Incidence, epidemiology and clinical features of Kawasaki disease in Catalonia, Spain

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ABSTRACT

Objective. *To assess the incidence, epidemiology and clinical features of Kawasaki disease (KD) in Catalonia (northeast region of Spain).*

Methods. *This was an observational population-based study including all Paediatric Units in Catalonia, under both public and private management. Retrospective data retrieval was performed for 10 years (2004–2013). A 12-month (March 2013 to March 2014) prospective collection of new cases of KD was carried out to determine the incidence of KD.*

Results. *Data from 399 patients over the 10-year study period was analysed, revealing that 233 (58.4%) had complete KD, 159 (39.8) incomplete KD and 7 (1.7%) were considered atypical KD. Mean annual incidence was 3.5/10^5 children <14 years old (yo) and 8/10^5 children <5 yo (mean age 37±33 months, range 1.3–191.3). KD was more frequent in boys (59.6%, p<0.001) and in rural areas (p<0.001). Patients with IVIG non-responsiveness, need of a 2nd IVIG dose, delay of treatment >10th day of illness, ages <1 yo and >8 yo and the presence of sterile piuria, aseptic meningitis, abdominal pain and uveitis at diagnosis were found to have higher risk of coronary aneurisms (CAA) (p<0.05).*

Conclusion. *This is the first population-based study on the epidemiology of KD in the western Mediterranean area. Incidence, clinical features and treatment plans in our cohort are similar to those described in other European studies.*

Introduction

Kawasaki disease (KD) is an acute self-limited systemic vasculitis of unknown aetiology presenting predominantly in toddlers and children under 5 years old (yo). It was described for the first time by Tomisaku Kawasaki in 1967.

Diagnosis is based on clinical criteria that include fever, exanthema, conjunctivitis, changes in the extremities, erythema of oral mucosa and lips and cervical lymphadenopathy. Prognosis depends on the extent of cardiac involvement; coronary aneurysms develop in 20–25% of untreated patients and these may lead to myocardial infarction and sudden death if properly treatment is not administered (1, 2).

The aetiology of KD is still unknown, although clinical, laboratory and epidemiological features suggest an infectious origin or trigger. However, many studies have failed to identify a unique aetiological infectious agent. It has not been proved to be related to exposure to any specific drug or in response to a super-antigen. On the other hand, activation of immune system is an evident characteristic of KD, and concentrations of many pro-inflammatory cytokines and chemokines are being studied in patients with KD, which may lead to improved anti-inflammatory therapy in the future (3). Some genome-wide association studies (GWAS) in KD have been published (4-6) and a number of biologically plausible loci involved in inflammation, immune responses and cardiovascular status have been identified. In the largest study to date (5), involving 2173 individuals with KD and 9383 controls from five independent sample collections, two variants exceeded genome-wide significance. The most significantly associated variants were a non-synonymous polymorphism in a high affinity receptor for immunoglobulin G (FCGR2A) and variants in the region of the T-cell regulator ITPKC, originally reported

in the Japanese. A reasonable open hypothesis for the aetiology of the disease is that KD is caused by a trigger (probably an infectious agent) that produces disease only in genetically predisposed individuals, particularly Asians (2).

Although KD is more prevalent in Asian countries, especially in Japan, with an annual incidence that has raised to 264.8 per 100,000 children under 5 yo in 2012 (7), it has an universal distribution and can be manifested in children of any ethnicity. In the US (8), KD has a global hospitalisation rate of 17.1 per 100,000 children, with higher incidence among Americans of Asian and Pacific Island descent (32.5/100,000 children <5 yo). In Europe, some studies establish KD incidences between 4.9 per 100,000 children under 5 yo in Denmark (9) to 9 per 100,000 children in France (10). In Spain, KD epidemiological studies are based on case series and retrospective reviews. One of the most recent published work took place from 1999 to 2002 in some hospitals in Madrid and it showed an incidence of 15.1/100,000 children <5 yo (11).

Materials and methods

Data source

Observational population-based study, including data of patients from all Paediatric Units in 33 hospitals in Catalonia (Spain), a 7.5 million population area.

A researcher was designated in each collaborating centre in order to complete data collection. A 12-month (March 2013 to March 2014) prospective collection of new cases of KD was carried out to determine the incidence of KD. Retrospective data retrieval was performed for 10 years (2004–2013).

The approval of the ethics committee of the coordinating centre (Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain) and the informed consent of patients or their guardians was obtained before initiating the study. All the procedures followed were in accordance with the standards of the Helsinki Declaration of 1975/83.

