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Perioperative Considerations of Kawasaki Disease

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ABSTRACT

Background: Kawasaki disease (KD) is an acute febrile illness that primarily affects young children. Coronary arteritis is an important clinical feature of KD because it is associated with aneurysms and thromboembolic events that can lead to ischemic heart disease, sudden death, and congestive heart failure. KD involvement in multiple organ systems provides a potentially challenging dilemma for clinicians.

Methods: This review discusses the pathogenesis of the disease, including diagnosis, clinical features, and treatments. An additional focus is the development of strategies for the successful surgical management of patients with a KD history, emphasizing the preoperative assessment and the operative arena.

Conclusion: Although treatments for KD are largely standardized, patients with the disease who require surgical interventions must be properly assessed to determine the degree of pathogenesis, especially the extent of cardiac involvement.

INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis of unknown etiology seen most commonly in childhood and characterized by fever, bilateral conjunctivitis, erythema of the lips and oral mucosa, cervical lymphadenopathy, and desquamation of the skin on the hands and feet. Although initially thought to be a rare condition, KD has surpassed acute rheumatic fever as the leading cause of acquired heart disease in children in the United States.[1] KD is a self-limiting disease in most children, with symptoms evolving over the initial 10 days of illness and spontaneously resolving. However, coronary artery aneurysm (CAA) or ectasia can develop in 15%-20% of untreated children and may lead to long-term consequences such as myocardial infarction, sudden death, and congestive heart failure.[2] Surgery on patients with a history of KD or on patients with a current onset of KD presents anesthesia challenges.

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EPIDEMIOLOGY

KD was first described by Tomisaku Kawasaki as mucocutaneous lymph node syndrome in 1967.[3] Although originally described in Japan, the disease occurs worldwide in both endemic and community-wide epidemic forms in the Americas, Europe, and Asia and in children of all races.[3] More than 4,000 hospitalizations were associated with KD in the United States in 2000, with a median patient age of 2 years.[4] KD is most commonly seen in Americans of Asian and Pacific Island descent but has also been documented in African Americans, Hispanics, and Caucasians.[3] The disease commonly affects male children younger than 5 years old in the winter and spring months.[5] The seasonality of the cases, epidemic occurrence, and self-limiting nature suggest an infectious cause; however, a specific infectious agent has yet to be identified.[6] Studies have tried to show a causal relationship with various risk factors, including carpet cleaning and proximity to a body of water, but the etiology of KD remains elusive.[1,2] The disease has an overall mortality rate of 0.17%, with all deaths resulting from coronary artery sequelae.[5]

PATHOLOGY

KD is a generalized systemic vasculitis that affects small- to medium-sized arteries, with a strong predilection for the coronary arteries.[7] The development of arteritis is caused by inflammatory infiltration, myointimal proliferation, destruction of the media, and dilation of the vessel.[8] Initially, an inflammatory stimulus causes margination of monocytes, platelets, neutrophils, and macrophages in the vessel wall.[9]

Secretion of vascular endothelial growth factor increases vascular permeability and endothelial swelling.[10] When the inflammatory infiltrates from the lumen and adventitia meet, transmural inflammation occurs and subsequently destroys the extracellular matrix and internal elastic lamina. Destruction of the vessel, coupled with fibroblast proliferation, leads to remodeling, intimal thickening, and thrombus formation/embolic phenomenon over a period of weeks to months.[11]

DIAGNOSIS

Classically, KD has been diagnosed by the presence of 5 or more days of fever along with 4 of 5 clinical features: physical changes of the extremities (erythema of the palms or soles, edema of the hands or feet, delayed desquamation), polymorphous exanthem, bilateral nonexudative conjunctivitis, changes in the lips or oral cavity (erythema, cracked lips, strawberry tongue), and cervical lymphadenopathy.[6] Recently, the term atypical Kawasaki syndrome has emerged to designate an incomplete form of the disease. The term is used for patients with at least 5 days of fever and 2 of 5 clinical features for KD.[6] The principal clinical features associated with KD are nonspecific and should be considered in the differential diagnosis of every child with fever of several days' duration. The lack of a specific and sensitive diagnostic test, coupled with nonspecific symptoms, poses major obstacles to the correct identification of patients with KD.

