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ORIGINAL ARTICLE

Kawasaki disease: the importance of early recognition

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Abstract

Kawasaki disease (DK) is a self-limited vasculitis of unknown etiology that predominantly affects children under 5 years of age. Studies show some risk factors, but still with no confirmation. The diagnosis is based on clinical criteria and the long-term prognosis is determined by the involvement of the coronary arteries. **Objective:** To describe the cases of patients hospitalized in the General Pediatrics ward of the Grupo Santa Casa de Belo Horizonte with diagnosis of Kawasaki disease. **Methods:** Patients admitted from January 2015 to December 2017 who were discharged with a diagnostic hypothesis of Kawasaki disease were selected. A descriptive study was carried out through the analysis of the medical records of these patients. **Results:** Eleven cases were analyzed, mean age was 3.1 years. Seven patients were diagnosed with Kawasaki disease on admission, along with other hypotheses. The fever time ranged from 6 to 30 days. Eight patients met criteria for the diagnosis of KD, the others fit the diagnosis of incomplete KD. Seven children received immunoglobulin; five became afebrile after taking the medication. All of these also started using acetylsalicylic acid (ASA). All patients underwent an echocardiogram, four of which presented alterations in the examination. **Conclusion:** The diagnosis of Kawasaki disease is still delayed and often confused with other diseases of childhood, causing delay in treatment, which may favor an increased risk of cardiac complications.

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INTRODUCTION

Kawasaki disease (KD) is a self-limiting form of vasculitis of unknown etiology that preferentially involves male children under the age of five years[1,2]. Tomisaku Kawasaki described the disease in Japan in 1967. A number of studies have been performed since to elucidate the disease, but many uncertainties still remain. Its pathogenesis is still unclear, although different genes have been considered to affect susceptibility to the disease, occurrence of complications, and response to therapy[1].

KD manifests with systemic inflammation of medium caliber arteries, multiple organs and tissues during acute fever episodes. The coronary artery may also be affected, giving rise to the most feared complication of the condition. Three pathological processes are in effect in vasculopathy: necrotizing arteritis, subacute/chronic vasculitis, and luminal myofibroblastic proliferation[1].

Clinical diagnosis is well established in the literature and is based on the presence of fever lasting for five or more days in association with at least four of the following clinical signs (Table 1): rash (diffuse macopapular being the most common); extremity changes (erythema, edema, pain, or peeling); bilateral nonexudative conjunctivitis; oral changes (erythema, cracked lips, peeling, strawberry tongue, bleeding of the lips) or cervical lymphadenopathy (nodal mass > 1.5 cm)[1,2]. The most recent guidelines of the American Heart Association (AHA) indicated that patients with four or more symptoms, particularly erythema and edema of the hands and feet, presenting fever for four days can be diagnosed with KD[1].

Many patients may present with persistent fever without however manifesting at least four clinical signs. Individuals with fever for five or more days associated with two or three of the clinical signs may be diagnosed with incomplete or atypical KD. The AHA designed a flowchart (Figure 1) to identify suspect cases[1,2]. The following altered laboratory findings are considered indirect signs of disease: increased C-reactive protein (CRP) level; elevated erythrocyte sedimentation rate (ESR); anemia; elevated platelet count; leukocytosis; hypoalbuminemia; liver function alteration; and sterile pyuria. A positive echocardiogram showing dilated coronary arteries associated with fever also helps diagnose patients with KD.

Although not curative, treatment offered in the acute phase of the disease attempts to decrease inflammation, arterial injury, and the risk of thrombosis, mainly when coronary artery anomalies are present. The literature has suggested a relevant role for immunoglobulin therapy and ASA, the first ideally started within ten days of the onset of fever. However, even when offered ideal therapy, 20% of pediatric patients develop some form of transient coronary artery dilatation[1]. Given the increased risk of cardiac alterations, echocardiography is mandatory for all patients diagnosed with KD. Ideally, echocardiography must be performed upon diagnosis and repeated within 1-2 weeks and after 4-6 weeks of treatment when the patient presents with normal or mildly dilated coronary arteries. Patients with coronary aneurysms must be offered earlier and more frequent individualized care based on the size and level of risk of the aneurysm. Presence of dilatation or aneurysm in the coronary artery, mitral regurgitation, ventricular dysfunction, or pericardial effusion confirms the diagnosis of incomplete KD[1,3]. A negative echocardiogram does not rule out a diagnosis of KD.

