ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Is Thrombocytopenia a Novel Risk Factor for Cardiac Complications in Kawasaki Disease? Findings to the Mexican Network of Kawasaki Disease

José de Jesús Coria-Lorenzo[1,2]*, Rodolfo Norberto Jiménez-Juárez[3], Sandra Enciso[4], Norberto Sotelo-Cruz[5], Daniel Ramírez-Bouchand[6], Omar Enríquez-Cisneros[7], José Luis Díaz-Luna[8], Jaime Julio Unda-Gómez[9], Roselia Ramírez-Rivera[10], Lucila Martínez-Medina[11], Alejandro Díaz-Toquero[12], Michel Gutiérrez-Ceniceros[13], Alfonso Reyes-López[14] and Víctor Cruz-Olivos[15]

[1]*Hospital Epidemiology Department, Children´s, Hospital of Mexico Federico Gómez, Mexico*

[2]*Research and Teaching, General Hospital ISSSTE Toluca, Mexico*

[3]*Pediatric Department, Infectious Diseases Hospital, Medical Center La Raza-IMSS, Mexico*

[4]*Laboratory Research on Nephrology and bone mineral metabolism, Children´s Hospital of Mexico Federico Gómez, Mexico*

[5]*Medicine Department, Sonora State University, Mexico*

[6]*Children´s and Woman Hospital, San Luis Potosí, Mexico*

[7]*West General Hospital, Guadalajara Jalisco, Mexico*

[8]*Hospital of Xalapa, Veracruz, Mexico*

[9]*Medical Center Iron Door, Zapopan, Jalisco, Mexico*

[10]*Hospital Specialties Child and Woman, Querétaro, Mexico*

[11]*Century Hospital Miguel Hidalgo, Aguascalientes, Mexico*

[12]*MEDICA KIDS Private Pediatrics, Mexico*

[13]*Unit of Research in Neurodevelopment, Hospital of Mexico Federico Gómez, Mexico*

[14]*Center of Economic and Social Studies, Hospital of Mexico Federico Gómez, Mexico*

[15]*Pediatric Internal Medicine Department, General Hospital "Gaudencio Gonzalez Garza", Medical Center La Raza-IMSS, Mexico*

***Corresponding Author:** José de Jesús Coria Lorenzo, Hospital Infantil de México Federico Gómez, Mexico City, Mexico.

Received: May 24, 2021; **Published:** June 16, 2021

Abstract

Background: Kawasaki disease is a systemic inflammatory disease, usually self-limited, characterized by fever and manifestations of acute inflammation. Complications such as coronary artery aneurysms, heart failure and acute myocardial infarction, among others, lead to significant morbidity and mortality. Is maybe the most common acquired heart disease cause in children. The aim of this study was to evaluated clinical features and epidemiology as potential risk factors for cardiac complications.

Methods: Multicenter, retrospective cross-sectional study was conducted in children with a discharge diagnosis of Kawasaki disease and almost one echocardiographic study. We made a bivariate analysis, then it fit a logistic regression model in order to assess the risk factors for cardiac complications, ectasias or aneurysms coronary.

Results: One hundred and eighty-two medical records were reviewed, 3 were excluded because no echocardiogram was performed, 179 records were analyzed, 68% had a complete presentation of Kawasaki. Cardiac manifestations occurred in 47% cases, 32.4% presented ectasia and 27.4% coronary aneurysms. Fever lasting more than 10 days' thrombocytopenia and spring and autumn seasons were identified as independent predictors for cardiac abnormalities in our study population.

Conclusion: Thrombocytopenia is a novel risk factor for aneurysms in KD in our Mexican children.

Keywords: *Kawasaki Disease; Thrombocytopenia; Coronary Artery Aneurysm; Vasculitis; IVIG*

Introduction

Kawasaki disease (KD) is one of the most common vasculitis in pediatric population. Is maybe the most common acquired heart disease cause in children. Occurs mainly in previously healthy children, about 50% of cases are children under two years of age. It has become the most common acquired heart disease in children, far exceeding rheumatic fever, in both developed and developing countries [1,2].

