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IMAGES in PAEDIATRIC CARDIOLOGY

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Cardiovascular involvement in Kawaski Disease

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MeSH: Kawasaki Disease, Child, Coronary Artery Aneurysms, Giant Aneurysms, Angiography, Echocardiography

Introduction

Kawasaki disease (KD), also known as Muco-cutaneous Lymph node Syndrome (MCLS) is an acute febrile multisystem illness of unknown etiology that primarily affects children younger than 5 years of age. Original description of this disease in the Japanese literature dates back to 1967, when Tomisaku Kawasaki reported 50 cases of “febrile oculo-oro-cutaneo-acrodesquamatous syndrome”.[1] The disease is usually self-limiting but can have serious cardiovascular manifestations, both in acute and chronic stages.
We describe here, a 19 month old child with Kawasaki Disease who developed bilateral giant coronary artery aneurysms.

Case report

A 19 month old African-American boy presented with high fever, bilateral nonexudative conjunctivitis, fissured lips, erythematous tongue, generalized erythematous maculopapular rash and erythema with swelling of the hands and feet. Based on the clinical criteria, a diagnosis of KD was made. Laboratory data revealed anemia, elevated white blood cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). He received a single 2-mg/kg dose of intravenous immunoglobulin (IVIG) and aspirin at 80mg/kg/day was initiated. A 2-dimensional echocardiogram was performed the next day, which revealed normal left ventricular size and function. There was a small amount of pericardial effusion located around the posterior aspect of the heart (Figure 1).
There was no valvular regurgitation. Both the proximal left coronary artery (LCA) and the right coronary artery (RCA) appeared slightly echobright without any ectasia or aneurysm formation (Figure 2).

Patient improved clinically and was discharged home in four days with instructions to take 3 mg/kg of aspirin daily. After 10 days, his fever reoccurred and lasted for approximately four days. He presented to the Infectious disease clinic three weeks later when he was clinically well and afebrile. The only physical finding at this time was desquamation of palms and soles. Laboratory data revealed persistent elevation of CRP, ESR, white count and platelet count. Recommendations included continuation of aspirin and a follow-up echocardiogram, with which the family was not compliant.
He presented to the cardiology division for an echocardiogram after four months. The family had discontinued aspirin four weeks prior to this visit. He had remained asymptomatic and his physical examination was entirely normal. A resting electrocardiogram (EKG) was normal without any evidence of ischemia or infarction. Echocardiogram revealed normal left ventricular size and contractility without any regional wall motion abnormalities. The pericardial effusion had resolved (Figure 3).
There were multiple giant saccular coronary artery aneurysms in both the LCA and RCA territories (Figures 4,5).

Figure 1 Parasternal short axis view at the level of the papillary muscles during the acute phase, demonstrating a small posterior pericardial effusion. The left ventricular contractile function is normal.

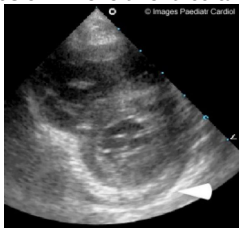


Figure 2 Parasternal short axis view at the base of the heart during the acute phase, demonstrating (a) prominent left coronary artery and (b) a slightly 'echobright' right coronary artery.

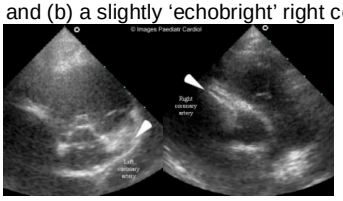


Figure 3 Parasternal short axis view at follow-up, demonstrating normal left ventricular contractility and resolution of pericardial effusion.

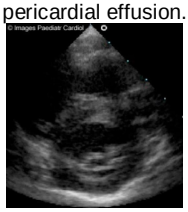


Figure 4 Parasternal short axis view at the aortic annulus demonstrating giant aneurysms in the right coronary artery, left anterior descending artery, and another giant aneurysm posteriorly in the left circumflex artery region.

