnicity was reported in 281 patients (88.1%). Of these 281 patients, 180 (64.1%) were reported to be of Caucasian origin. Of the remaining 101 cases (35.9%), either 1 or both of the parents were of non-Caucasian origin (among others: Chinese, Japanese, Vietnamese, Moroccan and Turkish).

All patients had persistent fever for ≥ 5 days, except for 13 patients (4.4%) who were treated on day 3 or 4. Rash was reported in 285 cases (89.6%), conjunctival injection in 276 (87.1%), oral mucositis in 277 (87.4%), changes of the peripheral extremities in 247 (77.4%) and lymphadenopathy in 228 cases (71.9%). Other clinical manifestations that were reported included gastrointestinal symptoms (ie, diarrhea, vomiting and abdominal pain; 26.3% of cases), arthritis/arthralgia (10.3%), coughing (16.9%), otitis media (11.9%) and jaundice (1.9%).

Incomplete KD with persistent fever and <4 clinical criteria was diagnosed in 71 patients (22.3%). Cases with an incomplete presentation were significantly younger than those patients with a complete presentation [median age, 1.1 years (range: 0.1–13.7) vs. 2.8 years (range 0.2–14.6), $P < 0.001$]. The median duration of hospitalization was 6 days (range: 1–71 days). The period of hospitalization was significantly longer in incomplete cases compared with the complete cases [median duration: 7 days (range 1–71 days) vs. 5 days (range: 1–47), $P = 0.007$]. Eleven patients (3.4%) were admitted to the pediatric intensive care unit for circulatory and/or respiratory support. No deaths were reported.

Laboratory Parameters

The mean laboratory values at admission before IVIG infusion are given in Table 2. Laboratory values were available in the

TABLE 1. Incidence Rates of KD in The Netherlands (2008–2013)

Year	Population <1 Year	Cases <1 Year	Incidence Rate*	Population <5 Years	Cases <5 Years	Incidence Rate†
2008	180,762	23	12.7	945,727	60	6.3
2009	184,408	17	9.2	931,556	51	5.5
2010	184,586	10	5.4	924,881	47	5.1
2011	184,007	13	7.1	923,106	57	6.2
2012	179,653	16	8.9	918,736	55	6.0
Total	913,416	72	8.7	4,644,006	270	5.8

*Incidence rate per 100,000 children under the age of 1 year.

†Incidence rate per 100,000 children under the age of 5 years.