CLINICAL FEATURES AND DISEASE PROGRESSION

Fever

The most important and consistent feature of KD is prolonged fever with peak temperatures greater than 102°F. Activation of the immune system produces proinflammatory cytokines, such as tumor necrosis factor and interleukin-6, that lead to vascular inflammation and increased core body temperature.[12] These high-spiking fevers are typically unresponsive to antipyretic agents and can continue for 3 to 4 weeks without appropriate therapy. However, with immediate treatment, the fever can resolve within a more acute period of time.[12]

Extremities

Erythema of the palms and soles and painful induration of the hands and feet are generally the last manifestations of KD. First, patients develop indurated edema on the dorsal surfaces of their hands and feet, with erythema covering the palmar and plantar aspects. Sheet-like desquamation of the hands and feet begins in the periungual region and extends to the palms and soles 2 or 3 weeks after the onset of fever. One to 2 months after the onset of fever, deep horizontal indentations in the fingernail, also known as Beau's lines, appear.[13] Arthritis has been reported in 25% of patients with KD, primarily involving multiple large joints such as the knee, ankle, and hip. In children with arthritis, increased levels of inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are typically observed. However, the presence or absence of arthritis has no effect on the clinical features or treatment outcome of the disease process.[14]

Rash

Five days after the onset of fever, an erythematous desquamating rash begins in the perineal area and progresses to a maculopapular, micropustular, or scarlatiniform sandpaper-like rash with variable areas of involvement. The rash has also been noted as urticarial exanthema or erythroderma lesions involving areas of the trunk and extremities.[15] KD may also trigger psoriasiform eruptions in children not previously known to have psoriasis.[16]

Conjunctiva

Bilateral bulbar conjunctival injection without exudates is present in 90% of patients. The bulbar injection manifests within days of the onset of fever, and patients present with a characteristic limbus-sparing erythema. Anterior uveitis visible with a slit-lamp examination may also develop. Although these ocular inflammations present in other disease processes, the presence of these symptoms can provide further evidence for the diagnosis of KD.[17]

Oral

Erythema, fissuring, peeling, and cracking of the lips; strawberry tongue; and erythema of the oropharyngeal mucosa are common in KD patients. Strawberry tongue is caused by the sloughing of filiform papillae and subsequent denuding of the inflamed tongue. However, the discrete oral vesicles, ulcers, and exudates present over the tonsils and associated with KD are common in other disease processes as well.[15]

Lymph Nodes

Unilateral cervical lymphadenopathy is the least consistent feature of KD, present in 25%-50% of children with the disease. When cervical lymphadenopathy is present, the anterior cervical nodes overlying the sternocleidomastoid muscle are most commonly involved. Studies have not shown any relationship between the presence of cervical lymphadenopathy and coronary artery complications.[18]

Macrophage activation syndrome or secondary hemophagocytic lymophohistiocytosis, characterized by the activation and proliferation of macrophages and T lymphocytes, is a rare complication in children with persistent fever even after intravenous immunoglobulin (IVIG) treatment.[19]

Cardiovascular

The cardiovascular findings in KD vary according to chronology and severity. KD occurs in 2 phases: the acute phase, occurring 12 days after the onset of fever and inflammation, and the convalescent phase, occurring after inflammation subsides. The most feared cardiovascular manifestation of KD is CAA that can develop during the acute phase and can subsequently lead to serious complications after disease resolution.

Abnormal cardiovascular findings during the first week of illness may include tachycardia out of proportion to fever, gallop sounds, and muffled heart tones.[6] Severely ill patients may develop fusiform aneurysms of the brachial arteries that are easily palpable or visible in the axillae. In addition, some may have Raynaud phenomenon with cold, pale, or cyanotic digits of the hands and feet from reduced blood perfusion. In rare cases, gangrene may cause loss of fingers or toes during the acute phase.

During the acute phase of KD, myocarditis may lead to depressed myocardial contractility. Electrocardiography can show left ventricular dysfunction as early as the time of diagnosis.[20-22] Although myocardial function generally improves rapidly after IVIG administration, some patients with left ventricular dysfunction are more likely to have coronary artery dilation 1 to 5 weeks after initial diagnosis. The left ventricular dysfunction is caused by impairment of load-dependent and load-independent measures of left ventricular contractility.[23] In terms of diastolic function, relaxation may be impaired during acute KD, and diastolic abnormalities (without systolic dysfunction) may occur chronically among patients with CAA.[24] In this early phase, the depressed myocardial contractility may progress to heart failure that is often manifested as an S3 gallop more evident with hydration.[25]

At baseline echocardiography, mild or moderate mitral regurgitation is present in approximately 25% of patients, with the incidence diminishing in the convalescent phase.[22] Aortic regurgitation is less common, occurring in approximately 1% of patients during the first 5 weeks of illness.[22] Mild aortic root dilation is common in the first 3 weeks of the disease and can persist during the first year of follow-up.[22]

