Kawasaki Disease Immunoglobulin Resistance. Diagnosis and Therapeutical Management

Abstract

Background: Kawasaki disease (KD) is an acute self-limited vasculitis that primarily affects children under 5 years. It is the leading cause of acquired heart disease in children in developed countries. Intravenous immunoglobulin (IVIG) and aspirin are the mainstay of treatment. 20% of patients are resistant to IVIG, presenting increased risk of coronary aneurysms. Several scores have been developed in Japan to identify patients with increased risk of resistance to IVIG.

Objectives and Methods: To analyze the cases of KD diagnosed during four years, in a tertiary hospital, and analyze the characteristics of patients who were resistant to IVIG. Retrospective study of cases that met clinical criteria for EK, in our hospital, during the years 2009-2013 was performed.

Results: 48 patients were diagnosed. The boy / girl ratio was 26/22. The age range was 3.3 months to 13 years. Thirteen patients had atypical age. The most common clinical manifestations were fever (100%), followed by polymorphous rash (89%), changes in oral cavity (83%), bilateral conjunctivitis (78%), changes in extremities (68%) and cervical lymphadenopathy (43%). 18% were incomplete forms and three patients developed shock. 25% had echocardiographic abnormalities in the acute phase. All were treated with IVIG and aspirin. There were 8 cases refractory to IVIG. None has cardiac sequelae.

Conclusions: To a KD with severity data (refractory to IVIG, persistently elevated CRP, <1 Year old or shock) there is an increased risk of developing coronary aneurysms.

Introduction

Kawasaki disease is an acute, self-limited vasculitis that primarily affects children under 5 years. It is the leading cause of acquired heart disease in children in developed countries.

It is characterized by fever, non-exudative bilateral conjunctivitis, erythematous lips and oral mucosa, changes in extremities, rash and cervical lymphadenopathy. Its importance is that 15-25% of the untreated children develop aneurysms in the coronary arteries can lead to myocardial infarction, sudden death or ischemic heart disease. There incomplete or atypical, more frequent extreme ages, that for delay in diagnosis and consequently in treatment have a higher risk of developing coronary aneurysms cases. Treatment with intravenous gamma globulin (IVIG) in the first 10 days of illness significantly decreases the prevalence of aneurysms, (from 20% to <5%).

20% of patients are resistant to IGIV V1. Several scores have been developed in Japan to identify patients at increased risk of IVIG treatment resistance, and therefore greater risk of developing coronary aneurysms.

Kobayashi et al they proposed in 2006 a model prediction refractory to treatment with IVIG [1], based on 7 variables: age <12 months start time of treatment <5 days and laboratory abnormalities (percentage of neutrophils> 80%, elevated AST> 100 IU / L, sodium <133 mmol / L, CRP> 10 mg / dl, platelets <300,000 / mm3) [2]. These scores have low sensitivity and specificity in no patients Japanese’s [3].

Objective

Describe the epidemiological, clinical, laboratory, treatment, cardiac involvement and sequelae of cases of Kawasaki disease, diagnosed for four years in a tertiary hospital and analyze the specific characteristics of the patients, who were resistant to treatment with IGIV and compare them with those responding properly.

Materials and Methods

Retrospective study of cases that met clinical criteria for EK in our hospital during 2009-2013. The stories were reviewed individual clinic discharge patients diagnosed with EK.

It was defined as refractory patients in the fever persisted 24-48 hours after the first dose of IVIG, or resorted to 36 hours or more after completing the infusion of IGIV EK.

We compared the variables of the score of Kobayasi of IVIG responders with no responders.

Results

EK was diagnosed 48 patients during this period. Nine cases were incomplete forms, and 3 cases developed cardiogenic shock and required admission to the Unit Pediatric Intensive Care (PICU). The boy / girl ratio was 26/22.

The mean age at diagnosis was 3.5 years, with a range of 3.3 months to 13 years. Thirteen of the patients had atypical age (less than six months or more than five years) to diagnosis.
seasonality, 33 cases (69%) occurred in the winter months and spring.

The most common clinical manifestations (Figure 1) were fever (100%) and polymorphous rash (89%). 83% had changes in the oral cavity, 73% non-exudative bilateral conjunctivitis, 68% changes in the extremities (edema or rash in the acute phase, peeling in subacute phase), and 43% had more cervical lymphadenopathy 1.5 cm.

As for the analytical data presented leukocytosis and anemia, income, 66.6% of patients, thrombocytosis 62%, 10% and thrombocytopenia. Average maximum PCR was 168.9 mg / L (range: 25.5-539). In half the cases increased GPT, with a higher average value of 83U / L.

All patients are undergoing at least one echocardiography, and 25% had alterations in it during the acute phase. The most frequent alterations were coronary ecstasy (6 cases), followed by the involvement of systolic function during acute myocarditis, (3 cases), the hiperrefrigency (or ability to refract light) of the walls of the coronary arteries (2 cases), and pericardial effusion (2 cases). In subsequent echocardiographic reviews patient has no cardiac sequelae.

