Kawasaki disease: A rare pediatric pathology in Mexico Twenty cases report from the Hospital Infantil del Estado de Sonora

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Summary

Background: Kawasaki disease (KD) is an etiological illness that is relatively unknown and scarcely identified in Mexico; it affects children mainly aged 1–4 years, evolves with fever, vasculitis in diverse organs, and in the heart the disease mainly affects the coronary arteries. **Objectives:** Our aim was to inform the clinical findings and evolution of 20 patients diagnosed with KD. **Materials and methods:** We reviewed the patient clinical files retrospectively and descriptively to obtain information with regard to age, sex, clinical signs, laboratory and consultory results, echocardiography findings, complications, evolution during hospitalization, follow-up, and out-patient ambulatory consultations. **Results:** Eighteen patients were male, two were female, six developed coronary damage, two aortic mitral-valve insufficiency, one pericardial shedding, and one, myocarditis. All patients received gamma globulin treatment with aspirin, and 16 were controlled during 6–8 months after the acute medical profile. **Conclusions:** The opportune clinical diagnostic it is fundamental to establish an early treatment with gammmaglobuline to avoid injuries in the arterial coronary level. This injury may cause eventualy ischemia or myocardial infarct

Resumen

Enfermedad de Kawasaki: una patología pediátrica rara en México. Reporte de 20 casos del Hospital infantil del Estado de Sonora

Introducción: La enfermedad de Kawasaki (EK) es un padecimiento de etiología, aún desconocida, poco identificado en México; afecta a niños principalmente entre el año y cinco años de edad, evoluciona con fiebre, vasculitis en diversos órganos y en corazón se afectan más las arterias coronarias. **Objetivos:** Informar sobre los hallazgos clínicos y evolución de 20 pacientes diagnosticados con EK. **Material y métodos:** Se revisaron de manera retrospectiva y descriptiva los expedientes clínicos para obtener información acerca de edad, género, signos clínicos, resultados de laboratorio y gabinete, hallazgos ecocardiográficos, complicaciones, evolución durante su hospitalización y seguimiento en la consulta ambulatoria. **Resultados:** 18 pacientes eran del género masculino, dos femeninos, seis desarrollaron lesiones coronarias, dos insuficiencia aórtica y dos insuficiencia de válvula mitral, uno con derrame pericárdico y uno con miocarditis; todos recibieron tratamiento con gammaglobulina y aspirina; 16 fueron controlados durante 6 a 8 meses después del cuadro agudo. **Conclusiones:** El diagnóstico clínico oportuno es fundamental para establecer un tratamiento temprano con gammaglobulina con el fin de evitar, en lo posible, lesión a nivel arterial coronario. Dicha lesión puede provocar, eventualmente isquemia o infarto del miocardio.
(Arch Cardiol Mex 2007; 77:299-307)

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Recibido: 6 de marzo de 2007
Aceptado: 9 de julio de 2007

Key words: Kawasaki disease. Vasculitis. Coronary aneurysms.
Palabras clave: Enfermedad de Kawasaki. Vasculitis. Aneurismas coronarios.

Introduction

Kawasaki disease (KD) is an unknown etiologic illness that is manifested by acute-course febrile syndrome associated with vasculitis that can involve diverse organs. KD was originally described by T. Kawasaki in 1967.[1]

From the epidemiological viewpoint, it is known that this disease is more frequently found in Asiatic, and principally in Japanese, population. In North America, the highest number of cases are reported annually in the U.S.[2,3] The etiology includes very diverse bacterial and viral agents, chemical substances and acaros (dermatophagoides) without fully convincing evidence.[4-6]

In Mexico, the first case of KD was reported by Rodríguez in 1977;[7] from that date, cases published in medical journals in Mexico have amounted to < 50.[7–14]