The relevance of this condition prompted the organization of a study to describe the cases of inpatients staying in the pediatrics ward of a quaternary care hospital in Belo Horizonte.

METHODS

This descriptive retrospective study included the charts of inpatients staying at the pediatrics ward of Santa Casa Group hospitals in Belo Horizonte (São Lucas Hospital and Santa Casa Hospital) between January 2015 and December 2017. A search was made for all discharged patients diagnosed with Kawasaki Disease. Some of the charts of patients seen in Santa Casa Group hospitals were not available in electronic format, thus requiring a manual search through the records of discharged patients seen in the pediatrics ward and later referred to follow-up. Patients with electronic records were searched based on ICD code M303 (mucocutaneous lymph node syndrome - Kawasaki disease).

RESULTS

The search yielded the charts of 12 patients. One of the patients was excluded for not having had fever throughout the entire manifestation of the disease. Seven of the 11 remaining patients were diagnosed with KD although other conditions were also considered. Diagnosis is eminently clinical (fever associated with four of five clinical signs), as mentioned before. Three children met the diagnostic criteria partially and were diagnosed with incomplete KD. Patient age ranged from nine months to ten years and three months, averaging 3.1 years. Seven children were males and four were females (1.7:1 male/female ratio).

Time with fever ranged from six to 30 days. Rash was the most prevalent clinical sign along with fever (n=11) followed by periungual desquamation (n=10), oral changes (n=8), and nonexudative conjunctivitis (n=7). Lymphadenopathy was seen in six patients. The least prevalent sign of disease was extremity changes (edema of the hands and feet; n=3). Periungual desquamation was a prevalent - albeit of late onset - sign of disease progression. One child without extremity changes in the beginning of the disease did not progress to desquamation (Table 2).

Seven of 11 patients were given human immunoglobulin therapy (2g/kg) and ASA (tapering doses starting at 80-100mg/kg/day). One patient was not prescribed immunoglobulin therapy and was started on ASA after undergoing echocardiography. All subjects had echocardiograms performed during

Table 1. American Heart Association modified diagnosis of classic Kawasaki disease[1].

Fever lasting for five days associated with at least four of the five clinical signs below:
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa.
2. Bilateral bulbar conjunctival injection without exudate.
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like.
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase.
5. Cervical lymphadenopathy (≥ 1.5 cm diameter), usually unilateral.

