KAWASAKI DISEASE
GENETICS, PATHOLOGY, AND A NEED FOR EARLIER DIAGNOSIS AND TREATMENT

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Identifying the etiology of Kawasaki disease has been a vexing problem. Some recent studies point to an as yet undiscovered viral agent as the cause. Other studies show the significant effects of the disease on coronary arteries. Researchers all agree on the urgent need for early diagnosis and improved treatment therapies.

Kawasaki disease (KD) remains the leading cause of acquired heart disease in children in developed nations. Presently, about 1% of Japanese children develop KD by 5 years; this rate surpasses that observed during the Japanese nationwide epidemics of 1982 and 1986.[1] The rate in white children is about 10-fold lower than in Japanese children, and the rate in black and Hispanic children intermediate.[2] Therefore, US practitioners caring for about 1,500 young pediatric patients in their practices might diagnose 1 or 2 patients with KD per year or a higher number if the practice includes a substantial percentage of children of Asian ethnicity.

Kawasaki disease epidemiologic and clinical features strongly support infection by a ubiquitous microbe that generally causes asymptomatic infection but that results in KD in a very small subset of genetically predisposed children. However, no known microbe has been consistently associated with KD, raising the possibility that the etiologic agent is "new" and remains currently undiscovered.[3]

Recent research has yielded several new findings of importance to clinicians. Genetic studies have identified single nucleotide polymorphisms (SNPs) in several genes related to immune response associated with KD or with the development of coronary artery abnormalities. New studies of pathologic findings in coronary arteries of fatal cases provide a better understanding of specific events in damaged arteries and how these events lead to specific, potentially serious outcomes for children with significant damage.

New research suggests that earlier diagnosis and treatment of KD are needed, well before the tenth day of illness. Additional treatment options for patients with KD who do not respond to intravenous immunoglobulin (IVIG) have been reported, and a new treatment regimen for primary therapy of KD in Japanese children at high risk of developing coronary artery abnormalities has been reported. In addition, a study of coronary artery dimensions in febrile children with non-KD

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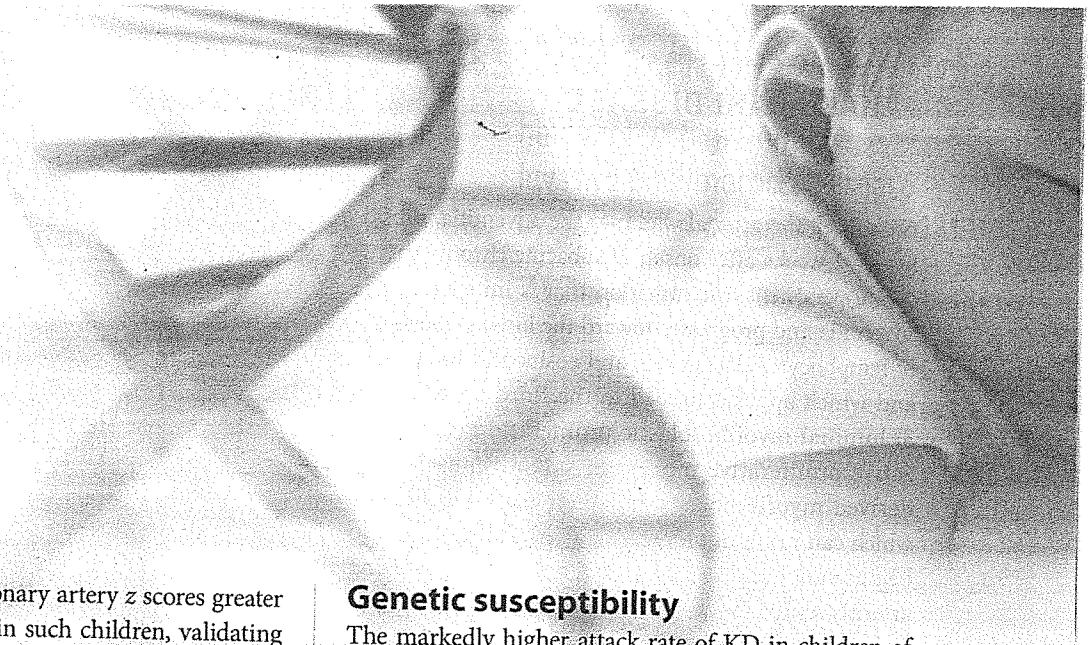

illnesses confirms that coronary artery *z* scores greater than 2.5 are not observed in such children, validating the use of coronary artery *z* scores as a diagnostic aid in children with possible incomplete KD.

