

Correct identification of incomplete Kawasaki disease

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Abstract

Incomplete Kawasaki disease (IKD) is characterized by a longer fever time, younger age of onset, and higher incidence of coronary artery disease compared with complete Kawasaki disease. Kawasaki disease is often difficult to diagnose early because of its incomplete clinical symptoms. This issue could delay treatment and harm the health of the child. This article reviews the clinical characteristics and pathogenesis of IKD to help clinicians understand the symptoms of IKD, make the correct diagnosis, and provide timely treatment.

Keywords

Incomplete Kawasaki disease, coronary artery lesion, children, fever, young age, aneurysm, intravenous immunoglobulin

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Introduction

Kawasaki disease (KD), also called mucocutaneous lymph node syndrome, was first reported by Tomisaku Kawasaki in Japan in 1967.¹ A diagnosis of classical KD, also called complete KD (CKD), is usually made when the patient has a fever lasting >5 days and four of the following five manifestations: (1) changes to the oral mucosa, such as lip fissures, erythema, or strawberry tongue; (2) changes to the extremities, including edema, redness, or desquamation; (3) polymorphous rash; (4) nonpurulent bilateral eye injection; and (5) nonpurulent

cervical lymphadenopathy (>15 mm).² The etiology and pathogenesis of KD are incompletely understood. Rigante recently investigated the potential role of viruses in

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triggering the inflammation that generates KD in genetically predisposed children.³ Findings appeared to suggest that a dysregulated immune response to various microbial agents, such as viruses, may be the main cause of the onset of KD. To date, however, no definite link has been irrefutably found between a single infection and KD.

The incidence of incomplete KD (IKD) has steadily grown over the last several years. Indeed, the incidence rate of IKD reported in Japan is 15.0% to 36.2%,⁴ and reports from many hospitals in China indicate an incidence rate of >40%.^{5,6} A hospital in India reported an incidence rate of 48.4% for IKD,⁷ which is similar to the rates published by most countries. Unfortunately, the incidence rate of IKD is even higher for small neonates.⁸ Diagnosing KD in a timely manner is fairly challenging, which means clinical treatment is often delayed. This disease poses a significant economic burden to society and affected families. Therefore, understanding KD and conducting a comprehensive analysis of IKD are necessary to correctly diagnose KD.

KD is an acute small-arterial vasculitis syndrome that mainly involves the coronary arteries, leading to their dilation. In severe cases, KD can lead to coronary aneurysm, ischemic cardiomyopathy, and myocardial infarction; KD is a leading cause of acquired heart disease worldwide.^{9–12} Because the clinical symptoms of IKD are incomplete, difficulties in diagnosis, treatment delays, and increased complications are fairly common. Misdiagnosis or missed diagnosis of KD may lead to further development of this disease and an increased incidence of coronary artery aneurysm, dilation of the coronary artery, and in severe cases, myocardial infarction or sudden death.¹³ As such, early identification and diagnosis of IKD have become a hot spot in pediatric clinical research.¹⁴ IKD has different characteristics compared with CKD. This article reviews the clinical

characteristics and pathogenesis of IKD to help clinicians understand the symptoms of IKD.

Features of IKD

Long duration of fever

Nie et al.⁶ analyzed the clinical symptoms of IKD and found that children with IKD tend to have a longer duration of fever before diagnosis than those with CKD. Tang et al.¹⁵ conducted a clinical analysis of 173 IKD cases and found that the duration of fever in children with IKD was 2 to 21 days, with a median of 7 days. They also found that the duration of fever in children with CKD was 2 to 21 days, with a median of 6 days, which is similar to Takahashi et al.'s results.¹⁶ There was a significant difference between these two populations. Wang et al.¹⁷ analyzed 1004 children with KD in Beijing Children's Hospital and found that the mean duration of fever in the IKD group (10.3 ± 5.7 days) was significantly longer than that in the KD group (7.4 ± 3.6 days). Therefore, these authors suggested that a differential diagnosis of IKD should be considered if a child has a long duration of fever and the treatment effect is not ideal. A long duration of fever could be attributed to the incomplete clinical symptoms of IKD, which may take some time to confirm. Moreover, some patients with IKD are not responsive to treatment, which leads to a prolonged duration of fever.

Frequent Bacille Calmette–Guérin scar reaction

Redness and swelling of Bacille Calmette–Guérin (BCG) scars are prominent features of KD, especially IKD. Nie et al.⁶ found that the incidence of BCG scar redness and swelling in the IKD group was significantly higher than that in the CKD group.