Systolic dysfunction can lead to KD shock syndrome, a potentially life-threatening complication. KD shock syndrome is defined as a decrease in blood pressure greater than 20% from baseline or the presence of clinical signs of poor perfusion, such as confusion; tachycardia; pallor; and cold, clammy, mottled skin. Patients with shock syndrome are more likely to have consumptive coagulopathy and cardiac abnormalities, such as impaired left ventricular systolic function, mitral regurgitation, and coronary artery abnormalities. Patients who present with shock have higher CRP levels, are less responsive to initial IVIG therapy, and more commonly require additional treatment for KD.[26,27]

The most serious cardiovascular sequela of KD is CAA. As early as 7 days after the onset of fever, CAA can be detected by echocardiography.[20] CAAs are located most commonly in the proximal left anterior descending and proximal right coronary arteries, followed by the left main coronary artery, circumflex coronary artery, distal right coronary artery, and at the take-off of the posterior descending coronary artery from the right coronary artery.[21] CAAs can vary in shape (ie, saccular, fusiform, or ectatic), and their shape and size can evolve over time. The prognosis of CAA depends on the size and shape of the aneurysm, with the best prognosis associated with smaller aneurysms. Aneurysms may continue to increase in size up to 6 weeks after disease onset. After reaching a peak diameter, approximately 50% of aneurysmal segments regress to a normal lumen diameter within 2 years after disease onset. However, after this time, further regression generally does not occur. In contrast, giant CAAs—those with an internal diameter $>$8 mm—have the highest risk of morbidity and mortality. Up to 33% of such aneurysms become obstructed and are associated with myocardial infarction, arrhythmias, or sudden death.[2]

In $<$5% of patients, pericardial effusions $>$1 mm can occur. Although rare, patients can develop pericardial tamponade.[22,28] Tamponade can also be a complication of giant aneurysm rupture into the pericardial space.[29] Among KD patients with giant CAAs, aneurysms can also occur in peripheral, medium-sized, muscular, extraparenchymal arteries of the axillary, brachial, or iliac regions.[7] This peripheral arterial obstruction can lead to ischemia and gangrene.[30] The vasculitis of KD generally spares visceral vessels; thus, involvement of other organ systems is unusual. However, any vascular bed may be affected, and case reports have included descriptions of KD presenting as a cerebrovascular accident or an acute surgical abdomen.[31,32]

Cardiac symptoms and events can occur as late manifestations of KD. These manifestations occur only in patients who had coronary artery disease. In the convalescent phase of KD, these patients are

often asymptomatic. Special care must be taken in treating patients with large or giant CAAs who later present with angina, abdominal pain, inconsolable crying, and syncope because they are at risk for ischemic heart disease.[2] KD can result in increased serum viscosity, which can result in reduced arterial and capillary blood flow. As such, KD is associated with thrombosis and embolic pathogenesis.

Gastrointestinal

Many nonspecific gastrointestinal symptoms can present with KD, such as diarrhea, vomiting, abdominal pain, and decreased appetite. Other gastrointestinal findings of KD include abdominal distention, gallbladder hydrops, and hepatobiliary dysfunction (such as intrahepatic bile duct damage and hepatomegaly).

An acute abdomen may be the initial presentation of patients with KD.[32] Gallbladder hydrops, otherwise known as acalculous cholecystitis, is a well-known entity associated with KD. Gallbladder hydrops occurs in 5%-20% of cases. Although the exact pathogenesis is unknown, research has suggested that reactive vasculitis leads to inflammation of the gallbladder wall. Gallbladder hydrops can cause hepatobiliary dysfunction, but absent this manifestation, the cause of hepatobiliary dysfunction in KD patients is unknown. Hepatomegaly occurs in approximately 14.5% of KD patients, and elevated liver enzymes are seen in 20%-30% of these patients.[33] Abdominal symptoms are more likely in older children and resolve with the typical treatment of KD. Surgery, such as percutaneous biliary drainage or cholecystectomy, is recommended for KD patients who develop complications from gallbladder hydrops.[33]

Central Nervous System

KD patients may experience extreme irritability, aseptic meningitis, and hearing loss. Neurological complications—such as hemiplegia, myositis, epilepsy, and facial nerve palsy—are rare, with a prevalence of 1.1%.[34,35] Sensorineural hearing loss has been identified in patients within the first 30 days and can also be present 6 months after the onset of disease. Persistent sensorineural hearing loss is associated with delayed use of IVIG and prolonged thrombocytosis, anemia, and elevated ESR.[36] Additionally, studies have shown an increased incidence of long-term behavioral problems, including difficulty with conduct and social interaction, in KD patients compared to hospital- and sibling-matched controls.[37]