Recently about etiology, at least in theory, a complementary auto- antigen has been invoked, suggesting that it is an infectious agent and that it is that it is a vasculitis-associated neutrophil plasma antibody trigger. New studies have reported the presence of parvovirus B19 and herpesvirus in giant-cell arteritis. In addition, a new virus has also been identified in humans, is named the New Haven coronavirus (Nco-NH), and has been found in the respiratory secretions of children with KD.[4–6]

In the disease pathology, the participation has been studied of different proteinases elaborated in the disease's acute phase, which damage the wall of the same vessels that play a primordial role in the genesis of aneurysms. There is also an overproduction of proinflammatory cytokines with endothelial-cell activation. RNA levels and the expression of Th1/Th2 cytokines, interferon gamma (IFN gamma), and interleukin 4 (1L-4) have been analyzed together ,along with Th1/Th2- inducing of transcription factors (T-bet and GATA-3), known for the role they play in the development of Th1/Th2,[3] interleukin 1 (IL-1), acting as an activator factor of leukocytes and endogenous pyrogen. This provokes an increase in tumor necrosis factor (TNF) alpha that itself stimulates IL1, increasing in the vascular endothelium the production of chemokines and adherence molecules. These in turn activate interferon B-generated polymorphonuclears that favour elevated and prolonged fever. The elevation of interleukin 7 (IL-7), serine proteases produced by activated TCD4 leukocytes, induce the production of the interleukin 6 (IL-6) factor, which is stimulated at the service of immunoglobins by plasmatic cells, the latter favoring thrombosis. There are other immunological mechanisms that are related with the different physical signs such as adenopathy, edema, and dilatation of the small blood vessels in the skin, these resulting in diverse interaction among IL-15, TCD4, and CD8-Th cells, alpha chemokines (XCL-O), and T-bet cells.[15–20] The transcendence of early identification of this disease lies in initiating treatment with gamma globulin and aspirin during the course of the first week of disease evolution and to avoid the development of coronary damage and other cardiovascular complications that leave sequel and place a risk the children's very live.[2,3,21,22]

Materials and methods

We reviewed the clinical files of 20 patients admitted to the Hospital Infantil del Estado de Sonora in whom a diagnosis of Kawasaki disease had been established between January 1988 and December 2006. Data obtained included the following: place from; age; sex; diagnosis at admission; season of the year; clinical manifestations, and the laboratory and consultory studies on which the disease diagnosis, complications, and evolution were sustained.

Results

In April 1988, the first cases of KD ($n = 20$) were identified at the Hospital Infantil del Estado de Sonora. Eleven patients were residents of the northern Mexican city of Hermosillo, Sonora, five lived in the Sonora desert area, one patient resided on the northern Sonora state border with the U.S., and three were residents in a rural area of Sonora state.

Season of the year

With regard to the season of the year in which the patients were hospitalized, three hospitalizations occurred during the month of February, 11 from March through May, three during the

Table I. Diagnoses at hospital admission in 20 children with Kawasaki disease.

Diagnosis	*N*	Proportion
Kawasaki disease	9	0.45
Unknown fever	5	0.25
Viral exanthema	1	0.05
Adenopathy	1	0.05
Neuroinfection, urinary tract infection	1	0.05
Gingivostomatitis	1	0.05
Guillain-Barre syndrome	1	0.05
Hepatitis	1	0.05

months of August and September, and three from October through December.

Sex, age, and diagnosis on hospital admission

With respect to gender, 18 patients were males and two, females. Patient ages fluctuated between 5 months and 15 years; younger patients included one aged 5 months, another aged 12 months, and another aged 18 months. There were 11 patients between the ages of 2 and 5 years, two between 6 and 8 years of age, and three patients aged 9–15 years. Diagnosis at hospital admission was KD in 9, unknown fever in five, with the remainder of the patients shown in Table I. In terms of disease evolution prior to hospital admission, the profile presented in nine children was between 5 and 10 days, and in the remaining patients, between 15 and 21 days.