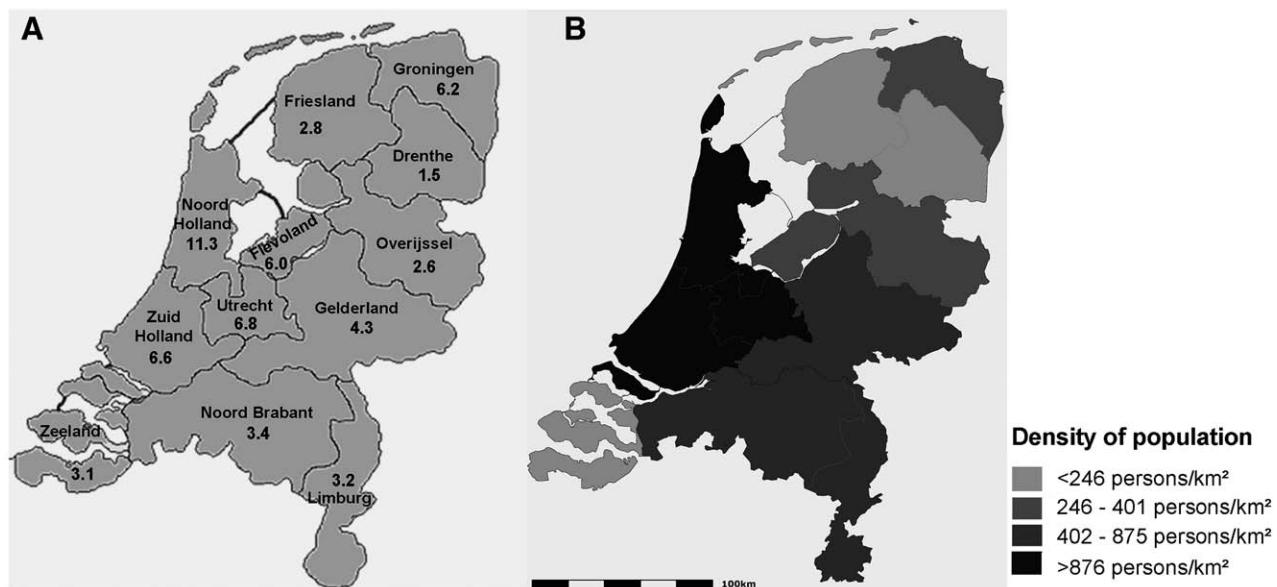


FIGURE 1. This figure shows A) the annual incidence of KD per province in The Netherlands during the 5-year study period and B) the density of the total population of the different provinces. In the different provinces of The Netherlands, the densities of the population of children <5 years of age follow a similar distribution as the densities of the total population: <13.5 children <5 years of age per km² in Drenthe, Friesland and Zeeland; 13.5–21 children/km² in Flevoland, Groningen and Overijssel; 21–50 children/km² in Gelderland, Limburg and Noord-Brabant and >50 in Utrecht, Noord-Holland and Zuid-Holland.

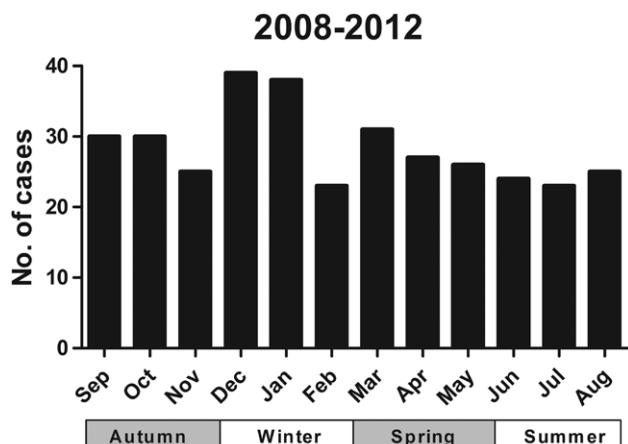


FIGURE 2. Monthly distribution of Kawasaki cases in The Netherlands for the total study period from 2008 through 2012.

following numbers of cases: hemoglobin in 290 cases (90.9%), CRP in 299 (93.7%), white blood cell count in 294 (92.2%), platelet count in 289 (90.6%) and albumin in 167 cases (52.4%). Incomplete cases had significantly lower albumin values at admission compared with complete cases (29.3 ± 6.2 vs. 32.8 ± 6.7 , $P = 0.005$).

Treatment

All patients received high-dose IVIG treatment (2 g/kg), except for 11 patients (3.4%) in whom the diagnosis was initially missed. In 8 of these 11 patients, treatment with high-dose aspirin was started when KD was diagnosed. The 3 remaining patients did not receive aspirin. A fourth patient was not treated with aspirin because he was known with hemophilia A.

Treatment was started within 10 days in 249 of the 308 patients (80.8%) who were treated with IVIG. Incomplete cases received IVIG about 1 day later than the complete cases [median, 8 days (3–46) vs. 7 days (3–28), $P = 0.020$] and the percentage of patients adequately treated within 10 days after the onset of fever was significantly lower (69.7% vs. 84.2%, $P = 0.008$). In 71 of the treated patients (23.1%), a second dose of IVIG was administered because of persistent or recrudescent fever after the initial IVIG dose. Seventeen treated patients (5.5%) also received treatment with steroids. Additional treatment with infliximab was reported in 2 IVIG non-responders, and the interleukin-1 receptor antagonist Anakinra was given in 1 case. Side effects of IVIG were reported in 7 patients (2.2%) and included hypotension, tachycardia, itching and rash. There was no difference between IVIG responders (1 dose of IVIG) and IVIG non-responders (IVIG retreatment) in terms of gender, age at disease onset, KD presentation or laboratory results.

Echocardiography

Results of echocardiography during the acute phase were available in all patients except for 1 female patient. Echocardiography results at 8-week follow up were missing in 3 patients. CAA was diagnosed at echocardiographic evaluation in 43 cases (13.5%) during the acute phase. In 18 of these patients (5.6%), the abnormalities persisted after >8 weeks. Giant aneurysms were identified in 3 male patients, 2 of them were aged <1 year and had an incomplete disease presentation. All three patients were IVIG non-responders. When compared with non-CAA patients, the proportions of male subjects, incomplete cases, young patients (<1 year of age), IVIG non-responders and patients with delayed treatment (>10 days) were higher in the patients with CAA (Table 2). The mean value of CRP and platelet count were increased, and hemoglobin and serum albumin were decreased in CAA-positive patients compared with CAA-negative patients (CRP: 167 ± 107 vs. 134 ± 93 , $P = 0.048$; platelet count: 519 ± 280 vs. 389 ± 165 , $P = 0.010$; hemoglobin: 6.5 ± 0.7

TABLE 2. Characteristics of the 319 Patients With KD in The Netherlands (2008–2013) for Whom the Questionnaires Were Returned by the Pediatricians