All patients with IVIG and ASA was treated. The average time from the onset of fever up IVIG infusion was 9 days. There were eight cases refractory to such treatment, so were given a second infusion of IVIG and six patients, bolus intravenous corticosteroids, two patients. The median hospital stay was 5 days.

Comparing the group of patients responding to the first dose of IGIV, with the group of patients with refractory latter EK, they had a higher average value of total leukocytes (24174 / mm3 vs 20974 / mm3), half-PCR (330.3 mg / L vs 172.5 mg / L), lower average sodium (128.6 mEq / L vs 132.8 mEq / L), and lower average value of platelets (52060 / mm3 vs 490,667 / mm3). However, there were no differences in the average value of GPT, and more patients had less than one year (0 patient vs 5 patients). In both groups the average number of days from the onset of fever and the first infusion of IVIG was more than 5 days (Table 1).

Three patients developed cardiogenic shock in the acute phase (severe impairment of systolic function left ventricle. With hypotension and signs of peripheral hypo perfusion), and required, therefore entry in the PICU for inotropic therapy IV (dopamine, dobutamine, levsimendan and milrinone). Two of them had more than five years old.

**Discussion**

Which it is diagnosed by clinical criteria that may appear sequentially. Clinical and laboratory data are, in many cases, overlap those of other pediatric diseases, which can delay diagnosis.

The characteristics of the patients in our series are similar to those published so far [4]. 16.6% of our patients (8/48) were refractory to IVIG.

The score of Kobayasi, has shown high sensitivity to predict refractory to IVIG, but low specificity in US patients [3].

The review of our cases we can say that our patients with the score of Kobayasi analytical data, are more likely to be refractory to IVIG, but non-compliance with these data not be excluded from power. Patient refractory to IVIG our series had mainly analytical data of more serious disease.

There is no consensus regarding what should be the treatment of this group of patients who do not respond to the first dose of IVIG. Recent studies (RAISE study) [5], demonstrating that, with a score of Japanese greater Kobayasi of 5 patients benefited from corticosteroids add the initial standard treatment, decreasing the occurrence of coronary aneurysms. There have also been studies that treatment with infliximab in patients do not respond or partially respond to IVIG provides good results in terms of reduction in the duration of fever, leukocytosis and PCR, although they have failed to demonstrate the decrease in the incidence of coronary aneurysms [6].

While this score is not applicable to our population (non-Japanese), it is recommended to use corticosteroids in patients refractory to IVIG, or in those who present with data from more severe disease, (under one year old patients, PCR persistently high, anemia or hypoalbuminemia, hypertransaminasemia, or who develop features of hemophagocytic lymphohistiocytosis and / or shock), as they are at the greatest risk of developing coronary aneurysms [7,8].

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**Figure 1**: Frequency of occurrence of clinical criteria. Description in the text.

**Table 1**: Analytical data (mean and range) and Score Kobayashi in groups of responders and no responders’ patients’ first dose of IVIG.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Score responders</th>
<th>Score No responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Age &lt; 12 months</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Maximum leucocytes</td>
<td>20974/mm3 (5970-34600)/mm3</td>
<td>24174/mm3 (11140-37200)/mm3</td>
</tr>
<tr>
<td>Maximum neutrophils</td>
<td>26900/mm3 (77.8%) (4500-26900)/mm3</td>
<td>15582/mm3 (69.1%) (8150-30000)/mm3</td>
</tr>
<tr>
<td>Minimum Platelets</td>
<td>490,667/mm3 (63000-535000)/mm3</td>
<td>52400/mm3 (51000-416000)/mm3</td>
</tr>
<tr>
<td>Level hemoglobin</td>
<td>106 g/L (77.146) g/L</td>
<td>7.5 g/L (66-115)g/L</td>
</tr>
<tr>
<td>Maximum Reactive C Protein</td>
<td>172.5 mg/L (26-413) mg/L</td>
<td>370.3 mg/L (60.2-539) mg/L</td>
</tr>
<tr>
<td>Maximum GPT, glutamate pyruvate transaminase</td>
<td>94.4 UI/L (11-472) UI/L</td>
<td>76.6 UI/L (22-440) UI/L</td>
</tr>
<tr>
<td>Minimum serum sodium</td>
<td>132.8 mEq/L (119-141) mEq/L</td>
<td>128.6 mEq/L (126-136) mEq/L</td>
</tr>
<tr>
<td>Lower total protein</td>
<td>7 mg/dL (5.3-8.6)mg/dL</td>
<td>3.8 mg/dL (1.8-7.6)mg/dL</td>
</tr>
<tr>
<td>Days (average) from start to 1st dose IVIG</td>
<td>6.4 days</td>
<td>5.6 days</td>
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References


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