Case definition

All patients under 16yo who had been diagnosed with KD in their origin hospitals were included in the study. Complete KD was defined by the presence of ≥5 days of fever and ≥4 the 5 classic criteria for KD. 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 (oedema, erythema and/or desquamation); (4) polymorphous rash and (5) cervical lymphadenopathy. Incomplete KD cases were defined according to the guidelines of the American Heart Association (2) as patients with ≥5 days of fever and 2 or 3 classic criteria, but who had CAAs upon echocardiography. Atypical KD was defined as the disease that, although fulfilling classic criteria, had no typical features of the disease, such as renal failure or pulmonary impairment.

Exclusion criteria were: those patients that do not fulfill the KD criteria, those whose fever duration data was missing and those who, despite having KD diagnosis established in another Spanish area were admitted for a second opinion.

Among the patients included in the prospective phase of the study, an informed consent was mandatory to participate.

Epidemiological, clinical and analytical information was collected for all patients. The presence of coronary aneurisms (CAA) and treatment plans were based on the z-scores and the criteria established in the 2004 guidelines of the American Heart Association (2). The echocardiography examinations were performed by paediatric cardiologists in all participant centres.

Analyses

Data collection was carried using a standardised questionnaire and a Microsoft Office Access 2007 database. For the statistical analysis it was used the statistical software SPSS 19.0 (Armonk, NY: IBM Corp.)

Data are expressed as mean ± standard deviation, median with range or number with percentage as appropriate. Parametric and nonparametric comparative tests for continuous data and χ^2 test for categorical data were used to compare variables between groups. The odds ratio (OR) and 95% confidence intervals were reported. $p<0.05$ was considered statistically significant. The annual incidence rates of KD in Catalonia and comparison with rural population and ethnicities were calculated based on census data from the Catalonia Statistics Institute (IDESCAT). Rural areas were defined as towns and cities with <2000 inhabitants.

Results

Report of cases and incidence rates

During 2004–2014, there were 399 KD cases diagnosed in Catalonia. Of those, 233 (58.4%) had complete KD, 159 (39.8%) incomplete KD and 7 (1.7%) were considered atypical KD. Mean annual incidence was 3.5/100,000 children <14 yo and 8/100,000 children <5 yo. Incidence distribution during the study period is shown in Figure 1.

Mean delay between onset of the disease and diagnosis was 7.2±5.3 days.

Analysing the seasonality and burden of cases, it was found that KD in Catalonia was more frequent in January and November and less frequent in October ($p<0.001$) (Fig. 2).

Patients' characteristics and laboratory parameters

There were 161 females (40.4%) and 238 males (59.6%). KD was more frequent among boys ($p<0.001$) and mean age was 37±33 months (range 1.3-191.3). Gender and KD subtypes distribution of the patients are shown in Table I. Assessing the presence of KD among children <1 yo or >8 yo, it was found that 25.8% of our patients were on the extremes of the age spectrum.

Among the 399 patients, 353 (88.5%) lived in non-rural areas (towns and cities with >2000 inhabitants) and 46 (11.5%) in rural areas. There is a significant difference ($p<0.001$) between the percentage of rural population observed in patients with KD (11.5%), and the expected 5% of the Catalan population.

Ethnicity was reported in 344 patients (86.2%). Of these, 279 (81.1%) were reported as Caucasian, 26 (7.5%) had a North African origin, 21 (6.1%) Amerindian, 14 (4.1%) Asian and 4 (1.2%) Sub-Saharan. A significant difference ($p<0.001$) between the percentages of ethnic groups observed in patients

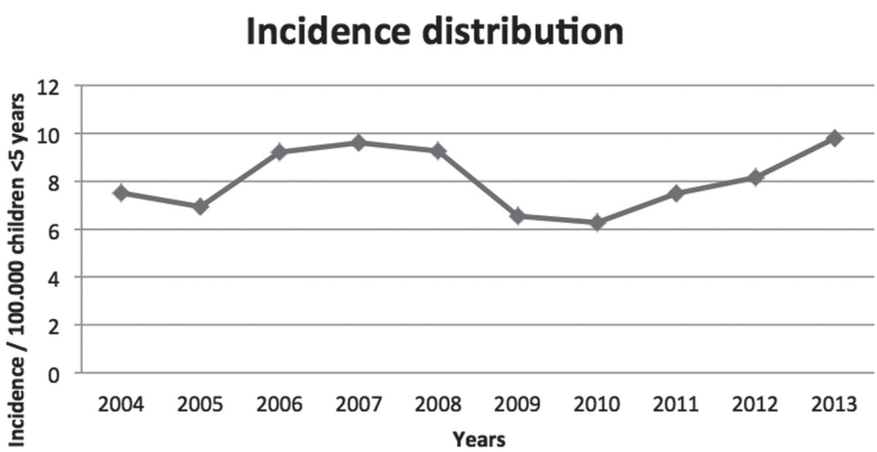

Fig. 1. Incidence distribution during de 10-year study period.