Clinical profile

Diagnosis was basically established on the following criteria: fever; non-suppurative, hyperemia conjunctival; macular-papullary exanthema; lesions on the lips and oral cavity; changes in the skin of the extremities, and aggregated signs such as precordial murmur, respiratory difficulty, abdominal pain, dysuria, hepatomegalia, arthralgia, neck ridigity, and seizure *(Table II)*.

Laboratory parameters

Nineteen patients accumulated globular speed, 18 presented leukocytosis con neutrophilia, 14 had thrombocytosis, C-reactive protein was positive in eight, including four patients with an elevation of > 6 μgr/dL, eight patients presented moderate elevation of aspartate and alanine aminotransferases of not > 100 μ/L (these patients had negative serology for hepatitis A, B, and C), one patient had an elevation of lactic dehydrogenase and creatine phosphokinase, one with an elevation of antistreptolysines of > 500 μ/L, and in one patient we observed an elevation of immunoglobulin E. During the study period, we carried out during the study period and on the majority of patients additional labo-

Table II. Clinical data found in 20 patients with Kawasaki disease.

Signs	Cases	Proportion
Basic		
Fever of 5 or more days of evolution	20	1.00
Conjunctival injection without exudate	20	1.00
Exanthema (maculopapullary in trunk,	20	1.00
multiform erythema multiforme (non-vesicular)	20	1.00
Changes in lips and oral cavity (pharyngeal erythema, labial fissures, strawberry tongue	20	1.00
Cervical lymphadenopathy of 1.5 cm	15	0.75
Changes in extremities		
Acute erythema and edema	20	1.00
Convalescence		
Scaling of the fingertips	19	0.95
Aggregated clinical dates		
Cough	6	0.30
Abdominal pain	6	0.30
Hepatomegalia	7	0.35
Irritability, neck ridigity	2	0.10
Generalized tonic-clonic convulsions	2	0.10
Pain in the articulations	5	0.25
Precordial murmur	3	0.15
Dysuria	4	0.20

Table III. Laboratory and consultory studies in 20 patients with Kawasaki disease*.

Study	Cases, *n*	Proportion
Laboratory studies		
Elevated erythrocytes sedimentation rate	19	0.95
Leukocytosis with neutrophilia	18	0.90
Thrombocytosis	14	0.70
Positive reactive C protein	8	0.40
Reactive C protein > 6 mg/dL	4	0.20
Aspartate aminotransferases and alanine		
Aminotransferase rise	8	0.40
Hemoglobin < 10 g/dL	9	0.45
Elevated E immunoglobulin	1	0.05
Antiestreptolysine > 500 µ/L	1	0.05
Positive urine culture	1	0.05
Hemolytic beta streptococcus pharyngeal culture	2	0.10
Billirrubins >2 mg/dL	2	0.10
Radiographies of thorax		
Bronchopneumonic infiltrate	5	0.25
Cardiomegalia	1	0.05
Electrocardiogram		
Tachycardia	8	0.40
Prolonged Qtc	3	0.15
PR-QT prolongation	2	0.10
Normal S-T segment	2	0.10
Echocardiogram		
Coronary artery dilatation > 4 mm (diameter)	6	0.30
Myocarditis	1	0.05
Pericardial effusion	1	0.05
Left ventricle dyskinesia	1	0.05
Aortic insufficiency	2	0.10
Mitral insufficiency	2	0.10

* All patients were administered an electrocardiogram and an echocardiogram.

ratory examinations including the following: febrile reactions; hemocultures; pharyngeal culture; cutaneous reactions to coccidioidomycosis and tuberculosis-purified protein derivative (PPD) tuberculosis; immunoglobulins IgA, IgG, IgM, and IgE; antimycoplasma antibodies (AMA) in five patients; rheumatoid factor; anti-DNA antibodies, and neutrophil anticytoplasma antibodies, with negative results *(Table III)*. In consultory studies, five patients showed infiltrated bronchopneumonic infiltrate and we observed cardiomegalia in one. We carried out an echocardiogram in all patients; six patients showed coronary artery dilatation with variable diameter, between 4mm to 6mm, in five was located in the left coronary and one with in the right coronary, all patients began after 10 days evolution , we observed valvular alteration in four patients, two patients had aortic insufficiency, and two presented slight mitral insufficiency *(Table IV) (Figs. 1 and 2)*.