	Total	Incomplete	Complete	P	CAA Positive *	CAA Negative *	P
Total group	319 (100)	71 (22.3)	248 (77.7)	NS	43 (13.5)	275 (86.2)	NS
Gender							
Male	193/319 (60.5)	44/71 (62.0)	149/248 (60.1)	NS	37/43 (86.0)	156/275 (56.7)	<0.001
Age at disease onset							
Age in years, median (range)	2.4 (0.1–14.6)	1.1 (0.1–13.7)	2.8 (0.2–14.6)	<0.001	1.7 (0.1–11.3)	2.7 (0.1–14.6)	0.036
<1 yr	75/319 (23.5)	34/71 (47.9)	41/248 (16.5)	<0.001	16/43 (37.2)	58/275 (21.1)	0.022
<5 yrs	255/319 (79.9)	59/71 (83.1)	196/248 (79.0)	NS	37/43 (86.0)	217/275 (78.9)	NS
Laboratory results							
Hemoglobin in mmol/L, mean ± SD	6.8 ± 0.7	6.7 ± 0.9	6.9 ± 0.7	NS	6.5 ± 0.7	6.9 ± 0.7	0.027
White cell count × 10 ⁹ /L, mean ± SD	16.5 ± 7.1	17.2 ± 7.8	16.3 ± 7.0	NS	16.5 ± 6.9	16.5 ± 7.2	NS
Platelet count × 10 ⁹ /L, mean ± SD	405 ± 187	440 ± 245	394 ± 165	NS	519 ± 280	389 ± 165	0.009
CRP in mg/L, mean ± SD	138 ± 95	128 ± 87	141 ± 98	NS	167 ± 107	134 ± 93	0.047
Serum albumin in g/L, mean ± SD	32.0 ± 6.7	29.3 ± 6.2	32.8 ± 6.7	0.005	29.2 ± 4.7	32.5 ± 6.9	0.021
Treatment							
High-dose IVIG	308/319 (96.6)	67/71 (94.4)	241/248 (97.2)	NS	40/43 (93.0)	267/275 (97.1)	NS
Start IVIG, median (range)	7 (3–46)	8 (3–46)	7 (3–28)	0.018	8 (3–46)	7 (3–28)	0.007
Start IVIG within 10 days	249/308 (80.8)	46/67 (68.7)	203/241 (84.2)	0.007	25 (62.5)	223 (81.1)	0.004
Repeat dose IVIG	71/308 (23.1)	16/67 (23.9)	55/241 (22.8)	NS	16/40 (40.0)	55/267 (20.6)	0.011
Steroids	17/308 (5.5)	5/67 (7.5)	12/241 (5.0)	NS	7/40 (17.5)	10/267 (3.7)	0.001
Infliximab	2/308 (0.6)	1/67 (1.5)	1/241 (0.4)	NS	2/40 (5.0)	0/267 (0.0)	0.018
Anakinra	1/308 (0.3)	0/67 (0.0)	1/241 (0.4)	NS	1/40 (2.5)	0/267 (0.0)	NS

Data presented as no (%), unless otherwise indicated.

P values indicate comparison of incomplete cases versus complete cases, and CAA-positive versus CAA-negative patients, respectively.

*Echocardiography results were not available for 1 patient.

NS, not significant.

vs. 6.9 ± 0.7 , $P = 0.014$; serum albumin: 29.2 ± 4.7 vs. 32.5 ± 6.9 , $P = 0.021$). Multivariate logistic regression analysis was performed to assess the effect of individual factors on CAA development. Laboratory variables were removed from the analysis to limit the number of variables in the model and because 10% and 47% of the laboratory values were missing. Multivariate analysis showed that male gender, delay of treatment (>10 days) and IVIG non-responsiveness were independent risk factors of CAA development (Fig. 3).

DISCUSSION

This is the first prospective epidemiological study of KD in The Netherlands. Our study revealed a mean annual incidence of 5.8 per 100,000 children <5 years of age from 2008 through 2012. As expected, this incidence is very different from the high incidence observed in Japan and other Asian countries (Table,

Supplemental Digital Content 2, <http://links.lww.com/INF/B811>, which shows the annual incidence of KD in different countries worldwide).^{5–7} The annual incidence varied between 5.1 and 6.3 during our 5-year study period. These incidences fall within the range from 3.6 to 15.2 reported in other European studies.^{3,4,11–15} The mean incidence in our study is relatively low, which could be explained by the method used. Despite the prospective surveillance system with a response rate of $>85\%$, some cases may not have been reported by the pediatricians. In addition, cases may have been missed because of the public health system in The Netherlands, where general practitioners see the children before referral to the pediatrician. Although general practitioners follow national guidelines to contact a pediatrician after 3 days of persistent fever (and earlier in infants and very young children), it is possible that they miss cases of KD because they are generally unaware of this rare disease. In addition, pediatricians may also underdiagnose KD because of the obvious resemblance with infectious disease and the lack of any diagnostic test. We therefore believe that the incidence of 5.8 per 100,000 children <5 years of age should be taken as a minimum estimate of the true incidence of KD in The Netherlands.