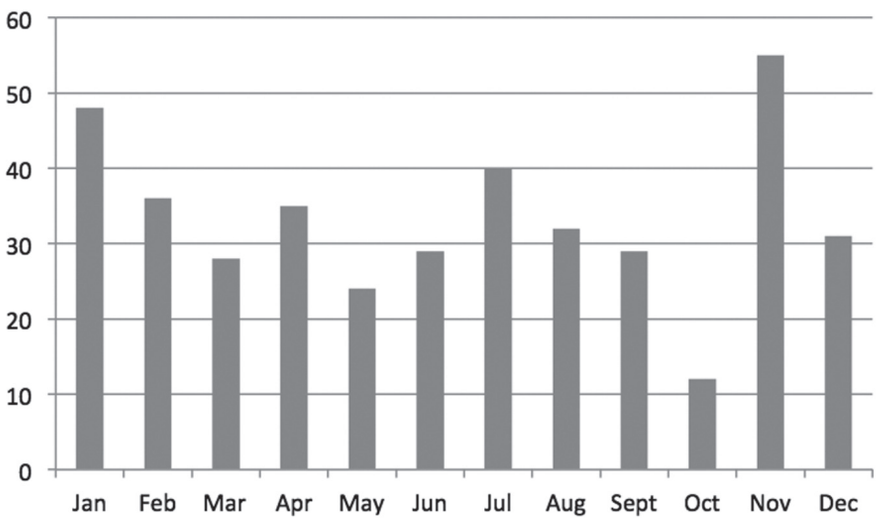

Fig. 2. Seasonal distribution.

Table I. Gender and KD subtypes distribution of the patients.

	Complete KD (n=233)	Incomplete KD (n=159)	Atypical KD (n=7)
Sex, n (%)			
Male	137 (58.8%)	97 (61%)	4 (57.1%)
Female	96 (41.2%)	62 (39%)	3 (42.9%)

Table II. Clinical findings.

Variable	n (%)
Classical criteria	
Conjunctivitis	318 (79.7%)
Lips and oral changes	
Cracked lips	262 (65.7%)
Strawberry tongue	222 (55.6%)
Pharyngitis	198 (49.6%)
Changes in extremities	
Oedema	131 (40.4%)
Erythema	116 (29%)
Desquamation	124 (31%)
Exantema	336 (84.2%)
Lymphadenopathy	
>1.5cm	115 (28.8%)
<1.5cm	14 (3.5%)
Multiple	110 (27.6%)
Other findings	
Sterile piuria	80 (20.1%)
Haematuria	11 (2.8%)
Irritability	119 (29.6%)
Aseptic meningitis	16 (4%)
Encephalitis	1 (0.3%)
Dolor abdominal	85 (21.3%)
Vomiting or nausea	96 (24.1%)
Arthralgia	55 (13.8%)
Arthritis	11 (2.8%)
Uveitis	11 (2.8%)
Transaminase elevation	120 (30.1%)
Jaundice	21 (5.3%)
Pancreatitis	3 (0.8%)
Bronchospasm	5 (1.3%)
Pneumonia	10 (2.5%)
Gallbladder distention	14 (3.5%)

with KD and those in the Catalan population has been found. In Catalonia, the disease is more common in non-Caucasian ethnicities. Among the non-Caucasians, the ones that present a higher proportional difference between the observed and the expected proportion are the Asian and the North African patients.

Clinical and blood-tests features in our population are shown in Tables II and III. Cardiologic findings were: perivascular brightness of the coronary wall in 42 (10.5%) patients, pericarditis in 9 (2.3%), mitral regurgitation in 28 (7%), myocarditis in 4 (1%) and CAA in 53 patients (13.3%). Among the 53 patients with CAA, 22 (21.4%) had <1 yo or >8 yo, 26 (49%) had normal echocardiography at the 2nd month from KD onset and 4 (1%) patients had giant CAA. We studied the association between analytical features and clinical and heart-related complications. Lower levels of haemoglobin (<10g/dL) and sodium (<132mEq/L) and higher levels of AST (>40U/L) were related to higher risk for suffering perivascular brightness of the coronary wall, myocarditis and mitral regurgitation but not statistically related to the risk of CAA. Patients with gallbladder distention and vomiting had higher risk of brightness of the coronary wall and mitral regurgitation and those with sterile piuria, aseptic meningitis, abdominal pain and uveitis had higher risk of CAA (p<0.05). Among patients at the extremes of the age spectrum (<1 yo or >8 yo) there was a significant higher risk of developing CAA (p=0.004) with an OR of 2.408 (CI 95%, 1.317–4.405).

