The Complexities of the Diagnosis and Management of Kawasaki Disease

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INTRODUCTION

Although Kawasaki disease (KD) has been recognized in Japan and the United States for decades, the etiology and pathogenesis of the illness remain major pediatric mysteries. The abrupt onset of clinical signs such as fever, exanthem, and enanthem in previously healthy children, the rarity of recurrence, the very young age group affected, and the well-documented epidemics and outbreaks of illness are strongly suggestive of infectious etiology, as well described in a classic epidemiologic study from the 1980s.1 The very high incidence of the illness in Japan, where approximately

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1 in 90 children develop KD by age 5 years, is highly suggestive of a ubiquitous infectious agent affecting young susceptible children who are genetically predisposed. Key features of KD are presented in Box 1. It is important to understand the major pathologic features of KD arteriopathy, briefly summarized in Box 1, because these features predict the adverse clinical outcomes observed in KD patients who develop coronary artery abnormalities. Moreover, knowledge of the many organs and tissues involved in the systemic inflammation of KD assists in understanding the many possible clinical manifestations of the illness (Box 2). Risk factors for KD and the development of coronary artery abnormalities are summarized in Box 3.

INCIDENCE AND MORTALITY RATES

The incidence of KD varies in different countries throughout the world (Table 1) and remains unknown in many regions, especially in those that continue to have a high prevalence of measles, which shares many clinical features with KD. In Japan, there is high recognition and early treatment of the condition, and mortality rates have fallen from 1.4% in 1970 to 0.01% in recent years; fatality rates began to decrease markedly after the introduction of intravenous gammaglobulin therapy in the late 1980s. In the United States, fatality rates are also very low; fatal cases are often associated with delayed or missed diagnoses. Peak months of KD incidence vary somewhat by country, but a consistent theme seems to be a peak during the winter in nontemperate climates.

PATIENT HISTORY

The history is particularly important in KD, as some clinical features of the illness may begin and abate before the patient’s presentation. It is recommended that the parent or guardian is asked nonleading questions about symptoms to avoid introducing recall bias. Box 4 lists common features in the history of children with KD. Excessive irritability, refusal to bear weight, redness and swelling of the hands and feet, and an
erythematous, peeling groin rash may be helpful in establishing the diagnosis, as these are not common features of most other diseases in the differential diagnosis. In a child who has received Bacillus Calmette-Guérin vaccine, redness at the site should prompt consideration of KD; the mechanism of this response is unknown.

**PHYSICAL EXAMINATION**

Physical findings in KD can be very striking in classic cases (Box 5, Figs. 1 and 2). However, young infants in particular can present with incomplete clinical signs (fever with fewer than 4 of the other findings) or signs that are relatively mild. The findings of classic KD are listed in Box 5. Although some clinicians refer to incomplete KD as atypical KD, it is important to recognize that these terms indicate a lack of full clinical features, not to the presence of unexpected signs not listed in Box 5. An alternative diagnosis should be strongly considered in a child who has signs or symptoms not generally associated with KD. Because hydrops of the gallbladder occurs commonly in KD, right upper quadrant pain may be present on abdominal examination. Marked irritability, greater than that observed in other routine childhood febrile illnesses, is also characteristic and commonly observed during physical examination.

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**Box 2**

**Systemic pathologic abnormalities reported in KD**

- Cardiovascular: vasculitis, endocarditis, myocarditis, pericarditis
- Gastrointestinal: sialoductitis, enteritis, hepatitis, cholangitis, pancreatitis, pancreatic ductitis
- Respiratory: bronchitis, segmental interstitial pneumonia
- Genitourinary: cystitis, focal interstitial nephritis, prostatitis
- Nervous system: aseptic leptomeningitis, choriomeningitis, ganglionitis, neuritis
- Hematopoietic: lymphadenitis, splenitis, thymitis


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**Box 3**

**Risk factors for KD**

*Factors associated with an increased risk of KD*

- Asian ethnicity
- Age less than 5 years
- Parent or sibling with prior history of KD

*Factors associated with higher risk of coronary artery abnormalities in children with KD*  
- Age less than or equal to 12 months or greater than or equal to 8 years
- Male gender
- Longer interval from disease onset to treatment with intravenous gammaglobulin
- Failure to respond to initial intravenous gammaglobulin therapy
- Laboratory features (albumin <3.0 mg/dL, anemia for age, elevated alanine aminotransferase, hyponatremia, thrombocytopenia)
Table 1
Incidence of KD in various countries, as reported in the last decade