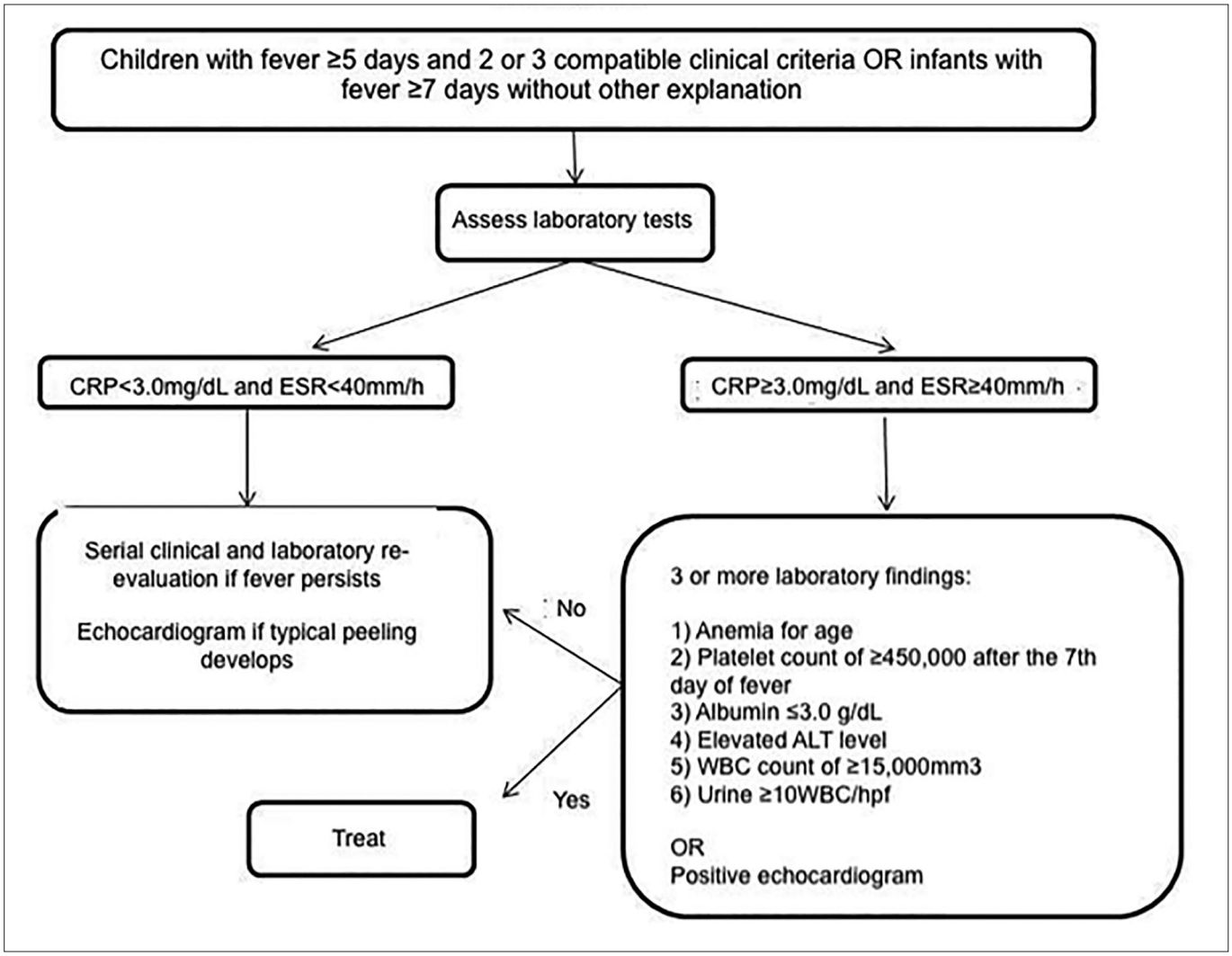


Figure 1. Evaluation of Suspected incomplete Kawasaki Disease - modified from the American Heart Association. 1 - Positive echocardiogram: coronary dilatation or aneurysm; ventricular dysfunction, mitral regurgitation or pericardial effusion. CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; ALT - alanine transaminase.

hospitalization and four were positive for coronary artery dilatation and pericardial effusion. Their families were advised of the relevance of following their children with clinical and imaging examination and of keeping the patients prescribed ASA during hospitalization on the medication after discharge.

DISCUSSION

Studies have reported an increase in the number of children diagnosed with KD in winter and early spring in North America[1], when the prevalence of respiratory viral infections is higher, questioning the existence of a possible

causal relationship between the two. Higher risk of developing KD has been assigned to individuals with relatives diagnosed with the condition, thus reinforcing the possible presence of a genetic element[1,4,5]. Our study enrolled a small number of patients and a link between the disease and seasonality was not observed. In the United States, KD is considered the main cause of acquired heart disease in childhood[6]. In Japan, overall incidence has also increased[1].

In Brazil, however, few studies have been carried out on the subject and epidemiological data is still scarce. Nonetheless, global epidemiological data indicate that incidence is on the rise. A study published in 2010 enrolling inpatients seen at the São Paulo University Hospital between 2000 and 2008 found an average of 2.1 cases of KD per year[6] versus 3.7 in our study. Although small, might our study have picked up an increase in incidence? Is KD taking over the role of rheumatic fever as the main cause of acquired heart disease in childhood in Brazil? Or was KD never diagnosed due to lack of information? As more publications discuss the disease and more knowledge is amassed, the more pediatricians will be able to consider KD in differential diagnosis.

Despite the many studies on the subject, diagnosing patients with KD is still challenging. The clinical signs of the disease may be seen in other conditions such as viral infection / pediatric exanthematous diseases (the likes of mononucleosis and adenovirus and enterovirus infection), infection by streptococcus and staphylococcus, or drug hypersensitivity. Differential diagnosis calls for serology tests before specific therapy for KD is started. Nonspecific signs such as vomiting, abdominal pain, irritability, and prostration may also occur and hamper prompt diagnosis. Incomplete KD with the absence of some classic signs of disease may also delay definitive diagnosis[7]. All patients had symptoms beyond the ones listed in diagnostic criteria. Gastrointestinal symptoms were the more prevalent: vomiting was observed in four children, while abdominal pain and diarrhea were seen in three individuals. One patient showed irritability at the start, but no signs of meningeal irritation (Table 3).