Mean admission days required number was 4.38±6.99 (range 0-45). Ten patients (2.5%) were admitted at intensive care units and 217 (54.4%) needed more than 5 days of admission, these patients having a higher risk of CAA. Of the 399 reported cases, 382 (95.7%) were followed for at least 2 months after discharge; echocardiography at the 2nd month after onset was performed in 311 patients (77.9%) and analytical

controls (platelet count and CPR monitoring) in 291 (73%).

No differences between patients included in the retrospective and the prospective phase of the study were found regarding clinical and laboratory findings or the risk of cardiac complications.

Treatment plans

Intravenous immunoglobulin (IVIG) was administered to 385 (96.5%) patients with a mean day of IVIG administration of 7.5±3.1. Of those, 249 (64.7%) patients received IVIG between 4th and 7th day of illness, 86 (22.3%) between 8th and 10th day and 48 (12.5%) patients received IVIG after 10th day of illness. A significant relationship between treating with IVIG after 10th day of fever and the presence of CAA was found (p<0.001). No differences between treating from 4th-7th day or treating from 8th–10th day were found.

Response to the 1st IVIG dose was found in 332 (86.2%) patients. Among the 53 (13.8%) patients that did not respond to the 1st IVIG dose, 46 (86.8%) received a 2nd dose with complete response in 32 (69.6%). Patients in need of a 2nd dose of IVIG were at higher risk of developing CAA (p=0.020). Only 7 patients received a 3rd IVIG dose, no statistically significance was found between the need of a 3rd IVIG dose and the presence of CAA. Sixty-nine (17.3%) of the treated patients also received oral or IV steroids.

Three of the four patients with giant CAA received abciximab. There was no registry of patients receiving other treatment plans like infliximab, anakinra, cyclosporine or plasma exchange. During the acute phase, 369 (92.5%) of patients received oral non-steroidal anti-inflammatory drugs (NSAIDs), either aspirin (100 mg/kg/day) or ibuprofen (30–40 mg/kg/day) until the disappearance of the fever. In the convalescence phase, once the fever disappeared, 390 (97.7%) patients received anti-platelet dose aspirin.

Table III. Laboratory findings.

Variable (units)	Mean±SD (range)
ESR (mm/h)	66.33 ± 48.57 (1-567)
CPR (mg/L)	121.70 ± 90.38 (0.8-668)
PCT (ng/mL)	4.57 ± 1.91 (0.05-94)
Haemoglobin (g/dL)	11.19 ± 1.31 (7.8-18)
Platelets (xmm^3)	426,703 ± 221,306 (30,900-2,850,000)
AST (UI/L)	58.36 ± 4.67 (10-769)
ALT (UI/L)	70.31 ± 5.45 (6-863)
Sodium (mEq/L)	135.39 ± 3.93 (123-165)
Albumin (g/L)	3.5 ± 0.7 (2-7)
Proteins (g/L)	6.83 ± 4.2 (2-9)
NT-proBNP (ng/L)*	816.9 ± 488.44 (6-5759)
CPK (UI/L)	45.15 ± 36.46 (11-192)

*NT-proBNP only available in 12 patients. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; NT-proBNP: amino-terminal pro B-natriuretic peptide.

Table IV. KD incidence in Europe.

Country	Incidence in children <5 years	Reference
Finland	3.1-7.2/100000	Salo 1993
England	4/100000	Harnden 2002
Denmark	4.5-5/100000	Fischer 2007
Netherlands	5.8/100000	Tacke 2014
Sweden	6.2/100000	Schiller 1995
Israel	6.4-11.2/100000	Bar-Meir 2011
France	9/100000	Heuclin 2009
Spain (Madrid)	15.1/100000	Martinez-Ruiz 2003

Discussion

To the best of our knowledge, this is the first prospective population-based epidemiological study of KD in the Western Mediterranean area. Our study revealed a mean annual incidence of 8/100,000 children <5 yo of age. The annual incidence varied between 6.2 and 9.5 during our 10-year study period. As expected, this incidence is much lower from the high incidence observed in Japan (7, 12) and other Asian countries (13, 14). Among European countries (15), lower incidences than we found are described in Nordic countries (9, 16) and The Netherlands (17), but, when compared with other Mediterranean countries, the incidence and clinical features in our population are similar to those described in countries such as Israel (18), Italy (19), Turkey (20), Greece (21) and France (10) (see Table IV for incidences in European countries). In Spain, one of the most recent published work on KD incidence took place from 1999 to 2002 in some hospitals in Madrid and it showed an incidence of 15.1/100,000 children <5yo (11). The differences between incidence in Madrid and Catalonia could be explained by differences in the demographic features and the fact that the study in Madrid was exclusively based on case series and retrospective reviews.