Table IV. Treatment received by 20 patients with Kawasaki disease.

Modality	Cases, *n*	Proportion
• Gammaglobulin		
400 mg/kg/day for 5 days	10	0.50
2 g/kg, one dose, 12-h infusion	9	0.45
• Aspirin		
80 mg/kg/day for 15 days	19	0.95
5 mg/kg/day for 10 weeks	19	0.95
• Dipiridamol		
1 mg/kg/day for 4–6 weeks	2	0.10
• Pentoxyphilin		
10 mg/kg/day for 15 days	2	0.10
• Prednisone	2	0.10

*One patient received 0.5 g intramuscularly divided in two doses for 5 days.

Therapeutic procedures

Nineteen children received gamma globulin, nine patients were administered gamma globu-

lin intravenously IGIV [1–4] at a dose of 400 mg/kg/day for 5 days. In the first case of KD diagnosed at the hospital in 1988, one 15-year-old adolescent, due to the lack of gamma globulin, was administered gamma globulina intramuscularly (i.m.) at a dose of 65 mg/kg/day for 5 days (total daily dose was 0.5 gr divided into two fractions for administration every 12 h). The remaining nine patients were administered IGIV (a sole dose at 2 g/kg/day in a 12-h infusion), 19 received aspirin at a dose of 80 mg/kg/day for 15 days and subsequently 5 mg/kg/day for 10–12 weeks. In one 6-year-old patient with coronary dilatation > 6 mm, it was required to administer two additional doses of gamma globulin due to fever that persisted for 3 weeks. Two patients received dypiridamol and pentoxyphillin, as demonstrated in *Table IV*. In eight patients, there was the need to utilize additionally penicillin-type antibiotics, and three of patients were also administered amikacin.

Evolution and control in ambulatory patient appointments

Hospitalization time of the first eight cases ranged from 1 week to 40 days: two patients were hospitalized for 1 week, five required during 15 to 21 days, and one patient remained on the hospital for 40 days. Of the 12 remaining patients, two were hospitalized for < 3 days, one was transferred to another hospital after treatment initiation, and yet another was taken to another secondary-level institution for treatment administration; nine patients remained hospitalized for 7 days, one for between 7 and 13 days.

Of the 16 patients who attended ambulatory control, the six patients with coronary dilatation, the average time for coronary dilatation involution were 10 weeks, evolved with improvement with follow-up for at least 8 months after hospital discharge; four patients with aortic and mitral valve insufficiency evolved without sequel, while evolution was unknown in two patients because they were seen at another institution. For patients with follow-up at our hospital , these were required to attend outpatient ambulatory appointments at the Internal Medicine and Cardiology Services until reaching the age of 18 years.

Discussion

Kawasaki disease principally affects children residing in Oriental countries. An annual incidence of KD has been reported for Japan and Korea of up to 150 cases per 100,000 habitants, while in Caucasian race incidence is between 6 and 10 cases per 100,000 inhabitants of < 5 years of age. In Latin America, it has been estimated that there are 3 cases per 100,000 inhabitants; in

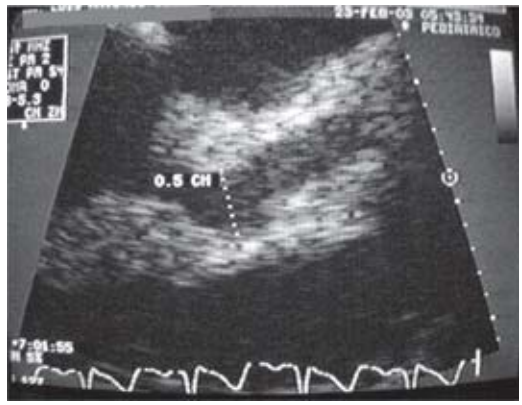

Fig. 1. Left coronary dilatation.

