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INCOMPLETE KAWASAKI DISEASE IN A PRESCHOOLER: A LITERATURE REVIEW AND REPORT

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Abstract: The term "incomplete Kawasaki disease (IKD)" was first used to describe patients with coronary complications who did not meet the classic diagnostic criteria for Kawasaki disease (KD). The risk of coronary artery involvement is similar, if not greater, in cases of IKD. However, recognition of IKD is challenging and often delayed, especially in infants. Several algorithms have been formulated to identify cases of IKD using supplemental clinical, echocardiographic, and laboratory features. Although fever is not required for the diagnosis of KD in the Japanese guideline, most current guidelines, including those from the American Heart Association (AHA), consider the presence of fever for at least seven days as a requirement for the diagnosis of both KD. and IKD in infants. A review of the literature identified similar cases with a growing consensus on the need to redefine the role of fever. The pediatrician must look for lesions in the coronary arteries in cases of high clinical suspicion, even if the febrile period is short, especially in children younger than six months. In addition, more groundbreaking research is directly needed to identify immunological and cellular markers that can be tested early in the disease course and guide management.
Keywords: Incomplete kawasaki disease in infants, coronary hypertension aneurysm, incomplete kawasaki disease.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis in children. Recent studies have implicated inflammatory cytokines and abnormalities in immune regulation as part of the pathophysiology of KD, creating new targets for adjuvant therapy. It is named after Tomisaku Kawasaki, a Japanese pediatrician who first described this febrile vasculitis in 1967. Coronary artery complications occur in 25% of affected children. It is currently recognized as the leading cause of acquired heart disease in developed countries[1].

The term "incomplete Kawasaki disease (IKD)" was initially used to describe patients with coronary complications who did not meet all diagnostic criteria for KD. Several studies have shown that the risk of coronary artery involvement is similar, if not greater, in cases of IKD. However, recognition of IKD is challenging and often late.[2,3]. Infants younger than six months represent a special age group, as they are more likely not to have classic manifestations and are at greater risk of coronary artery involvement[4]. Several algorithms have been formulated to identify cases of IKD using supplemental clinical, echocardiographic, and laboratory features. Although fever is not required for the diagnosis of KD in the Japanese guideline, most current guidelines, including the American Heart Association (AHA), consider the presence of fever for at least seven days a requirement for the diagnosis of KD and IKD infants[5]. We present a case of incomplete Kawasaki disease (IKD) in a four-month-old child who had a fever for less than three days and did not follow the current AHA algorithm for IKD.

Publications on the epidemiology and available drugs and treatment regimens for children with acute KD in Latin America are scarce. One of the largest previous case summaries of children with KD in Mexico reported only 250 children over 32 years. In a case study in Central America (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama) Ulloa-Gutierrez et al. found that from 2000 to 2010, there were only 11 reports from four countries, most consisting of single case reports and small series. Of all countries, Costa Rica contributed the most cases (124 cases in 13 years). However, no cases have been reported in Nicaragua or Guatemala.

The Latin American KD Network (Kawasaki Disease Network in Latin America,

REKAMLATINA) is a standardized registry where data from patients with acute KD in Latin American countries have been collected retrospectively and prospectively since January 2009. The network gathers information on demographic data, clinical characteristics, laboratory evaluation, response to treatments and results. The initial and standard treatment for KD has been the use of high doses of IV immunoglobulin (IVIG) in combination with aspirin. However, in some parts of Latin America, IVIG is not available for the first-line treatment of KD, and even when available, it can be difficult to acquire or administer early.

Although IVIG resistance rates are unknown in Latin America, 10 to 20% of KD patients in the United States, Europe, and Asia have IVIG-resistant KD, increasing the risk of developing coronary artery abnormalities (CAA). This population, in particular, may benefit from adjuvant therapy, as recently recommended in the 2017 revised American Heart Association KD guidelines. Furthermore, certain populations, such as infants with KD, are at increased risk of developing AAC and therefore may warrant additional adjuvant therapy. There are several therapies for treating IVIG-resistant KD and those at high risk of CAA, including second dose IVIG, steroids, infliximab, or other immunomodulatory therapies. However, treatment options are limited in some regions of the world, including Latin America. Furthermore, as no studies have determined which treatment is best for treating IVIG-resistant KD or high-risk KD patients, the choice of treatment is left to the attending doctor. This study aimed to report on adjuvant therapies used to treat high-risk, IVIG-resistant KD patients in Latin America.