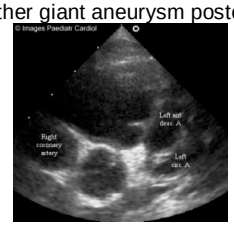
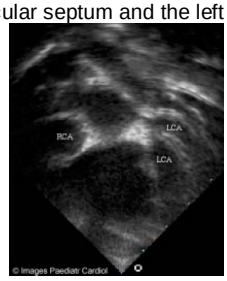


Figure 5 Apical four chamber view with anterior angulation demonstrating all three giant aneurysms. The right coronary aneurysm lies at the atrioventricular groove (AV) and the left sided aneurysms are noted along the interventricular septum and the left AV groove.



The aneurysm in the proximal left anterior descending artery (LAD) measured 9.5 mm (Figure 6) and the one in the proximal RCA measured 14mm (Figure 7). Another saccular aneurysm measuring 5 mm was noted in the left circumflex artery region. An area of increased echogenecity was noted along the aneurysmal wall of left circumflex artery that was suspicious of a thrombus (Figure 8).

Figure 6 Still frame image showing the diameter of the right coronary artery aneurysm.

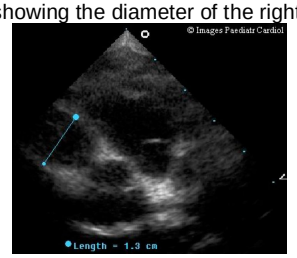


Figure 7 Still frame image showing size of the coronary artery aneurysms of the left anterior descending artery and circumflex artery.

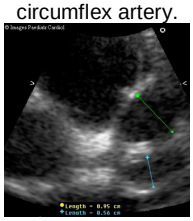
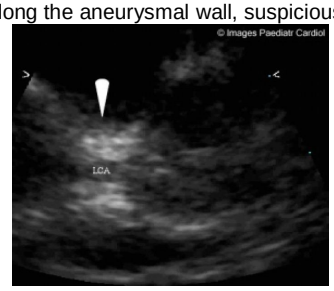


Figure 8 Aneurysm in the region of the circumflex branch of left coronary artery with an area of increased echogenecity along the aneurysmal wall, suspicious of a thrombus.



Cardiac catheterization with coronary angiography was performed to better define the size and extent of aneurysm formation. The aneurysm of the LAD measured 19×10 mm (Figure 9). What appeared to be a circumflex artery aneurysm echocardiographically was actually an aneurysm of the ramus branch of the LCA that measured 9×10 mm. This aneurysm had an irregular contour and the contrast lingered along the wall suggesting presence of a thrombus (Figure 10). Selective RCA angiography revealed multiple saccular aneurysms throughout the course of the artery with the most proximal one being giant sized, measuring 14 mm (Figure 11). There was no evidence of coronary artery stenosis or obstruction.

Management of this patient posed a significant therapeutic dilemma. Systemic intravenous thrombolysis was considered but not offered, since the patient was asymptomatic. Aspirin was re-initiated at 5mg/kg/day and coumadin was added to the regimen with a target International normalized ratio (INR) of 2.5 to 3. Intravenous heparin therapy was given for 72 hrs to achieve early anticoagulation before coumadin reached a steady state. Discharge instructions included avoidance of contact and high-impact sports and trauma to the chest. At his follow-up visit, 2 months later, he continued to be asymptomatic with normal physical exam and EKG. Repeat echocardiogram showed persistence of the three giant coronary aneurysms at the same size. However the echogenicity noted previously in the ramus aneurysm was not evident anymore. A plan to repeat angiography in one year was made, unless change in clinical status dictates otherwise.

Figure 9 Selective left coronary artery angiogram in slight left anterior oblique view with caudal angulation. The left main coronary artery appears normal and trifurcates into the left anterior descending (LAD), ramus and circumflex branches. The giant aneurysm in the LAD appears globular in this view and is densely opacified. The ramus aneurysm is long and saccular, located inferior to LAD. There is ectasia of the circumflex branch.

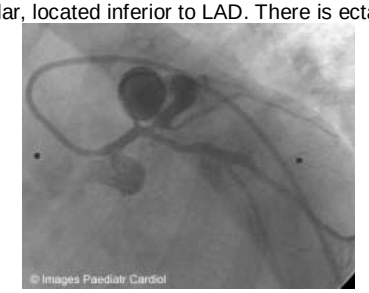


Figure 10 AP view of the same demonstrating overlapping of ramus and LAD aneurysms.