Etiology

Identification of the etiology of KD continues to be one of the most vexing problems in pediatrics. The theory that best supports the epidemiologic data is that a very common infectious agent, one that usually results in asymptomatic infection, causes KD in a subset of genetically predisposed children. Recent data support the theory of a new virus without substantial homology to known viruses as the cause.[4]

An interesting recent study related the incidence of KD to wind patterns, suggesting a potential mechanism of spread of an infectious etiologic agent.[5] It is hoped that use of new molecular techniques such as high-throughput sequencing of KD tissues will yield the etiologic agent(s); identification of the causative agent(s) would allow for urgently needed diagnostic test development, improved therapies, and preventive measures.

It is important to recognize that KD cases occur most commonly in the winter and spring in nontemperate climates, a time when many known respiratory viruses are circulating. Therefore, some patients with classic acute KD have concurrent infection with 1 of these viruses, and this concurrent infection does not exclude the diagnosis of KD. Although adenovirus infection can present with some clinical features resembling KD, detection of adenovirus in the respiratory tract of a patient with KD could result from prolonged, low-level viral shedding. Caution should be exercised in excluding a diagnosis of KD in a patient with clinical features supporting the diagnosis and a positive respiratory viral assay for adenovirus.[6,7]

Genetic susceptibility

The markedly higher attack rate of KD in children of Asian ethnicity strongly supports a genetic predisposition to the illness. In addition, siblings of patients with KD are at a 10- to 30-fold increased risk of KD compared with the general population, and children with KD are twice as likely as those in the general population to have a parent who had KD.[8,9] It is clear that host genetics profoundly influence susceptibility to infections,[10,11] and genetic susceptibility to KD could be based on differences in host immune response to the etiologic agent(s).

Single nucleotide polymorphisms of several genes involved in immune response, including *ITPKC*, *CASP3*, *FCGR2A*, *HLA*, *BLK*, and *CD40*, have been found to be associated with KD and/or with increased risk for coronary artery abnormalities.[12-16] However, none of these gene SNPs when present alone or in combination explains the higher incidence of KD in Asian populations nor allows for an accurate genetic predictive model of KD.[17] It is likely that additional susceptibility genes will be identified in future studies.

Three pathologic processes of KD vasculopathy

A recent pathologic study of arterial tissues from 41 patients with KD[18] led to the recognition that the traditional model of KD pathogenesis, briefly summarized as a process of initial infiltration of coronary arteries by neutrophils with rapid transition to lymphocytes and macrophages, followed by resolution of inflammation within 2 months and subsequent "scar" formation in the arteries,[19,20] does not fully explain the complexities of KD arteriopathy. Instead, pathologic features in the arterial tree are best described as 3 processes: 1) necrotizing arteritis, which is a self-limited neutrophilic

IMAGE: GETTY IMAGES/INGRAM PUBLISHING/THE AGENCY COLLECTION (DNA); THINKSTOCK/ISTOCKPHOTO (BABY)

necrosis of the arterial wall into the adventitia, subsiding by 2 weeks after onset; 2) subacute/chronic vasculitis, a persistent inflammation that is initiated in the adventitia and progresses toward the lumen, consisting of lymphocyte, plasma cell, and eosinophil infiltration and which appears to lead to the third process; and 3) luminal myofibroblastic proliferation (LMP), an active proliferative process of smooth muscle cell-derived myofibroblasts and their matrix products, which can result in progressive arterial stenosis; it also begins early but can persist indefinitely.[18] Necrotizing arteritis results in saccular aneurysms that can thrombose and is consistent with an innate immune response to a pathogen such as a virus; subacute/chronic vasculitis is consistent with an acquired immune response.

These pathologic findings should change the way practitioners think about so-called "regression" of coronary artery aneurysms after KD. Large saccular aneurysms have lost their intima, both elastic lamina, the media, and variable portions of their adventitia. The lumen of saccular aneurysms becomes smaller over time because of deposition of sequential layers of thrombi; this decrease in lumen size does not represent "healing" of the arterial wall.