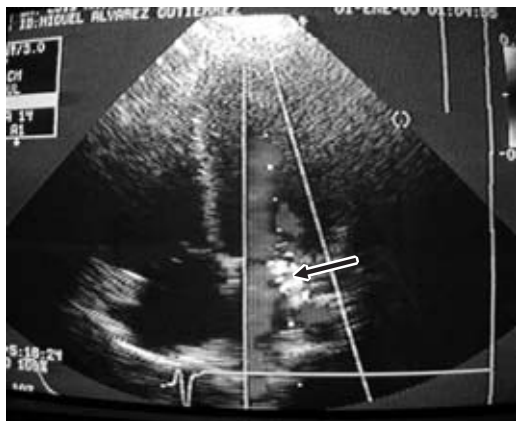

Fig. 2. (A) Mitral valve; (Arrow) regurgitation.

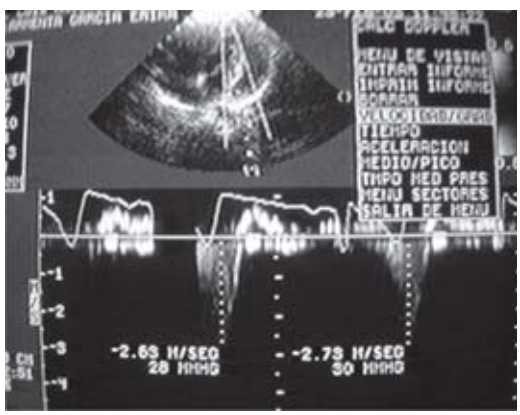

Fig. 2. (B) Mitral valve: Doppler high frequency showed regurgitation.

Mexico, there are no precise statistics, the first cases of KD identified from 1977, 10 years after Dr. T. Kawasaki's description of the disease.[1]

At the moment of writing this article, there had been 53 cases of KD reported in pediatric medical journals in Mexico; these 53 cases were reported in 29 years, indicating the rarity of KD in Mexico, although it is possible that additional cases exist that were identified and treated but not published.[7–14,24–26]

KD is most frequently diagnosed in children < 5 years of age and it predominates in males at a ratio of 1.5:1; in this series, we have patients from breast-feeding age, the youngest 5 months of age, and we also have two adolescents. The greatest number of patients were aged between 2 and 6 years, as described in the literature, although cases have also been identified in infants aged < 3 months.[6,10,11,26–28]

Regarding the season of the year for KD presentation, it is known that epidemic outbreaks[29] can occur during the winter and spring months. In this series, the largest number of cases were registered in the period from February through May.

To date, the causal agent of KD has not been identified. During 40 years, many causal agents have been applied as being possible, although during the past decade insistence has been placed on the participation of viral and bacterial infectious agents, among these *Staphylococcus aureus*, streptococcus, influenza virus, morbilivirus, paramyxovirus, bunyavirus, and the action of bacterial super antigens.[15–20] More recently, evidence has increased in importance concerning the participation of adenovirus and a novel human coronavirus denominated New Haven coronavirus (Nco-NH), identified in respiratory-tract secretions from a 6-months-of-age breast-feeding infant with typical KD. In addition, Nco-NH was found to be positive in eight of 11 children utilizing the reverse transcription-polymerase chain reaction technique; also, *Mycoplasma pneumoniae* infection has been reported of late.[6,30,31]

With regard to the cases with which we are concerned here, affirmations cannot be set forth with respect to the etiology, due to the fact of having found Antiestreptolysin O, of 500 u in one patient and a pharyngeal culture positive for beta-hemolytic streptococcus in other two.