CASE REPORT

The work in question refers to a case of a 6-year-old preschooler. This is a male child, attended at the maternity of the institution: '' Hospital Escola de Valença", hospitalized in September 2021 for 6 months and 25 days in an in-hospital environment with a diagnosis of incomplete Kawasaki disease.

Kindergarten without drug allergies, without comorbidities, without use of regular medication, with previous hospitalization at 2 years of age for pneumonia and complete immunization record suitable for age. Preschool patient started a fever of 38.3º, odynophagia for 3 days, and was diagnosed with tonsillitis in the emergency room where amoxicillin was prescribed. Due to no clinical improvement, the patient returned to the emergency room for laboratory tests that showed pyuria in the EAS. After that, the antibiotics were changed to amoxicillin with clavulanate. Because she did not show clinical improvement, she sought help from the assistant pediatrician who prescribed benzathine penicillin. After returning to the emergency room to be evaluated by the doctor on duty, edema was observed in the lower limbs with arthralgia in the knees and elbows and lymph node enlargement in the left cervical region. We opted for hospitalization for diagnostic investigation. Upon admission, a dose of benzathine penicillin 600,000 iu was given. On the 4th day of hospitalization, the preschooler was diagnosed with incomplete Kawasaki disease due to fever for more than 10 days and increased inflammatory tests. Venous human immunoglobulin 2g/kg was prescribed and ASA 50mg/kg day. ASA dose was reduced to 5mg/kg day due to the last fever on September 26, 2021. Blood test requested by the assistant pediatrician was: non-reactive waaler rose, Vhs 60, Rheumatoid Factor negative, uric acid 1, 9; Hmc 4.46; Hb 11.5; Vcm 77.6; Hcm 25.8; Leukocytes 14030; (1/0/0/2/2/4/63/20/8). The laboratory tests requested upon admission were: EAS (undetectable leukocyte, undetectable nitrite,

5 pyocytes, 3 red blood cells, undetectable microbiota, Ecg sinus rhythm, probable Hve without arrhythmia, Aslo negative, ANA non-reactive, Ecott heart structurally and functionally normal, coronary arteries with normal diameters, laminar pleural effusion.

LITERATURE REVIEW

Kawasaki disease is a nonspecific acute systemic vasculitis related to immune dysfunction that primarily affects infants and children in East Asia under 5 years of age[1]. Full KD predominantly occurs in the age group of six months to five years. Diagnostic criteria include fever for more than five days along with at least four of the following clinical features: erythema of the lips and oral mucosa, bilateral non-exudative conjunctival hyperemia, polymorphous rash, changes in the extremities, and unilateral painless cervical lymphadenopathy. In the presence of ≥4 main clinical criteria, especially when redness and edema of the hands and feet are present, the diagnosis can be made after only four days of fever. Typically, the clinical features are not all present at a single point in time, and it is often difficult to establish the diagnosis very early in the course. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases[5,6]. Echocardiography must be obtained at the time of diagnosis, one to two weeks later, and six weeks after discharge. Computed tomography, magnetic resonance imaging, or conventional angiography must be considered for further risk stratification and complete coronary evaluation in children with significant arterial aneurysms on echocardiography[6].

However, pediatricians sometimes encounter febrile children who do not present the full clinical picture but have several findings consistent with those of KD. In this situation, the identification of IKD is a clinical challenge, which can lead to delays in diagnosis and treatment. Echocardiographic changes take time to develop and are usually identified after the first week of illness5. It is well established that prompt recognition of KD and early initiation of IVIG, specifically within seven days, can decrease the incidence of coronary artery aneurysms from 25% to 4%[7,8]. Several studies have shown that the risk of coronary artery involvement is similar, if not greater, in cases of IKD[3]. Therefore, current diagnostic criteria for KD are insensitive indicators for having or developing coronary complications.