Fusiform aneurysms generally have preserved media, providing smooth muscle cells that transition to proliferative myofibroblasts, which with their matrix products can produce an expanding luminal mass. Decrease in size of the lumen of fusiform aneurysms may result from thrombus formation or from LMP stenosis. Although it is unlikely that aneurysmal arteries return to normal, nonaneurysmal arteries that develop mild dilation as a result of edema and minimal inflammatory infiltrate likely can return to normal or near normal. The 3-processes model of KD vasculopathy leads to a better understanding of the potential dangers facing KD patients with severe coronary artery abnormalities over time.

Moving toward earlier diagnosis and treatment

Two recent studies highlight the importance of early diagnosis (Table 1)[21] and treatment (Table 2)[22-24] of KD. Of particular interest is a study examining the timing of the first abnormal echocardiogram by day after onset in 210 patients with KD admitted to a large children's hospital.[25] The researchers found that 57 of the 210 children (27%) had coronary artery abnormalities detected within the first month after fever onset and that 37 of these 57 children (65%) had coronary abnormalities detected on an initial echocardiogram within the first 10 days of illness. The median day of illness when abnormalities were first identified was day 7 (interquartile range, 5-8). This study demonstrates that coronary artery abnormalities are more prevalent in patients with KD and occur earlier in the course of illness than previously recognized; these findings were made possible because more accurate coronary artery size assessments using *z* scores based on body surface area are now standard.[26] This study strongly argues for treatment of KD as soon as possible after diagnosis.

Risk factors for the development of coronary artery abnormalities were recently studied in more than 2,000 patients in California with KD, and a lower

TABLE 1 Diagnosis of acute Kawasaki disease

Classic case

- Fever for ≥5 days,[a] intermittent and high spiking
- Four of the following 5 clinical features:
  - Conjunctival injection (primarily bulbar, without significant exudate)
  - Oral mucosal changes (strawberry tongue, dry cracked lips, erythema of lips, mouth, pharynx)
  - Erythema and swelling of the hands and feet
  - Erythematous rash on trunk and extremities (maculopapular, scarlatiniform, erythema multiforme; marked erythema and peeling in the groin may be present)
  - Cervical adenopathy >1.5 cm in diameter
- Exclusion of disease with similar clinical features[b]

Incomplete ("atypical") case

- Fever for ≥5 days
- Two of 5 clinical features observed in classic cases
- C-reactive protein ≥3.0 mg/dL and/or erythrocyte sedimentation rate ≥40 mm/hr
- Compatible laboratory findings[c] or positive echocardiogram[d]

a. An experienced physician can make the diagnosis before the fifth day of fever in the presence of the other classic clinical features.
b. Such as measles, scarlet fever, toxic shock syndrome, drug hypersensitivity reaction.
c. At least 3 of the following: albumin, ≤3.0 g/dL; anemia for age; elevation of alanine aminotransferase; platelets after seventh day, ≥450,000/mm^3; white blood cell count, ≥15,000/mm^3; urine, ≥10 white blood cells/high-powered field.
d. *Z* score of left anterior descending or right coronary artery ≥2.5 or ≥3 other suggestive features, including perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores of left anterior descending or right coronary artery 2-2.5.
Adapted from Newburger JW, et al.[21]

prevalence of coronary disease in children who were treated before the fifth illness day compared with after the fifth illness day was reported.[27] A potential confounder in this study is that the group treated on or after the fifth illness day could have included patients treated after the tenth illness day, exaggerating the apparent protective effect of early treatment. However, biologic plausibility is on the side of earlier treatment because there are few medical conditions in which a delay in initiation of appropriate therapy is of benefit to the patient.