Kawasaki disease is an acute systemic vasculitis that affects small and medium size arterial vessels, including coronary arteries, causing injury or cardiovascular complications ranging from simple arteritis, valvular disease, coronary aneurysms, pericardial effusion to heart attack and death, as well as the fact that can affect arteries elsewhere [2,3]. It is also a cause of long term morbidity and mortality, because it can result in ischemic heart disease in young adult population due to the inflammatory process that favors development of atheromatous plaque. So, children who have aneurysmal disorders in childhood who are not detected early can present heart attack or sudden death in adolescence or adulthood [3,4]. In Mexico there are reports of KD, none is multicentric, so no local information about the epidemiology and possible associated cardiac complications. Currently, gammaglobulin (IVIG) administration with aspirin remains the treatment of choice for KD [2] although it has also been used in conjunction with gamma globulin, other therapy such as methylprednisolone and monoclonal antibodies against tumor necrosis factor alpha (TNF-α).

Objective of the Study

The main objective of this study was to analyze clinical, epidemiological and cardiac complications, as well as risk factors for heart complications in Mexican population.

Materials and Methods

A retrospective cross-sectional study was performed in 9 hospitals across the country (referral centers and counties hospitals). Clinical records were reviewed from January 1st -2008 to December 31, 2012. The study was approved by the ethical internal commission of each institution**.** Inclusion criteria included discharge diagnosis of Kawasaki disease according to the ICD-9-CM code 446.1, diagnostic criteria of The American Heart Association (AHA) and Japan's Ministry of Health American Heart Association (AHA) files reviewed had to have at least one echocardiographic study. Data collected were: age, sex and year of diagnosis, if it was considered a complete or incomplete Kawasaki, atypical clinical manifestations. Laboratory data included hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets and leukocytes count. The variables taken into account from the echocardiographic study were: presence and localization of ectasia and or coronary aneurysm, pericardic effusion, and other cardiac findings. The first day of fever recorded by parents was considered as the first day of KD disease. Patients with fever after 36 hours of completing the first dose of IVIG were considered refractory to treatment.

Statistical analysis

Descriptive analysis including simple and cumulative frequencies were calculated. To estimate the association between cardiac complications and the studied variables was performed Xi square or Fisher's exact tests for dichotomous variables; Student´s T test was used for compare continuous variables. Logistic regression model was performed using variables that were potentially significant in the bivariate analysis. The evaluation of goodness of fit multivariate models was performed with the Hosmer-Lemeshow test, while the discriminatory capacity of these models was determined by calculating the area under the curve and contingency tables for sensitivity, specificity and predictive values. Data was analyzed with statistical software STATA version 13 (College Station, Texas USA).

Results

One hundred eighty-two records were reviewed, and three were eliminated for not having echocardiogram. One hundred seventy-nine cases that met the definition of Kawasaki disease were included and fullfied diagnostic criteria for Kawasaki disease. The institutions that

reported more cases were Children´s Hospital of Mexico (23.5%) and CMN (National Center Medical) La Raza (18.4%), male children predominated in 60.3%, classic presentation of KD was 68.7%, however, the percentage of incomplete presentation varied significantly between 0% in 4 centers and 82.6% at the Children´s Hospital of Sonora ($p < 0.001$). The median age at presentation was 24 months with 25-75 interquartile range from 13 to 44 months. Winter was the season with more cases of KD (34.1%) followed by spring (26.3%).

Clinical features

Median duration of fever was 7 days (IQ range 5.75 - 12 25 - 75th), 28.7% of cases had more than 10 days with fever at diagnosis. Clinical manifestations were: conjunctival injection 88.8%, rash 85.5%, lip fissures 83.8%, strawberry tongue 63.7%, pharyngeal erythema 70.4%, prominent papillae 46.9%, limb edema 65.9%, palmar or plantar erythema 53.6%, and desquamation of fingertips 52.5%, 69.9% lymphadenopathy (Cervical 57.6%). Table 1 shows other demographic and clinical features of children both with complete and incomplete Kawasaki disease.