By contrast, the incidence of chapped lips, molting of the fingers (or toes), perianal desquamation, skin rash, and swollen cervical lymph nodes was significantly lower in IKD than in CKD. This finding suggests that redness and swelling of BCG scars are more common in children with IKD than in those with CKD. A multicenter clinical study in Mexico reported that redness and swelling of BCG scars have important implications in the acute stage of KD in children aged younger than 5 years.¹⁸ Novais et al.¹⁹ reported that the BCG scar reaction in children aged younger than 6 months is a specific indicator for a diagnosis of IKD. Therefore, long-term fever combined with redness and swelling of BCG scars is an important indicator of IKD.

Young age of onset

Gao et al.²⁰ showed that the incidence of IKD in infancy was fairly high and the age of onset was relatively low. A study in Italy of 32 children aged younger than 1 year with KD found that 22 (68.7%) had IKD.⁷ This result is consistent with the conclusions obtained from an analysis of clinical data of 300 infants with KD in Shengjing Hospital of China Medical University.²¹ A transnational multicenter study in Latin America showed that the majority (78.1%) of infants and children aged 6 months or older were initially diagnosed with KD or IKD, while only 38.2% of infants aged younger than 6 months were diagnosed with KD.²² Nearly all cases of KD in infants aged younger than 3 months have incomplete clinical features.²³ Xiong et al.²⁴ reported a 26-day-old neonate with KD who showed dilation of the coronary artery and Du²⁵ described the case of a 24-day-old neonate with IKD complicated by aseptic meningitis. Therefore, the correct diagnosis of KD is important for the health or prognosis of young children.

High incidence of coronary artery lesions

The clinical manifestations of IKD are often incomplete, and clinical diagnosis and treatment are easily delayed. The risk of coronary artery lesions (CAL) is greater in IKD than in CKD. In Japan, the incidence of CAL in children with IKD is 15.0% to 25.0%.⁴ A study conducted by the Wenzhou Medical University-affiliated Yuying Children's Hospital showed that the incidence of CAL in children with IKD was higher than that in children with CKD (33.9% vs. 23.0%), which was also found after gamma globulin therapy (27.5% vs. 14.8%).²⁶ You et al.²⁷ showed that infants aged younger than 6 months had a higher incidence of incomplete KD (30%) and cardiac complications (12%) than older children (23% and 2.9%, respectively). The most serious cardiac complication that these authors observed was a coronary artery aneurysm, which may have been caused by severe dilation of the coronary artery. Zhang et al.²⁸ analyzed 1514 children with KD who were diagnosed at the Children's Hospital Affiliated with Chongqing Medical University. They found that the incidence of CAL in all children with KD was 51.9%; the incidence rates of CAL in the CKD and IKD groups were 57.2% and 37.9%, respectively. Additionally, the incidence of massive coronary artery aneurysms and thrombosis was significantly higher in the IKD group than in the CKD group. In Italy, 59% of the children with IKD aged younger than 1 year had cardiac involvement.⁸ These findings indicate that age is an important risk factor for CAL in patients with KD. A younger age and incompleteness of KD may be independent risk factors for CAL. Incomplete cases are usually younger and have more coronary aneurysms than complete cases, especially among infants aged younger than 1 year.^{29,30}

Enhanced immune tolerance to immunoglobulin

KD is a systemic febrile, inflammatory, vascular disease that commonly causes CAL. Initial treatment of intravenous immunoglobulin (IVIG) can reduce the incidence of CAL.³¹ However, some children with KD show complete nonresponse or only a partial response to IVIG. These children may have immune tolerance to this treatment. Downie et al.³² believed that complete nonresponders are more likely to develop coronary artery aneurysms than partial nonresponders. At present, the reason why this immune tolerance occurs is unclear. Abe et al.³³ found that variable gene expression profiles were correlated with the responses of patients with KD to IVIG administration. Polycythemia rubra vera-1 and granulocyte colony-stimulating factor levels may be good biomarkers for predicting the response to IVIG in patients with KD. Lee et al.³⁴ provided the first evidence supporting an association between TARC/CCL17 polymorphisms, susceptibility of KD, and IVIG responses in KD. Genetic susceptibility might be an important cause of immune tolerance in IVIG. Dionne et al.³⁵ considered that KD combined with infection may promote immune tolerance to IVIG, but further research on this possibility is necessary.