To date, the most important elements for diagnosis are based on the clinical findings; 19 patients presented the five principal criteria for KD, although we also observed additional clinical signs such as hepatomegaly, abdominal pain, arthralgias, and dysuria. Cases have been described with an atypical beginning, and clinical signs have presented during the course of the first 10 days of the disease;[6] one of our patients initially manifested fever, ictericia, uretritis, and pyuria, developing the characteristic signs of KD in the second week, with a 6-mm left coronary dilatation.[10]

At the time of patient hospital admission, 4 of 10 patients were considered to have KD and other diverse ailments. During the hospital stay, the necessary clinical elements were identified for definitive KD diagnosis, as expressed in *Table I*.

There are no specific laboratory studies, although the following trend appears to be observed with greater frequency during the first 2 weeks: leukocytosis; increase in globular sedimentation speed; discrete billirrubin elevation in 10% of patients, as well as moderate elevation of transaminases in 40% of cases, the general urine examination can demonstrate elevated leukocytes in 6 of every 10 patients, thrombocytosis with a duration of 3–6 weeks, and also the positive C- reactive protein and in concentrations > 6 mg/L. Other studies have been recommended that suggest vasculitis, such as antinuclear antibodies (ANA), neutrophil anticytoplasma antibodies, endothelial anti-cell antibodies that have not fully demonstrated usefulness and that can give rise to confusion.[19,20,32,33]

X-ray thorax can show bronchopneumonic infiltrate and especially in patients who present cough and difficulty in breathing in 15% of cases and as a mean in five of the patients, although radiological changes can also be provoked by pneumonitis, haemorrhages, and vasculitis-associated pulmonary nodules.[22,34]

The electrocardiogram can be normal in the first phases on demonstrating changes such as tachycardia, PR-QT prolongation, and abnormal Q waves (data of an infarction); this study was performed in all patients, finding predominantly tachycardia and prolonged QT.[2,6,8–10] Echocardiograph studies form an important part of KD diagnosis and are crucial, particularly in children with atypical or incomplete clinical profiles who manifest fever and fewer than four basic signs.[2,16]

Coronary-artery damage was found in 6 of the 20 patients; in five, this affected the left coro-

nary artery, and in one patient there was dilatation in the right as well as in the left coronary artery. Four patients additionally presented aortic and mitral insufficiency; in two, this was associated with coronary-artery dilatation. In the remaining two patients and as a unique finding, one child manifested left ventricular dyskinesia and cardiomegalia without coronary damage. Aortic and mitral vascular damage has been reported less frequently, although this type of lesion can be expected as a consequence of cardiac value inflammation. In paediatrics areas it is very important the knowledge of the following coronary disease risk factor: Male gender, Age less than one year old, pericarditis, myocarditis, fever more than 10 days, haemoglobin less than 10 g/dL, C reactive protein more 10 mg/dL, recurrent fever.[2,6,12,26,33,35]

There are two additional more precise tests that are utilized in the identification of coronary damage: included among these are myocardiac and coronariograph perfusion gammagrams. In addition, coronary angiography by magnetic resonance (MRA) provides images equivalent to coronary angiography that additionally inform on flow in dilated arteries. Other procedures include Electron beam computed tomography (EBCT) that is used to estimate the characteristics of myocardial ischemia and that is useful in detecting progressive myocardial ischemia, as well as Multislice spiral computed tomography.(MSCT) a non-invasive resource comparable to coronary angiographies for visualizing arterial stenosis in children with KD. Some of these procedures may constitute the standards for diagnosis[6,33,36,37] at our hospital in the future. In the meanwhile and during the time during which we do not possess this technology, patients can be transferred to other medical centers in the city of Hermosillo for angiographies.