	Complete (n = 123)	**Incomplete (n = 56)**	**p**
Female n (%)	46 (37.4)	25 (44.6)	0.35
Age (month)/Median (IQR 25th - 75th)	25 (14 - 44)	23.5 (11 - 44)	0.47
Winter, n (%)	46 (37.4)	15 (26.7)	0.19
Spring, n (%)	29 (23.5)	18 (32.1)	0.19
Fever days at diagnostic, Median (IQR 25th - 75th)	7 (5.75 - 13)	7 (5.25 - 10)	0.48
Leucocytes > 12,000/mm^3, n (%)	83 (67.47)	35 (62.5)	0.34
Thrombocytopenia, n (%)*	(5.6)	(16.3)	0.023
Cardiac finding, n (%)	56 (45.5)	28 (50)	0.67
Aneurism, n (%)	33 (27)	16 (28.5)	0.95
Ectasia, n (%)	42 (34)	28.5 (16)	0.57

Table 1: *Demographic and clinic characteristic in children with complete and incomplete KD.*
**: Platelets < 150,000 in the 2 weeks to start disease.*

Atypical manifestations

The most frequently identified atypical manifestations of KD were piuria, vomiting and abdominal pain figure 1.

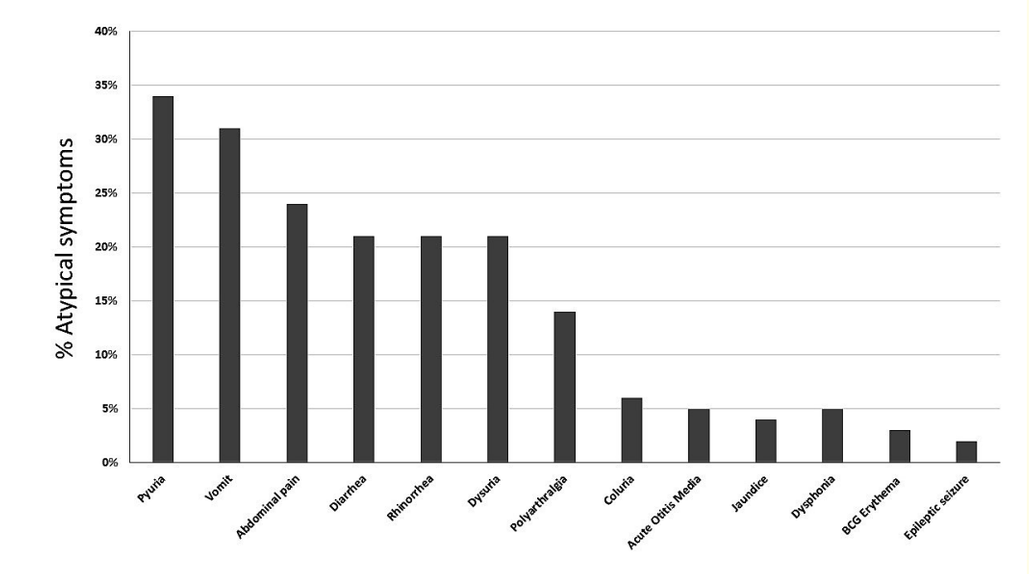

Figure 1: *Atypical findings in children with Kawasaki Disease. BCG (Bacillus Calmette-Guerin).*

Treatment

Ninety-five percent of patients were treated according to universal AHA recommendations [2]. Patients were treated with IVIG (2 g/kg) and acetylsalicylic acid at a dose of 80 - 100 mg/kg/day divided in four doses. ASA was reduced after 48 hours of last fever. No record data regarding use of another antiplatelet agent was administrated. Due to misdiagnosis or late referral five percent of population did not received timely management.

Cardiac complications

Cardiac manifestations were reported in 84 cases (46.9%), 58 patients (32.4%) with ectasia and 49 patients (27.4%) with coronary aneurysms. Twenty subjects developed pericardial effusion, 15 hypertensions, 15 valvular disease and 8 ventricular dilatations. Left coronary artery ectasia was documented in 51 subjects and right coronary in other 31, aneurysms occurred in the left coronary artery in 35 subjects and 39 in the right coronary.

Risk factors for coronary disorders

According to bivariate analysis, fever for more than 10 days, seasonality and low platelet count were significant risk factors for cardiac manifestation and coronary aneurysm. For coronary ectasia were having more than 10 days with fever and seasonality. It is important to note that in our country it is standardized that 150,000/mm^3 to 400,000/mm^3 is the cut-off value for platelets.