A remarkable finding on the incidence rates is that it seems to be related to the population density which varies throughout the country. We observed a difference in the incidence of KD within the different provinces of The Netherlands with the highest incidences in the most densely populated provinces. Urbanization and industrialization have been previously suggested to be related to the occurrence of KD,¹¹ which may be accompanied by important sociocultural differences between the highly populated areas and the agricultural regions in The Netherlands.

Cases of KD were reported throughout the year, but peaked in the winter months of December and January. In 30% of cases, the onset of KD occurred in winter. This is in agreement with the results of a recent large study by Burns et al¹¹ with data from >25 countries distributed over the globe. In this study, a statistically significant seasonal cycle was observed in the Northern Hemisphere extra-tropics with the highest numbers in winter months.

FIGURE 3. Risk factors associated with the development of coronary artery aneurysms in Dutch patients with KD reported to the Dutch Pediatric Surveillance Unit (2008–2013). Results of the multivariate logistics analysis are shown as OR with 95% confidence intervals.

The beneficial effect of IVIG treatment on the development of CAA and duration of fever is well-recognized in KD.¹⁶ Patients should be treated with IVIG (2 g/kg) in a single infusion over 10–12 hours, rather than multiple infusions (400 mg/kg/d for 4–5 consecutive days), as was advocated before 1991.¹⁷ In our study, 96.6% of patients were treated with IVIG, and the patients all received IVIG in a single infusion of 2 g/kg. Delay of treatment after 10 days has been described as a risk factor for CAA development, which was confirmed in our study.¹⁸ More than 80% of the Dutch patients were treated within 10 days. Although treatment was started later in the incomplete cases than in the complete cases, many of the incomplete patients (69%) also received IVIG treatment within 10 days after the onset of fever. These observations support our idea that Dutch pediatricians are aware of the disease and treat possible cases adequately. However, we should still aim at enhancing awareness of KD to increase the number of patients diagnosed and adequately treated within 10 days to minimize the CAA rate.

In 23% of the Dutch patients, a second dose of IVIG was administered, which is comparable to other studies.¹⁶ The optimal treatment for IVIG non-responsive patients remains controversial as controlled trial data are lacking to date. The current recommendations of the American Heart Association are to administer a second dose of IVIG in patients non-responsive to the first dose of IVIG and to limit treatment with steroids to those children in whom 2 IVIG infusions were ineffective.² All 71 non-responsive patients received a second dose of IVIG. Steroids were subsequently administered in the 17 patients not responding to the 2 prior infusions of IVIG. Infliximab was used in 2 patients who were non-responsive to retreatment with IVIG and steroids and suffered from severe coronary artery pathology. The interleukin-1 receptor antagonist Anakinra was given in 1 case with a beneficial outcome, as we had previously reported.¹⁹

The overall proportion of children with CAA was 13.5% during the acute phase. Most patients had transient abnormalities and only 5.6% of all cases had persistent CAA after 8 weeks. This is in agreement with other studies reporting an incidence between 5% and 10%.^{2,17} Regarding risk factors of CAA development in patients with KD, we found that male gender, IVIG non-responsiveness and delay of treatment were risk factors. A large study in 15,940 Japanese patients also reported in IVIG non-responders a significantly higher risk of CAAs (OR: 10.4 with 95% confidence intervals: 7.0–15.5) and giant CAAs (OR: 54.1 with 95% 12.8–227.7). In our study, only 3 patients developed giant CAAs. These were all IVIG non-responders.

The strength of our study was the use of a prospective surveillance system with participation of all clinically active pediatricians in the country. However, our study must be viewed in the light of some limitations. First, some cases of KD may not have been reported leading to an underestimation of the real KD incidence. Second, the availability of data was limited to those details asked and returned by the pediatricians. Third, patients were stratified for CAA based on the Japanese Ministry of Health criteria instead of z-scores with adjustment for body surface area, and some patients with mild coronary dilatations may therefore be misclassified as normal.²⁰ The Japanese definition is still routinely used in The Netherlands to identify CAA. We tried to collect data of length and weight of the patients to calculate z-scores ourselves, but too many data were not returned by the pediatricians. However, McCrindle et al²¹ studied independent risk factors for CAA development before and found the same results with the use of either the Japanese definition or z-scores.

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