The most utilized treatment is the application of IGIV at a single dose of 2 g/kg for 12-h infusion; this is the most acceptable treatment and has allowed to reduce the prevalence of aneurysms by < 5% and mortality from 2–0.3%,[14] although we have also employed an IGIV scheme at two gamma-globulin doses at 400 mg/kg/day for 5 days, in addition to aspirin at 80–100 mg/kg/day. According to the patient response, the IGIV dose can be repeated or corticoids may be added, especially in refractory cases. Other therapeutic agents have been recommended, such as cyclosphosphamide, cyclosporine, and ulinastatin in a limited number of cases.[6] A product has been recently recommended that is based on monoclonal antibodies against the alpha tumor necrosis factor, namely, Infliximab, which has been employed successfully.[3,6,33] And even more recently, a monoclonal antibody has been utilized that inhibits the IIb/IIIa platelet glicoprotein IIb/IIIa receptor and known by the name Abciximab, this favoring the more rapid resolution of aneurysms.[3,6,38]

In the present report, nine patients received gamma globulin at a dose of 400 mg/kg/day during a 5-day period associated with aspirin in all cases treated between 1989 and 2000; later, IGIV was administered in a sole dose of 2 g/kg, and aspirin at conventional doses. In two patients, we additionally utilized prednisone; one of these patients presented an atypical disease course and there was the need to apply two additional doses of IGIV due to the persistence of fever and coronary dilatation. This treatment permitted coronary artery-damage remission and improvement, and the patient experienced an evolution without sequel during the following 9 months of patient follow-up in out-patient consultations. Special mention is merited for the case of the first adolescent diagnosed in 1988 with the characteristic KD profile and who presented left coronary dilatation. Because IGIV was unavailable at the time, after a desperate decision gamma globulin i.m. was used at a dose of 65 mg/kg/for 5 days, with a total dose of 0.5 gramos daily divided into two fractions and aspirin at 80 mg/kg/day orally. The patient was followed up for a period of 3 months in out-patient consultations and later transferred to control at another medical care center. The patient at present is 32 years of age and exhibits no manifestations of the cardiovascular problem.

The use of gamma globulin i.m. treatment is not recommended, primarily because product presentations do not cover dosage requirements. In addition, there is the risk of side effects due to the mercurials used as a vehicle.[39–42]

In eight patients administered IGIV at doses of 2 g/kg, none developed coronary changes and hospitalization time was notably better. Sixteen patients were followed up for periods of 6–8 months in out-patient medical and cardiologic consultations without sequel, although surveillance is on-going for these patients.

According to the actually criteria to following evolution of coronary disease in KD are: The

limits for a coronary diameter: In children younger than 3 years old should not have more 3 mm, and children of 5 years not more than 4 mm. Also the irregular lumen or when the front segment has a diameter of 1.5 times bigger.

Nowadays through the surface body area, we can establish the percentile values for the coronary diameter.

The coronary aneurysms is small if it has only 5 mm of diameter. His medium when the diameter is between 6 to 8 mm, and it is giant if the diameter is bigger than 8 mm. The echocardiography review it is very important to take a look of the proximal coronary artery.

The following of coronary dilatation should be done by bidimentional echocardiogram between the second week and a month. If the coronary artery persisting dilated a coronary gammagraphy would be necessary and a coronary angiographies after 6 to 12 months initial diagnostic of KD.

The patient with giant aneurysm (> 8 mm) 5 mg/K of aspirin once a day indefinitely.

The next clinical control of the patient by the paediatrician and cardiologist would be every 6 months and the echocardiogram once on a year. The effort proof, most be starting at 5 years old, and more over remember: 1. Clinical control during two year of aneurysms > 8 mm diameter, 2. Only 50% of the aneurysms with > 8 mm diameter have involution and the stenosis risk it is greater, 3. the revascularization surgery should be made before the myocardial infarction.[2,14,33]

It is well known that if KD is recognized in a timely fashion, it is possible to diminish considerably the possibility of coronary damage and also of cardiovasculary sequel. In Mexico to date, the exact number is unknown of patients who have presented KD and who have arrived at adulthood manifesting early-onset myocardial ischemia.[2,35]

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