A significant proportion of the disease burden occurs in infants under six months of age (10%)9. This age group tends to have fewer typical clinical manifestations and has a higher prevalence of incomplete and atypical KD (40%) compared to older patients (10-12%)[10,11]. Fever and excessive irritability may be the only clinical manifestations of KD in infants. The presence of fever and pyuria in a child can be mistakenly attributed to a urinary tract infection. Due to the elusive nature of the presentation, it is easy to understand why diagnosis and subsequently treatment of KD is delayed in the infant cohort. As a result, they are often diagnosed late and are at increased risk for coronary artery abnormalities, coronary artery aneurysms, and cardiac complications including giant coronary artery aneurysms, shock, and death. Morbidity and mortality in this age group are higher compared to any other age group[6,12,13].

Park et al. compared patients with KD less than and more than six months old and reported a higher incidence of coronary artery abnormalities (21.0% vs. 18.7%) and coronary artery aneurysms (4.7% vs. 3.1%) between the youngest group14. Mastrangelo et al., in their recent single-center cohort of 113 patients younger than one year with KD, reported that infants with incomplete KD appear to have

more severe disease and a greater predilection for coronary involvement compared with infants with complete KD[13].

The most recent IKD algorithm by the AHA for infants includes ≥7 days of unexplained fever plus three or more complementary laboratory findings or typical echocardiographic findings (left anterior coronary artery (LAD) or right coronary artery (RCA) Z-score is ≥2, 5). Additionally, the diagnosis can be considered in the following situations in infants younger than six months: (1) prolonged fever and irritability; (2) prolonged fever and unexplained aseptic meningitis; (3) prolonged fever and unexplained shock or negative culture; (4) prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy; (5) prolonged fever and retropharyngeal or parapharyngeal phlegm unresponsive to antibiotic therapy[5].

The duration of fever has been confirmed as an important risk factor for coronary artery abnormalities. [6,15]. There is a dearth of large-scale studies exclusively on KD below the age of 12 months on this topic. Non-febrile KD has been reported in the available literature; however, it remains poorly defined, with no clear consensus on its natural history and prognosis. Of the few reported cases, it seems to be more common in young children, and most cases had a mild course and few coronary artery abnormalities were identified 16,17. In contrast, we were able to identify only two cases of non-febrile childhood KD in the English literature. All reported cases, including our case, had significant echocardiographic findings reported. [16,18].

Most existing guidelines consider the presence of fever for at least seven days to be a requirement for the diagnosis of KD and IKD in infants. Therefore, it may induce a delay in management and postpone the diagnosis of IKD until confirmation of coronary artery abnormalities, similar to our case. A diminished ability to display a febrile response may be present in some infants, further contributing to the difficulty of diagnosing KD in this age group. Salgado et al., Singh et al., and Pilania et al. all expressed similar concerns[12,19,20]. We believe that the role of fever and the duration required to fulfill the criteria (especially in infants) need to be redefined in the future.

There are many treatment options in the management of IKD, but no consensus has yet been established. The backbone of therapy includes IVIG and aspirin. Adjunctive therapies in treatment have included corticosteroids and biologics 5,6. In our case, the patient was treated with IVIG as soon as the diagnosis of IKD was made; the patient had an excellent response with reduced coronary artery dilation and no new aneurysms on the control echocardiogram two weeks later. This case highlights that the diagnosis of IKD must be considered in infants who have unexplained fever, even in the absence of the main clinical findings of KD, especially in children younger than six months.

FINAL CONSIDERATIONS

Currently, the diagnosis of incomplete Kawasaki disease can be made in cases with fewer classic diagnostic criteria and with several compatible clinical, laboratory or echocardiographic findings. However, the diagnosis of IKD in children younger than six months of age remains a clinical challenge. This results in an increased rate of late diagnosis and subsequent risk of developing cardiac complications in this age group. The pediatrician must look for lesions in the coronary arteries in cases of high clinical suspicion, even if the febrile period is short, especially in children younger than six months. In addition, more groundbreaking research is much needed to identify immunological and cellular markers that can

be tested for early in the disease course and guide management. This study indicates that a better understanding of treatment trends in Latin America can help improve the standard of care for KD patients in this region.