Various models of binary logistic regression were adjusted, one for each outcome variable (heart manifestation, coronary ectasia and coronary aneurysm). Co-variables in bivariate analysis with a value of $p < 0.1$ were included in the multivariate analysis. Included variables were fever over 10 days (dichotomous variable), season (categorical variable being spring the reference one) and thrombocytopenia (dichotomous variable).

First model shows that patients who were diagnosed with KD in autumn have 3.2 times higher risk of cardiac events, compared with those diagnosed during spring; this effect was statistically significant because the 95% CI of the OR does not include the null value (the unit). Additionally, subjects with thrombocytopenia have 4.2 times more risk of MC and those with fever for more than 10 days have an increased risk of MC in 3.34; all these effects were significant according to the 95% reported (See table 2). The Hosmer-Lemeshow (H-L) test resulted with a value of 1.32 ($p = 0.97$), indicating a good fit to the data model. This was corroborated with quantile probability predicted by the model, shown in the table Hosmer-Lemeshow, where it can be seen that the estimated risk to have cardiac manifestations throughout its entire distribution probability exhibits values very close to the probability observed. This is also reflected in the predictive ability of the model whose area under the curve resulted in 0.73.

Cardiac findings		
Variable	OR**	CI 95%***
Fever > 10 days	3.35	1.60 - 7.00
Summer	1.85	0.71 - 4.79
Autumn	3.20	1.21 - 8.50
Winter	0.64	0.27 - 1.48
Thrombocytopenia*	4.24	1.33 - 13.48
Coronary ectasia		
Fever >10 days	2.48	1.22 - 5.02
Summer	1.07	0.40 - 2.9
Autumn	2.53	0.97 - 6.58
Winter	0.70	0.28 - 1.73
Thrombocytopenia*	0.82	0.24 - 2.79
Coronary aneurism		
Fever >10 days	5.98	2.78 - 12.86
Summer	2.85	0.92 - 8.77
Autumn	3.15	1.011 - 9-70
Winter	1.28	0.44 - 3.72
Thrombocytopenia*	4.98	1.51 - 16.42

Table 2: *Multivariate analysis for risk factors to cardiac findings in Kawasaki Disease.*
**: Thrombocytopenia: Platelets < de 150,000/mm^3; **: OR Odds Ratio; ***CI: Confidential Interval.*

In the model where coronary ectasia was the outcome to predict, it is observed that the fever for more than 10 days increases the risk of ectasia 2.48 times, while association between disease onset in the autumn with the presence of ectasia (OR 2.53) was significant only with an alpha value of 6%.The fit of the model was adequate (H-L test 2.26, p = 0.94), showing a slight distance in the fourth decile of the predicted probability value of area under the curve of 0.68. And regarding the third adjusted model to predict coronary aneurysms in patients with KD, fever for more than 10 days increases the risk of aneurysms almost 6 times, thrombocytopenia increases the risk almost 5 times and the season played a role similar to the first model as a risk factor. The evaluation of goodness of fit also showed good results (HL 2.27 test; p = 0.89) as a spacing of 2 units was observed in decile 9, which have no impact on the proper functioning of the model, as the area under the curve it was 0.76.

Discussion

This is the first multicenter study in Mexico. The importance of knowing regional and local data is that there is a clear association with race and the incidence of Kawasaki disease. There has been previous data indicating the incidence of KD in different countries, in Japan the incidence is of 216.9 x 100 000 children under 5 years between 2007 - 2008, while in Northern Europe and US incidence is 10 times lower (8.4 - 19 x 100 000 children younger than 5 years), interestingly Hawaii in 2006 reported an incidence of 50.4 x 100 000 children under 5 years [5-7] which supports racial differences hypothesis in the incidence of the KD.

Percentage of incomplete presentation varied significantly between the different centers, most cases reported in a center located in north of the country and adopted the Clinical Guidelines of AAP for diagnosis and treatment of KD [2]. Those patients were younger than one year of age and were considered incomplete because they had fever plus incomplete clinical presentation, without cardiac involvement, according to echocardiography. It has been widely reported that patients younger than 1 year tend to have less clinical manifestations and increased the percentage of KD incomplete post-implementation of the Clinical Guidelines of the AAP [8]. In Mexico average age is similar to that reported in North America but higher than reported in Japan where the highest incidence is about 9 months (450/100,000 for children 1 year old) [6,9]. Noteworthy that there was no difference in age between full and incomplete Kawasaki reported cases, being that reported incomplete Kawasaki patients are younger [2,6-8].