<table>
<thead>
<tr>
<th>Country</th>
<th>Approximate Risk of Child Developing KD by Age 5 y&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Authors, Ref. Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>1 in 90</td>
<td>Nakamura et al, 2 2012</td>
</tr>
<tr>
<td>Korea</td>
<td>1 in 150</td>
<td>Kim et al, 10 2014</td>
</tr>
<tr>
<td>China</td>
<td>1 in 400</td>
<td>Du et al, 11 2007</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1 in 300</td>
<td>Huang et al, 12 2013</td>
</tr>
<tr>
<td>Continental USA</td>
<td>1 in 1000</td>
<td>Holman et al, 13 2010</td>
</tr>
<tr>
<td>Hawaii—Japanese American</td>
<td>1 in 95</td>
<td>Holman et al, 14 2010</td>
</tr>
<tr>
<td>Hawaii—Native Hawaiian</td>
<td>1 in 230</td>
<td>Holman et al, 14 2010</td>
</tr>
<tr>
<td>Hawaii—Chinese American</td>
<td>1 in 240</td>
<td>Holman et al, 14 2010</td>
</tr>
<tr>
<td>Hawaii—Other Asian</td>
<td>1 in 235</td>
<td>Holman et al, 14 2010</td>
</tr>
<tr>
<td>Hawaii—Caucasian</td>
<td>1 in 1000</td>
<td>Holman et al, 14 2010</td>
</tr>
<tr>
<td>Canada</td>
<td>1 in 770</td>
<td>Lin et al, 15 2010</td>
</tr>
<tr>
<td>France</td>
<td>1 in 2200</td>
<td>Heuclin et al, 16 2009</td>
</tr>
<tr>
<td>Australia</td>
<td>1 in 2200</td>
<td>Saundankar et al, 17 2014</td>
</tr>
<tr>
<td>Finland</td>
<td>1 in 1750</td>
<td>Salo et al, 18 2012</td>
</tr>
<tr>
<td>Norway</td>
<td>1 in 3700</td>
<td>Salo et al, 18 2012</td>
</tr>
<tr>
<td>Sweden</td>
<td>1 in 2700</td>
<td>Salo et al, 18 2012</td>
</tr>
<tr>
<td>Chile</td>
<td>1 in 2600</td>
<td>Borzutzky et al, 19 2012</td>
</tr>
<tr>
<td>Israel</td>
<td>1 in 1680</td>
<td>Bar-Meir et al, 20 2011</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on yearly incidence per 100,000 children younger than 5 years in each country.

Box 4
Common features in the history of children with KD

- Prolonged intermittent high-spiking fevers (ask parent how temperatures are taken; oral or rectal temperatures are most accurate)
- Excessive irritability when compared with other previous febrile illnesses
- Refusal to bear weight or hold objects in hands
- Redness and swelling of hands and feet
- Redness and peeling of the skin in the groin area
- Red eyes
- Red lips and tongue
- Red rash on body, primarily on trunk, arms, and legs
- Swollen glands in neck
- Vomiting
- Diarrhea
- Cough
- Redness at site of bacillus Calmette-Guérin injection (children born in countries where this vaccine is routinely administered)
Box 5
Physical examination findings (classic diagnostic criteria)

- Intermittent high fever
- Plus 4 of the following 5 features:
  - Bulbar conjunctival injection, generally without exudate and often with limbal sparing (see Fig. 1)
  - Oral changes: redness of the throat, strawberry tongue, redness of the lips, sometimes with bleeding or peeling of the lips (see Fig. 1)
  - Rash: erythematous maculopapular (see Fig. 2), scarlatiniform, or erythema multiforme, sometimes with marked groin erythema and desquamation
  - Extremity changes: redness and swelling of the hands and feet during the first week; typical periungual desquamation occurs in the second or third week (Fig. 3)
  - Cervical lymphadenopathy 1.5 cm or more in diameter
- Illness not explained by other known disease process

Fig. 1. Conjunctival injection and red lips in a child with acute Kawasaki disease (KD).
OTHER CLINICAL MANIFESTATIONS OF KAWASAKI DISEASE

Children with KD can present with shock syndrome; such patients are at higher risk of intravenous gammaglobulin (IVIG) resistance and of developing coronary artery abnormalities. Although cervical lymphadenopathy is the least commonly observed clinical feature among the classic diagnostic criteria for KD, it can be the dominant clinical feature, and some of these patients also have retropharyngeal phlegmon (without abscess) documented by neck imaging studies. KD should be considered in the differential diagnosis of any infant with prolonged fever and aseptic meningitis.