REFERENCES

1. IDRIS, Isra et al. Incomplete Kawasaki Disease in an Infant: A Case Report and Literature Review. **Cureus Journal of Medical Science**, v. 14, n. 2, 2022.

2. YANG, Zhao-Yu et al. Clinical experience in the treatment of incomplete Kawasaki disease with no response to intravenous immunoglobulin: a case report. **Zhongguo Dang dai er ke za zhi= Chinese Journal of Contemporary Pediatrics**, v. 24, n. 12, p. 1311-1312, 2022.

3. YU, Jeong Jin. Diagnosis of incomplete Kawasaki disease. **Korean journal of pediatrics**, v. 55, n. 3, p. 83, 2012.

4. RIVERA-FIGUEROA, Elvia I. et al. Incomplete Kawasaki disease in a child with Covid-19. **Indian pediatrics**, v. 57, n. 7, p. 680, 2020.

5. LI, Tianhua et al. Correct identification of incomplete Kawasaki disease. **Journal of International Medical Research**, v. 49, n. 3, p. 03000605211001712, 2021.

6. PERRIN, Laurence et al. Comparative study of complete versus incomplete Kawasaki disease in 59 pediatric patients. **Joint Bone Spine**, v. 76, n. 5, p. 481-485, 2009.

7. MONEY, Nathan M.; WALLACE, Sowdhamini S. A "Kawasaki Disease Test": When Will We Get There?. **Hospital Pediatrics**, p. e2022007079, 2023.

8. THADCHANAMOORTHY, V.; DAYASIRI, Kavinda; RAGUNATHAN, I. R. Atypical Kawasaki disease presenting with macroscopic hematuria in an infant: a case report. **Journal of Medical Case Reports**, v. 17, n. 1, p. 10, 2023.

9. THANGRAJ, Abarna et al. Onychomadesis in an adolescent male: an important clinical sign in Kawasaki disease. **Rheumatology**, p. kead041, 2023.

10. THANGRAJ, Abarna et al. Onychomadesis in an adolescent male: an important clinical sign in Kawasaki disease. **Rheumatology**, p. kead041, 2023.

11. FORTUNA-REYNA, Brenda et al. Use of adjunctive therapy in acute Kawasaki disease in Latin America. **Frontiers in Pediatrics**, v. 8, p. 442, 2020.

12. LAM, Jonathan Y. et al. Intravenous immunoglobulin resistance in Kawasaki disease patients: prediction using clinical data. **Pediatric Research**, p. 1-6, 2023.

13. CIMAZ, R.; SUNDEL, R. Atypical and incomplete Kawasaki disease. **Best Practice & Research Clinical Rheumatology**, v. 23, n. 5, p. 689-697, 2009.

14. SUDO, Daisuke et al. Coronary artery lesions of incomplete Kawasaki disease: a nationwide survey in Japan. **European journal of pediatrics**, v. 171, p. 651-656, 2012.

15. FUKUSHIGE, J. et al. Incidence and clinical features of incomplete Kawasaki disease. **Acta Paediatrica**, v. 83, n. 10, p. 1057-1060, 1994.

16. YU, Jeong Jin. Diagnosis of incomplete Kawasaki disease. **Korean journal of pediatrics**, v. 55, n. 3, p. 83, 2012.

17. RIVERA-FIGUEROA, Elvia I. et al. Incomplete Kawasaki disease in a child with Covid-19. **Indian pediatrics**, v. 57, n. 7, p. 680, 2020.

18. LI, Tianhua et al. Correct identification of incomplete Kawasaki disease. **Journal of International Medical Research**, v. 49, n. 3, p. 03000605211001712, 2021.

19. ROHANI, Pejman et al. Persistent elevation of aspartate aminotransferase in a child after incomplete Kawasaki disease: a case report and literature review. **BMC pediatrics**, v. 20, p. 1-5, 2020.

20. RAUT, Sumantra et al. Incomplete Kawasaki disease as presentation of COVID-19 infection in an infant: a case report. **Journal of Tropical Pediatrics**, v. 67, n. 3, p. fmaa047, 2021.