Another recent study examined coronary artery *z*-score measurements in 45 children with febrile illnesses other than KD.[28] Because normal coronary artery measurements have been established in healthy children without fever, a question has been raised regarding the possibility that fever itself might cause mild coronary artery dilation. Transient coronary artery dilation has been reported in some patients with juvenile idiopathic arthritis[29]; however, none of the 45 febrile control children had coronary artery *z* scores of 2.5 or higher, the commonly used criterion for dilated coronary arteries.[28]

Although it will be important to study additional febrile children, this preliminary study provides support for the American Heart Association recommendation that echocardiography can be an important ancillary diagnostic tool in incomplete KD cases.[21]

Progress toward improving treatment

Primary therapy. Since the initial recognition that KD results in coronary arterial inflammation, there has been interest in the possible efficacy of steroid therapy. Steroid treatment was commonly administered to patients in Japan with KD in the 1970s, at least until a report of worse outcomes in steroid-treated patients was published (a study that has been widely criticized).[30]

Despite the widespread use of corticosteroid therapy for KD in Japan, KD mortality remained significant until IVIG was introduced in the mid-1980s.[31] However, because other forms of vasculitis respond to corticosteroid therapy, interest continues in the possible role of this therapy for primary treatment of KD.

A previous study in which a single high-dose of prednisolone was administered with IVIG for primary therapy of KD failed to show benefit.[32] Most recently, the Randomized Controlled Trial to Access Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease (RAISE) study, a Japanese multicenter trial of IVIG plus prednisolone for primary therapy of KD in patients at high risk of developing coronary artery abnormalities, demonstrated a significantly lower incidence of coronary artery abnormalities in the prednisolone group at 1 month after KD onset.[22] Although the results were potentially promising, prednisolone was administered for a long duration (15 days after the C-reactive protein normalized, a median of 21 days), and the patient follow-up was short (4 weeks). Most important, illness severity scores accurately identify

TABLE 2 Therapy for Kawasaki disease

Primary therapy

- **Established primary therapy**
  Intravenous gammaglobulin 2 gm/kg infused over 8-12 h, with aspirin given orally at 80-100 mg/kg/d divided q 6 h; aspirin reduced to 3-5 mg/kg/d on the fourteenth illness day or when patient has been afebrile for 3 d and continued until echocardiogram remains normal 6 wk after onset of fever or indefinitely in children who develop coronary artery aneurysms.
- **New primary therapy for Japanese children at high risk**
  For Japanese children with Kobayashi risk score ≥5 (this risk score has low sensitivity in non-Japanese children). Intravenous prednisolone is given for at least 5 d (until patient is afebrile) in addition to established primary therapy of intravenous gammaglobulin and aspirin, followed by oral prednisolone until C-reactive protein normalizes, at which time prednisolone is tapered over 2 wk.
- **Primary therapies under study** (to reduce primary therapy nonresponse)
  - Established therapy plus infliximab (antibody to tumor necrosis factor α)
  - Established therapy plus etanercept (tumor necrosis factor α antagonist)

Rescue therapies

Optimal regimen for children who remain febrile after primary therapy is unknown. Several regimens have been used:

- Additional 2 gm/kg intravenous gammaglobulin infusion
- Intravenous prednisolone 30 mg/kg/d for 1-3 d (with or without subsequent oral prednisolone)
- Infliximab

Potential future rescue therapies

- Cyclosporin
- Tacrolimus
- Anakinra (IL-1 receptor antagonist)

From Kobayashi T, et al[22]; Newburger JW, et al[23]; Kobayashi T, et al.[24]

Japanese children at high risk of developing coronary artery abnormalities[24] but have not so far been sensitive enough in non-Japanese children, making this approach difficult to implement at present outside Japan.[33]

Rescue therapy. In patients who do not respond to primary therapy with IVIG and aspirin, the best management approach remains unclear. Additional therapy options include a second dose of IVIG, pulse prednisolone therapy, and infliximab. Most recently, the use of calcineurin inhibitors, particularly cyclosporine, has been described for treatment of patients who failed multiple other therapies.[34] Because the clinical symptoms of KD are self-limited, it is difficult to determine whether case reports of patients who apparently responded to rescue therapies represent true clinical responses. The small number of IVIG nonresponders and high cost of performing such studies hamper multicenter trials of rescue therapies.

The future

Identification of KD diagnostic or prognostic biomarkers is a major goal for the future. Additional genetic studies are in progress, which will hopefully lead to identification of the genes responsible for the higher incidence of KD in Asian patients. The key to rapid advances in KD remains identification of the etiologic agent(s), and it is hoped that use of new molecular technologies such as high-throughput sequencing of KD tissues will bring this elusive goal to reality.

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