Genitourinary

Except for sterile pyuria, urinary abnormalities and renal disease are uncommon in KD patients. However, select cases have demonstrated acute interstitial nephritis, mild proteinuria, and acute renal failure (ARF). ARF is a rare complication seen with a myriad of pathologic processes, such as hemolytic-uremic syndrome, immune complex–mediated glomerulonephritis, and acute interstitial nephritis.[38] Along with the more common clinical findings of KD, laboratory findings such as elevated CRP, leukocytosis with neutrophilia and immature forms, hypoalbuminemia, increased serum transaminase concentrations, and sterile pyuria can be helpful in its diagnosis.[33]

TREATMENT

Because of the serious complications associated with untreated KD, early treatment is important. The 1993 American Heart Association guidelines state that the diagnosis can be made on day 4 of fever; consequently, only 4 days of fever are needed before starting therapy.[6] KD can be diagnosed solely on cardiac abnormalities such as coronary enlargement, in which case treatment with aspirin and IVIG should be initiated immediately. In the acute phase of KD, high doses of aspirin, 80 to 100 mg/kg/d (divided in four doses), given with 2 g/kg in an initial dose of IVIG, work additively to provide an antiinflammatory effect. Currently, the exact mechanism of action of IVIG in KD is unknown. Researchers have hypothesized that IVIG modulates cytokine production, neutralizes bacterial superantigens, augments T-cell suppressor activity, suppresses antibody synthesis, and provides antiidiotypic antibodies.[6] However, the progression of KD may be rapid, and surgical management (i.e., coronary artery bypass grafts for obstructive lesions) may be an appropriate therapy for some patients.

Anesthetic Considerations

The literature addressing KD anesthetic issues consists mainly of single case reports and is sporadic. In the small number of publications on KD and its impact on anesthesia, the greatest concern has been the cardiac manifestations such as CAAs, pericardial effusion, arrhythmias, and myocardial infarction. Morrison et al[39] conducted a retrospective 15-year review of children with a discharge diagnosis of KD. The investigators recorded the type of surgical procedure performed, anesthetic used, perioperative monitoring done, and postoperative complications reported. They identified various surgeries, including hip aspiration; exploratory laparotomy; cervical lymph node exploration; hernia repair; and orthopedic, urologic, and dental procedures and found that 26.4% of the KD patients received general anesthesia or deep sedation. Although no patients died, 1 child developed congestive heart failure immediately after

surgery. Only 15% of the children evaluated in the study had not been diagnosed with KD prior to surgery or had not undergone cardiac evaluation, suggesting that KD patients undergoing anesthesia have the potential for associated higher morbidity and mortality.[39]

The increasing numbers of children with a history of KD present both surgical and anesthetic challenges. Pediatric anesthesiologists are encouraged to consider a KD diagnosis in patients with prolonged fever and rash and should evaluate the potential for myocardial compromise if the patient experiences rapid deterioration perioperatively.[39] Because KD is difficult to diagnose correctly in younger children, the use of ultrasound examination for cardiac involvement has been recommended.[40]

As patients with a history of KD begin to age, more and more will require surgery. Children with KD and coronary involvement should be treated like adults with CAAs. A cardiac assessment should occur preoperatively to detect any cardiac abnormalities. The preanesthetic evaluation should include 12-lead electrocardiography and 2-dimensional echocardiography to identify any involvement of the coronary arteries. Perioperative management should involve standard American Society of Anesthesiologists monitoring, including temperature, heart rate, end-tidal oxygen, pulse oximetry, and blood pressure, as well as ST segment analysis, including leads II and V5, and invasive arterial monitoring. Myocardial injury can be detected early with troponin measurements. Additionally, anesthetic considerations for patients with KD should properly balance myocardial oxygen demand and myocardial oxygen supply by using drugs to manipulate heart rate, contractility, filling pressure, and peripheral vascular resistance as needed. Central venous pressure and pulmonary artery pressure monitoring can be used when warranted.[41]

CONCLUSION

KD is an acute vasculitis of childhood affecting predominantly the coronary arteries. Though the etiology of KD remains uncertain, it is a rare condition that lacks specific laboratory and physical examination findings. Although treatments have become largely standardized, on many occasions both diagnosed and undiagnosed KD patients require surgical interventions. The prudent surgeon and anesthesiologist must properly assess the degree of pathogenesis, especially with regard to cardiac involvement, to ensure appropriate intraoperative and postoperative monitoring and an anesthetic plan that results in the best outcome.

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