In our series on average the treatment is established between the day 9 or 10. Varying the beginning as such between day 2 and more than 20 days after starting disease, 5% of patients diagnosed with full KD didn't received IVGI. This suggests that in Mexico there is still delay in diagnosis, appropriate reference and initiation of treatment with gamma globulin and aspirin. Importance of early treatment was demonstrated in Japan where complications rate decreased from 25 - 30% to 3 - 5% [2].

Percentage of cardiac complications (47%) was like that reported in countries in Europe such as Poland and Greece [10,11] but much higher than that reported in other countries such as Italy (15.6%) North America (19%), Israel (2.9%), Austria (18.7%), Croatia (18%) [12-16]. In this work, maybe it was secondary to delay in diagnosis and timely initiation of appropriate treatment. Findings from our study show that fever with duration of more than ten days, platelet count less than 150,000 and disease onset in autumn are independent risk factors for the development of cardiac manifestations that include the development of coronary artery disease. Various authors have described that duration of the fever more than 10 days prior to the administration of intravenous gamma globulin is a major risk factor for developing coronary artery disease [2,17].

Although thrombocytosis has been described as independent risk factor for coronary artery disease and lack of response to treatment, this was not consistent in our study population [16]. However, thrombocytopenia was observed as independent risk factor for development of coronary heart disease. Nofech-Mozes is the one to have reported the same association, though he reported one case and literature review of 30 additional cases, where 45% of the subjects had aneurysms [18].

Some time ago in 2014, Burçin Beken., *et al*. reported about thirty-seven patients with KD and concluded that thrombocytopenia can also be seen as a presenting feature in KD instead of thrombocytosis and thrombocytopenia should alert the clinician of severe disease and coronary artery aneurysm development, and closer follow-up with more frequent echocardiographic examinations may be a safer approach in these patients [19]. As suggested in the cardiovascular sequelae management guidelines, because the severity assessment in the acute phase includes initial assessment of severity of symptoms and then coronary sequelae 1 month after onset. Assessment related to the prognosis of coronary arteries is the most important from a long-term perspective (Class IIa, Level B) [20].

Our study is the first to report the strength of association between thrombocytopenia and the presence of coronary aneurysms, using a sufficiently robust statistical model to propose thrombocytopenia as a predictor of aneurysms factor in KD.

Inflammation causes imbalance between procoagulant and anticoagulant properties of the endothelium, causing a local stimulus in the inflammatory cascade, such as TNF alpha, which is a cytokine that promotes a procoagulant state by inhibiting protein C synthesis and preventing the production of tissue factor by the endothelium. However, one of its pleiotropic effects, under stimulation with nitric oxide, a potent inhibitor of platelet activation, decreases release of Wibel Palade corpuscles and reduces platelet adhesion and platelet count. Platelet-leukocyte interactions mediated by P-selectin and P-selectin glycoprotein 1 have been described, which is believed to be an important factor in the response of different diseases where it's involved an altered regulation of inflammatory response [21,22]. Both could promote decreased platelet count and platelet adhesion. It is possible that the observations of our study regarding the intensity of the inflammatory response that favors cardiac abnormalities has also been the cause of thrombocytopenia and this is found to be a factor associated with the presence of heart disease and aneurysms manifestations. We did not assess the remaining factors of coagulation cascade, however, in our group of patients is clear that thrombocytopenia is an independent predictor for the presence of aneurysms.

Conclusion

The main limitation of this study is that it was retrospective. However, a significant number of children were analyzed and this is the first multicenter Mexican population report.

Our results provide evidence with a robust model to propose thrombocytopenia as a risk factor (Table 2) for the development of coronary aneurysms and ectasia; it is desirable that prospective, multicenter studies to confirm these findings are made. It is extremely important to emphasize that thrombocytopenia not excluded KD diagnosis.

Bibliography

1. Newburger JW., *et al*. "Guidelines for long-term management of patients with Kawasaki disease. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association". *Circulation* 3.3 (2004): 169-170.