In a recent publication, the AHA reinforced the fact that clinical signs may not be present concomitantly, but that their existence at any point in the progression of the disease should suffice to diagnose patients with KD[1,8]. Fever and rash were the first signs of disease observed in most of the children seen in our service. In the past, patients were diagnosed with KD after five or more days of fever, but the more recent guidelines of the AHA state that four days of fever associated with four of five clinical signs should suffice to establish a diagnosis of KD[1,8].

Fever may last for as long as 3-4 weeks or longer in a few rare cases[2]. The shortest duration of fever was six days in our group of patients. One individual had fever for 30 days, with symptoms stopping a day after the start of immunoglobulin therapy. Studies have listed other signs suggestive of KD, such as perineal scaling and reactivation of the site of BCG vaccine injection, but the 2017 AHA publication did not include these symptoms in the diagnostic criteria[8]. In our study, four patients progressed to perineal scaling, but none had alterations on the site of BCG vaccine injection.

Although helpful, no single laboratory test can provide clues leading to a definitive diagnosis of KD. Since it is a form of vasculitis, CRP and ESR - nonspecific workup markers - help to diagnose patients with incomplete KD. CRP is more frequently used in patient follow-up, since it decreases progressively and more quickly than ESR as inflammation resolves. ESR may also increase after immunoglobulin therapy and become useless to assess response to treatment[1,2]. The patients included in our study had CBC and CRP tests during the progression of the disease. One patient had the two inflammation markers within reference levels, and in one individual only the CRP level was altered. All remaining patients had altered test results.

Table 2. Patient clinical signs indicative of Kawasaki Disease.

Case	Age	Sex	Fever	Time with fever	Rash	Lymphadenopathy	Rash / feet & hand edema	Periungual desquamation	Nonexudative conjunctivitis	Oral changes
1	3 y 9m	F	yes	6 days	yes	yes	yes	yes	yes	yes
2	1 y 5m	F	yes	10 days	yes	yes	yes	yes	yes	yes
3	3 y 7m	F	yes	6 days	yes	yes	no	yes	no	no
4	10 y 3m	M	yes	10 days	yes	yes	no	yes	yes	no
5	5 y 8m	M	yes	12 days	yes	yes	no	yes	no	yes
6	2 y 2m	M	yes	6 days	yes	no	no	no	yes	yes
7	9m	F	yes	11 days	yes	no	yes	yes	yes	yes
8	4 y 1m	M	yes	8 days	yes	no	no	yes	yes	yes
9	2 y 8m	M	yes	30 days	yes	no	no	yes	no	no
10	1 y 1m	M	yes	6 days	yes	no	no	yes	yes	yes
11	3 y 6m	M	yes	8 days	yes	yes	no	yes	no	yes

y: years; m: months; F: female; M: male

The treatment prescribed to patients diagnosed with KD has been extensively described in the literature and associated with significant reduction of complications from the disease. Ideally, therapy should be initiated before the tenth day from the start of fever, with a single dose of human immunoglobulin of 2g/kg infused for ten to 12 hours and ASA (80-100mg/kg in the acute phase of the disease tapered to 3-5mg/kg/day after 48-72 hours free of fever or 14 days after the start of the disease).

Most patients respond well to treatment with cessation of fever and reduction of inflammatory markers (ESR and CRP). Five of the seven individuals given immunoglobulin therapy in our study became afebrile after medication. One patient had fever after spending 24 hours without fever after immunoglobulin therapy. However, within the same time period the patient had symptoms of influenza, to which fever was linked. Another patient had an isolated bout of fever four days after immunoglobulin therapy in association with fleeting exanthem.

Two of the four patients not prescribed immunoglobulin were afebrile upon admission (although they had had fever for more than five days); one had a last bout of fever upon admission; and one had been afebrile for four days, did not meet all the criteria, but was diagnosed with KD after an echocardiogram showed coronary artery dilatation. This last patient was started on high dose ASA and was placed on outpatient follow-up.