IMAGING AND ADDITIONAL TESTING

Laboratory findings in KD are nondiagnostic, but can support the diagnosis. In particular, a child with a low or normal peripheral white blood cell count with a lymphocyte predominance does not have a compatible laboratory profile of KD. In nontemperate climates KD is most prevalent in the winter, when many respiratory viruses are circulating. Therefore, some children with KD will concurrently have infection with one of these viruses; this should not preclude the diagnosis in cases with clinical and laboratory features of KD. Echocardiography can be very useful in assessing a child for possible KD, as a right or left anterior descending coronary artery z score
greater than 2.5 is highly supportive of the diagnosis\textsuperscript{31,32} and 30\% of KD patients have abnormal coronary artery $z$ scores at the time of initial diagnosis, in the first 10 days of illness.\textsuperscript{33,34} The presence of 3 of the following echocardiographic findings should also increase clinical suspicion of KD: pericardial effusion, lack of tapering of the coronary arteries, a coronary artery $z$ score of 2 to 2.5 of the right or left anterior descending coronary arteries, decreased left ventricular function, and mitral regurgitation.\textsuperscript{7}

Fig. 3. Periungual desquamation of the fingers 2 weeks after fever onset in a child with KD.

<table>
<thead>
<tr>
<th>Box 6 Laboratory findings</th>
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<tbody>
<tr>
<td><strong>Normal peripheral white blood cell count with left shift, or elevated white blood cell count with predominance of neutrophils</strong></td>
</tr>
<tr>
<td><strong>Elevated erythrocyte sedimentation rate ($\geq$40 mm/h) and/or C-reactive protein ($\geq$3.0 mg/dL)</strong></td>
</tr>
<tr>
<td><strong>Anemia for age</strong></td>
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<tr>
<td><strong>Albumin less than 3.0 mg/dL</strong></td>
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<tr>
<td><strong>Hyponatremia</strong></td>
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<tr>
<td><strong>Thrombocytosis in second to third week</strong></td>
</tr>
<tr>
<td><strong>Sterile pyuria ($\geq$10 white blood cells/high-powered field)</strong></td>
</tr>
<tr>
<td><strong>Elevated serum transaminases with or without elevated serum gamma glutamyl transpeptidase or bilirubin</strong></td>
</tr>
<tr>
<td><strong>Cerebrospinal fluid pleocytosis, usually with normal glucose and protein levels</strong></td>
</tr>
<tr>
<td><strong>Leukocytosis in synovial fluid</strong></td>
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</tbody>
</table>
DIAGNOSIS OF INCOMPLETE (ATYPICAL) KAWASAKI DISEASE

Although the classic diagnostic criteria are the mainstay of diagnosis, some children with KD, particularly infants, manifest fever with fewer than 4 of the 5 clinical signs described in Box 5; these children are considered to have incomplete KD. In some infants, the clinical findings are mild, and may not be noted unless there is a high index of suspicion for KD. Unfortunately, coronary artery abnormalities in incomplete cases can be as severe as in classic cases. Because incomplete KD can be difficult to diagnose and has potentially severe consequences that may be prevented by early treatment, the American Heart Association Committee on Endocarditis, Rheumatic Fever, and Kawasaki Disease developed a treatment algorithm combining laboratory and echocardiographic findings with clinical signs and symptoms to identify patients who may benefit from therapy for incomplete KD (Fig. 4).7