In addition to being younger in age and having incomplete symptoms, children with IKD are more prone to immune tolerance to IVIG or a delayed immune response than those with the complete form of disease.³⁶ This characteristic is also a factor affecting the long duration of fever in children and the risk of coronary artery and heart involvement. Li et al.³⁷ analyzed the clinical data of 121 patients with KD who were hospitalized in the Pediatric Department of the China–Japan Friendship Hospital. These authors found that the incidence of CAL and nonresponsiveness to IVIG in

patients with IKD was significantly higher than that in patients with CKD. In their study, the incidence of nonresponsiveness to IVIG in the CKD group was 8.9%, whereas that in the IKD group was 32.3%. Wu et al.³⁸ found that serum interleukin-6 levels were significantly elevated in patients with incomplete KD compared with their complete counterparts. Additionally, serum interleukin-6 levels were significantly elevated in patients with IVIG-nonresponsive KD compared with their IVIG-responsive counterparts. These findings suggest that IKD is more resistant to IVIG than CKD. IVIG-resistant KD is a main risk factor for coronary artery involvement in children.³⁹

Indicators for diagnosis of IKD

KD should be suspected if a child has a fever that lasts for longer than 5 days, especially if the body temperature exceeds 38.5°C or remains as high as 39°C to 40°C, even after anti-infective treatment. IKD should also be considered if any of the following clinical symptoms of KD occur simultaneously: (1) acute hard edema of the hands and feet, and subsequent finger (toe) molting and perianal desquamation; (2) multiform erythema; (3) nonpurulent conjunctival hyperemia; (4) changes to the lip and oral mucous membranes, such as erythema, fissuring, strawberry tongue, or oral mucosa hyperemia; and (5) nonpurulent cervical lymphadenopathy, which is usually unilateral with at least one lymph node >1.5 cm in diameter.⁴⁰ Echocardiography of the heart and great blood vessels should be performed in a timely manner, and various hematological examinations should be conducted to confirm the diagnosis. If an imaging examination shows coronary artery disease or other large-vessel disease and other diseases are excluded, the diagnosis should be IKD.⁴¹

A Scientific Statement for Health

Professionals From the American Heart Association included several related laboratory indicators for a diagnosis of IKD, such as an increased white blood cell count, increased C-reactive protein levels, increased erythrocyte sedimentation rate, increased platelets, increased alanine aminotransferase levels, hypoalbuminemia, aseptic pyuria, and cerebrospinal fluid mononucleosis.² KD or IKD usually causes the acute phase of the erythrocyte sedimentation rate to significantly increase. When the erythrocyte sedimentation rate is >40 mm/hour, diagnosis of KD can be made, and its sensitivity can exceed 90%.⁴²

Besides incomplete manifestation of classic symptoms of IKD, IKD may be combined with other complications, including those related to the digestive system (e.g., abdominal pain, diarrhea and vomiting, pancreatitis, cholecystitis), the respiratory system (e.g., cough, runny nose, pulmonary infiltrates), the nervous system (e.g., convulsion, disturbance of consciousness, extreme irritability, aseptic meningitis, facial nerve palsy, sensorineural hearing loss), arthritis, arthralgia, urethritis, hydrocele, skin desquamation, phlegmon, and anterior uveitis, among others.¹ Manlongat and Allen⁴³ reported a case of a 2-year-old boy with persistent fever and claudication manifesting as bilateral hip synovitis that remained unresolved after repeated antibiotic treatment. A cardiology review and echocardiogram showed dilated and ectatic left coronary arteries involving the left main stem coronary artery, left anterior descending artery, and circumflex artery. The final diagnosis of their case was IKD. Agha and Hamza⁴⁴ reported two similar cases, one of a 4-year-old girl and another of a 3-year-old boy. The girl presented with a fever lasting for 1 month that was misdiagnosed as chicken pox, and she also had nonpurulent conjunctivitis and periungual desquamation. The boy presented with a high-grade fever lasting for

7 days and jaundice. In his case, dark urine manifested 2 days after the onset of fever and resolved after 3 days. Laboratory findings and echocardiography confirmed that these two cases were IKD. Goyal and Shah.⁴⁵ reported an interesting case of IKD with unusual pustulovesicular skin lesions. This case involved a 12-year-old girl with a history of fever and abdominal pain for 10 days and swelling all over her body for 4 days. Swelling initially developed over her left leg and arm, followed by the right extremities, and eventually, the entire body. She had pustulovesicular lesions all over the right forearm and right knee joint, along with an erythematous skin rash over her buttocks and back. Her laboratory test results were consistent with a diagnosis of KD.

Conclusion

Because manifestations of KD commonly occur in other illnesses, such as infection or rheumatic immune disease, KD may be difficult to diagnose, especially in children who present with the incomplete form of this disease. Therefore, the diagnosis of IKD is challenging. Any child presenting with unexplained fever must be carefully monitored and clinicians must be highly vigilant about the possibility of KD.

In summary, early identification of IKD is important for preventing complications from this disease. Obtaining the detailed medical history of a patient and performing a careful physical examination are imperative for detecting the clinical manifestations of KD as soon as possible. Knowledge of potential issues will help health practitioners recommend relevant and appropriate laboratory examinations, and perform a heart and large blood vessel color Doppler ultrasound examination in a timely manner. This strategy can help promote early identification, correct diagnosis, and timely treatment of IKD.


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