Some 10-20% of the patients do not respond to medication, and develop persisting fever 36-48 hours after immunoglobulin therapy. These children are at higher risk of developing coronary artery aneurysms[1,9]. The mechanism is still unknown, but recommendations indicate the need to prescribe additional immunoglobulin therapy, while studies have suggested infliximab as adjuvant therapy to try and reduce inflammatory markers and duration of fever[1,9,10]. Since KD is an inflammatory condition, studies have also looked into the use of glucocorticoids as primary or salvage therapy for immunoglobulin therapy non-responders and high-risk patients[1,11,12]. None of the patients in our study was given additional immunoglobulin therapy or alternative treatments with infliximab or glucocorticoids.

Patient morbimortality is strongly linked to heart disease and possible complications such as coronary artery dilatation/aneurysms, hence the relevance of performing examination with echocardiography as soon as possible. The AHA uses the system based on the Z-score to define dilatation and categorize patients for risk. A Z-score between 2 and 2.5 characterizes dilatation by aneurysm, an anomalous finding. Values above 2.5 characterize coronary artery aneurysms of small (Z-score ≥2.5 and <5), medium (Z-score ≥5 and <10 and absolute size <8 mm), or large (Z-score ≥10 or absolute size ≥8 mm) sizes[1].

These alterations help to define follow-up and future workup required. All patients underwent echocardiography in our service. One patient initially had a negative echocardiogram, but one week after diagnosis he had a pericardial effusion that progressed to right coronary artery dilatation (Z 2.06). Further examination during follow-up evinced the resolution of the alteration. Three patients had positive echocardiograms, two with coronary artery dilatation and one with pericardial effusion. However, we were unable to find their control workup. Although the three did not meet the criteria for KD, they were diagnosed with the condition based on their echocardiogram findings. Two of the patients with positive echocardiograms were not prescribed immunoglobulin therapy for being afebrile after examination. This indicates the relevance of knowing about and considering KD and of performing diagnosis and ordering adequate tests in a timely fashion.

Table 3. Diagnosis upon admission vs. time until diagnosis of KD vs. associated nonspecific symptoms.

Case	Diagnosis Upon Admission	Time From Symptom Onset Diagnosis	Associated Nonspecific Symptoms
1	Cervical lymphadenopathy	6 days	Vomiting, abdominal pain, diarrhea
2	Kawasaki disease	9 days	Irritability
3	Reactive lymphadenopathy	8 days	Neck pain
4	Nonspecific febrile disease, pneumonia, Kawasaki disease	22 days	Headache, abdominal pain
5	Scarlet fever, Kawasaki disease, staphylococcus infection	16 days	"Sandpaper-like" rash, pruritus, odynophagia
6	Kawasaki disease	7 days	Cough
7	Enterovirus infection, exanthema subitum, erythema multiforme, Kawasaki disease	5 days	Vomiting, diarrhea, prostration
8	Kawasaki disease	7 days	Headache, nasal discharge
9	Bacterial gastroenteritis, appendicitis	30 days	Vomiting, diarrhea, abdominal pain, "sandpaper-like" rash, joint pain
10	Kawasaki disease	5 days	Vomiting, prostration, cough
11	Allergic hives	12 days	Pruritus, "sandpaper-like" rash, AOM

KD may introduce complications other than coronary artery disease, such as myocardial ischemia, and coronary artery stenosis and thrombosis, which may occur long after the acute stages of the disease are gone. Although infrequent, these events require individualized care, including measures such as thromboprophylaxis, drug therapy, imaging tests, and physical activity restrictions[1,13].

Risk stratification models described in the literature, the most recent of which published by the AHA in 2017, segregate cardiac alterations and dictate how patients should be followed in the long run and which children might require care in adult age. Heart complications become more frequent in cases of recurrent disease[14]. None of the patients included in our study had records of treatment of recurrent disease in our center.

Despite the scarcity of epidemiological data, attention is required when considering KD and the diagnosis of the condition. Pediatricians must consider Kawasaki disease in the differential diagnosis of febrile disease, particularly when seeing younger, harder-to-diagnose patients. Thinking about KD introduces significant changes to how each case is managed. Patients undergo more specific testing and are prescribed medication such as immunoglobulin to change the course of the disease and its potential complications.

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