PRIMARY THERAPY

All patients diagnosed with KD should be treated with 2 g/kg IVIG with oral high-dose aspirin (80–100 mg/kg/d divided every 6 hours) as soon as possible after diagnosis.35 IVIG significantly reduces the prevalence of coronary artery abnormalities when given within the first 10 days of illness,35,36 and improves myocardial function.37 However, improved echocardiographic imaging and use of body surface area-adjusted $z$ scores to identify coronary artery dilation has led to the realization that coronary artery injury...
likely occurs in many patients in the first week of illness, and that coronary artery z scores greater than 2 can be observed in 18% of KD children at about 6 weeks after onset even with treatment within the first 10 days. This finding emphasizes the need for early diagnosis and treatment. At least 80% of KD patients respond to initial therapy with IVIG and aspirin with resolution of fever, improvement in clinical signs and symptoms, and decreased laboratory markers of inflammation. Aspirin is maintained at high doses for anti-inflammatory effect until the patient is afebrile for 2 to 3 days; at some centers, it is continued until the 14th day of illness. Aspirin is then reduced to antiplatelet doses of 3 to 5 mg/kg/d in a single daily dose, and continued until echocardiography at 6 to 8 weeks after the onset remains normal and acute-phase reactants have normalized. In patients who develop coronary artery abnormalities, low-dose aspirin is continued indefinitely. In patients with severe coronary artery abnormalities, clopidogrel and/or anticoagulation therapy with warfarin or low molecular weight heparin may be indicated, and consultation with a pediatric cardiologist is advised.

RESEARCH STUDIES ON ADJUNCTIVE PRIMARY THERAPY

Unfortunately, approximately 15% to 20% of children with KD do not respond to initial IVIG therapy, with persistence of fever 36 hours after completion of IVIG infusion, and these patients are at increased risk of developing coronary artery abnormalities. Some KD patients, especially infants, can develop coronary artery abnormalities despite apparent clinical response to IVIG treatment given in the first 10 days of illness. Therefore, recent research has focused on the study of combination immunomodulatory therapies given with IVIG as primary therapy for KD. A randomized study of a single 30 mg/kg dose of methylprednisolone administered with IVIG did not reveal a significant improvement in outcomes. A randomized, double-blind, placebo-controlled trial of infliximab (a tumor necrosis factor inhibitor) for intensification of primary therapy for KD did not show a reduction in treatment resistance nor a reduction in the overall prevalence of coronary artery abnormalities when infliximab was administered with IVIG, although the addition of infliximab did result in lower levels of C-reactive protein and absolute neutrophil counts 24 hours after the infusion. More promising was the Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease (RAISE study), which demonstrated improvement in coronary artery outcomes in Japanese patients with high-risk KD when prednisolone was given with IVIG and continued for 15 days after normalization of the C-reactive protein level. A randomized trial of cyclosporin with IVIG for Japanese children with high-risk KD is presently under way in Japan, and the results of this study will also be of interest. Because the identification of risk scoring systems with high sensitivity for the prediction of coronary artery abnormalities in mixed ethnic populations has proved elusive, application of the RAISE study protocol or other high-risk protocols to KD children in countries such as the United States and Canada is not presently feasible.

REFRACTORY KAWASAKI DISEASE

Refractory KD generally refers to the persistence of fever for 36 hours or longer after completion of initial IVIG infusion. Patients with IVIG resistance have a higher prevalence of coronary artery abnormalities. Most of these patients respond to a second 2 g/kg dose of IVIG. For those patients who do not respond to a second dose of IVIG, several options for treatment exist, although controlled data are lacking.
CLINICAL OUTCOMES AND COMPLICATIONS

Most children with KD respond to IVIG, and those who do not develop coronary artery abnormalities by 4 to 6 weeks after the onset of fever have no known adverse outcomes. In patients who develop coronary artery dilation or aneurysm formation, outcomes depend on the severity of coronary artery disease. In severe cases giant coronary artery aneurysms can form, which can rarely rupture, and virtually always thrombose to a varying extent. Patients with this severe complication of KD are generally maintained on antiplatelet and anticoagulation therapy, and are at the highest risk for thrombotic occlusion and myocardial infarction, in some cases requiring catheter interventions or coronary artery bypass surgery. However, coronary artery stenosis in KD patients can also be caused by luminal myofibroblastic proliferation (LMP) with or without thromboses. LMP is an active proliferative process of smooth muscle cell–derived myofibroblasts and their matrix products that can result in progressive arterial stenosis. In rare cases, LMP or thrombosis can result in such significant stenoses of multiple coronary arteries that heart transplantation is required. KD can affect all medium-sized muscular arteries outside of the central nervous system, but peripheral arterial aneurysms seem to occur only in children with severe coronary artery disease. The most commonly affected arteries are the axillary, brachial, and inguinal arteries; aneurysms in these arteries rarely result in morbidity or mortality.

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