Among the cases of KD registered in our study, 39.8% were considered as incomplete KD. Rates for incomplete forms of KD vary from 15% to 33% in studies performed in Canada (22), Italy (23), The Netherlands (17), France (10) or Turkey (20). In this last Turkish study it seems that the percentage of incomplete KD is increasing. The true reason for this increase remains unclear, but it may be associated with the increased awareness of the physicians although there is the possibility to miss the true diagnosis as other childhood febrile diseases with rash may resemble KD (23).

Seasonal changes found in our study were similar to those described in other studies. In a study based on Japanese population by Burns *et al*. (24) they found bimodal seasonality with peaks in January and June/July and a nadir in October. We also found a bimodal distribution with higher incidence rates in January and November and fewer cases in October. Further investigations are needed to determine whether these

peaks are secondary to any infection or environmental trigger.

A remarkable finding on the incidence rates in our study is that KD seems to be more frequent among those children living in non-urban areas although these are less densely populated. This could be related to the presence of extensive areas of intensive farming (25), sociocultural differences (26) or other no identified environmental or genetical factors. Further studies are necessary to establish the aetiology of this finding.

The beneficial effect of IVIG treatment on the development of CAA and duration of fever is well-recognised in KD (27, 28). Delay of treatment after 10 days has been described as a risk factor for CAA development (29), which was confirmed in our study. No differences between treating from 4th–7th day with respect to treating from 8th–10th day were found. In our population, we found high rate of early treatment with 87.5% of the patients treated within 10 days of illness and high rates of response to the IVIG 1st dose (87.5%). These data suggest general paediatricians are aware of KD and usually treat suspicious cases as early as they suspect them and, probably, in the right way.

Among the 13.8% of Catalan patients that needed a 2nd IVIG dose, 69.6% had complete response and 17.3% also received oral or IV steroids. These patients were found to be at higher risk of developing CAA. Although the optimal treatment for IVIG non-responsive patients remains controversial, adding steroids to the 2nd IVIG dose has proven to be effective to reduce the incidence of CAA and improve the prognosis of resistant KD (30, 31). Other treatment plans for KD resistant patients have been described, such as treatment with infliximab (32), plasma exchange (33) or cyclosporine (34), but no patients in our population received these treatments.

Treatment with abciximab has proven to be effective to enhance regression of CAA (35, 36). Among our patients, 3 of the 4 patients with giant CAA received abciximab. Prospective data of these patients is not available to establish its effectiveness.

The overall proportion of children with CAA was 12.3% during the acute phase. Half of the patients had transient abnormalities but 51% had persistent CAA after 8 weeks. Despite the high rates of early treatment and IVIG response we observed, the incidence of CAA in Catalan KD patients is slightly higher than those described in other studies reporting an incidence between 5% and 10% (2, 37).

Regarding risk factors of CAA development in patients with KD, we found that IVIG non-responsiveness, need of a 2nd IVIG dose, delay of treatment >10th day of illness, ages <1yo and >8yo and the presence of sterile piuria, aseptic meningitis, abdominal pain and uveitis at diagnosis were independent risk factors for the CAA development. This is consistent with other published studies (38, 39). Other risk factors related to laboratory abnormalities such as high white blood cell count, low albumin or high erythrocyte sedimentation rate are described in other studies (2, 40), but we did not find any statistically significant differences.

The strength of our study was the use of a combined population-based surveillance system, both prospective and retrospective, with participation of all Catalan hospitals attending children. However, as other retrospective studies, our study has some limitations and some cases of KD may not have been recognised as making a retrospective diagnosis of KD from hospital records may be difficult, leading to an underestimation of the real KD incidence.

Conclusions

This is the first population-based study on the epidemiology of KD in Catalonia and the Western Mediterranean area. Incidence, clinical features and treatment plans in our cohort are similar to those described in studies in other European countries, especially those in the Mediterranean area.

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