2. McCrindle BW., *et al*. "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease. A Scientific Statement for Health Professionals From the American Heart Association". *Circulation* 135 (2017): e927-e999.

3. Falcini F. "Kawasaki disease". *Current Opinion in Rheumatology* 18.1 (2006): 33-38.

4. Diaz RA., *et al*. "Severe aneurismal coronary artery disease probably caused by Kawasaki disease. report of one case". *Revista Médica de Chile* 135.9 (2007): 1182-1185.

5. Uehara R and Belay ED. "Epidemiology of Kawasaki Disease in Asia, Europe, and the United States". *Journal of Epidemiology* 22.2 (2012): 79-85.

6. Nakamura Y., *et al*. "Epidemiologic Features of Kawasaki Disease in Japan: Results of the 2009–2010 Nationwide Survey". *Journal of Epidemiology* 22.3 (2012): 216-221.

7. Salo E., *et al*. "Incidence of Kawasaki disease in northern European countries". *Pediatrics International* 54.6 (2012): 770-772.

8. Ghelani SJ., *et al*. "Increased incidence of incomplete kawasaki disease at a pediatric hospital after publication of the 2004 american heart association guidelines". *Pediatric Cardiology* 33.7 (2012): 1097-1103.

9. Yanagawa H., *et al*. "Epidemiologic pictures of Kawasaki disease in Japan: from the nationwide incidence survey in 1991 and 1992". *Pediatrics* 95 (1995): 475-479.

10. Gorczyca D., *et al*. "The clinical profile of Kawasaki disease of children from three Polish centers: A retrospective study". *Rheumatology International* 34.6 (2014): 875-880.

11. Alexopoulos A., *et al*. "Kawasaki disease in Greek children: A retrospective study". *The Journal of the European Academy of Dermatology and Venereology* 27.5 (2013): 580-588.

12. Rigante D., *et al*. "Responsiveness to intravenous immunoglobulins and occurrence of coronary artery abnormalities in a single-center cohort of Italian patients with Kawasaki syndrome". *Rheumatology International* 30.6 (2010): 841-846.

13. Callinan LS., *et al*. "Kawasaki syndrome and factors associated with coronary artery abnormalities in California". *The Pediatric Infectious Disease Journal* 31.9 (2012): 894-898.

14. Bar-Meir M., *et al*. "Kawasaki disease in Israel". *The Pediatric Infectious Disease Journal* 30.7 (2011): 589-592.

15. Binder E., *et al*. "Kawasaki disease in children and adolescents: clinical data of Kawasaki patients in a western region (Tyrol) of Austria from 2003—2012". *Pediatric Rheumatology* 12.1 (2014): 37.

16. Maric LS., *et al*. "Risk factors for coronary artery abnormalities in children with Kawasaki disease: a 10-year experience". *Rheumatology International* 35.6 (2015): 1053-1058.

17. Tang Y., *et al*. "Epidemiological and Clinical Characteristics of Kawasaki Disease and Factors Associated with Coronary Artery Abnormalities in East China: Nine Years Experience". *Journal of Tropical Pediatrics* 62.2 (2016): 86-93.

18. Nofech-Mozes Y and Garty B-Z. "Thrombocytopenia in Kawasaki disease: a risk factor for the development of coronary artery aneurysms". *Pediatric Hematology and Oncology* 20.8 (2003): 597-601.

19. Burçin Beken., *et al*. "The Relationship Between Hematological Findings and Coronary Artery Aneurysm in Kawasaki Disease. Letter to the Editor". *Turkish Journal of Hematology* 31 (2014): 199-200.

20. Fukazawa R., *et al*. "AL JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease". *Circulation Journal* (2020): 1-60.

21. Dong ZM., *et al*. "Prominent Role of P-Selectin in the Development of Advanced Atherosclerosis in ApoE-Deficient Mice". *Circulation* 101.19 (2000): 2290-2295.

22. Lindemann S., *et al*. "Activated platelets mediate inflammatory signaling by regulated interleukin 1?? Synthesis". *Journal of Cell Biology* 154.3 (2001): 485-490.

Volume 10 Issue 7 July 2021