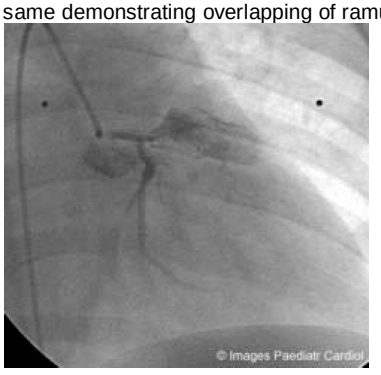
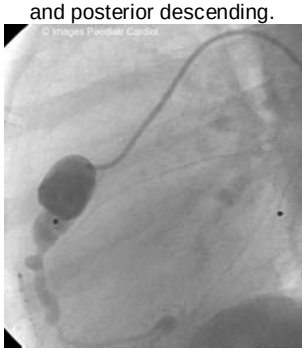


Figure 11 Straight lateral view of a selective right coronary artery angiogram demonstrating a giant aneurysm just distal to the coronary ostium. Multiple small aneurysms are noted throughout the course of the right coronary artery and posterior descending.



Discussion

Epidemiology

KD is extraordinarily prevalent in Japan but has been reported to occur worldwide. The estimated annual attack rate in the United States is 9.2 per 100,000 children, with attack rates being 6 and 1.5 times higher in the Asian and African-American population respectively.[2] It usually affects infants and 76 % of the patients with KD are under 5 years of age. It rarely affects adults, but cases have been reported in literature. It affects boys 1.4 times more often than girls; fatalities are more common in boys. It has winter-spring seasonality and community-wide outbreaks have been reported occasionally. Epidemiologic and clinical data suggest an infectious etiology, but no agent has been identified so far. Activation of the cytokine cascade, endothelial cells, monocyte/macrophages and plasma cells support an immunologic basis. The occurrence of KD in siblings of index cases, twins and children of parents affected in their childhood suggests a genetic predisposition.[3,4]

Pathology

KD results from inflammation and generalized vasculitis that may be described in four stages:
Stage I (days 0-12): endothelial cell swelling and subendothelial edema, with initial neutrophil infiltration that is replaced by mononuclear cells and lymphocytes. Along with this acute vasculitis and perivasculitis, myocarditis, pericarditis, valvulitis and inflammation of conduction system may occur.
Stage II (days 12-25): aneurysm formation is most likely to occur during this time.
Stage III (days 26-40): remodeling of coronary arteries with intimal proliferation.
Stage IV (day 40 and beyond): intimal thickening, fibrosis, calcification and thrombosis.

Diagnosis

Since there are no pathognomonic clinical features or specific diagnostic tests for KD, the diagnosis rests on the classic clinical features described in Table 1:

Table 1 Classic diagnostic criteria for KD[4]

1. Fever for at least 5 days *PLUS*
2. Presence of at least four of the following:
    a. Bilateral non-exudative conjunctivitis
    b. Changes in lips and oral cavity (erythematous, dry fissured lips; erythema of pharynx; strawberry tongue). (Figures 12 and 13)
    c. Changes of the hand and feet (redness and swelling in the acute phase, periungual desquamation in the sub acute phase)
    d. Polymorphous Exanthem, primarily on the trunk (maculopapular, erythema multiforme, or scarlatiniform; not vesicular). (Figure 14)
    e. Cervical Lymphadenopathy (node diameter, >1.5 cm). (Figure 15)
3. Illness not explained by other known disease process

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Figure 12 Erythematous dry and fissured lips

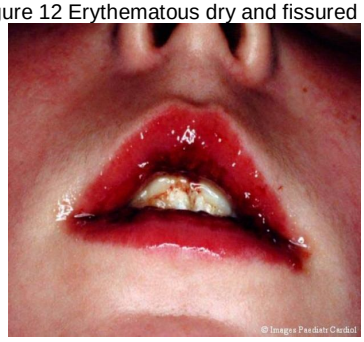

Figure 13 Strawberry tongue

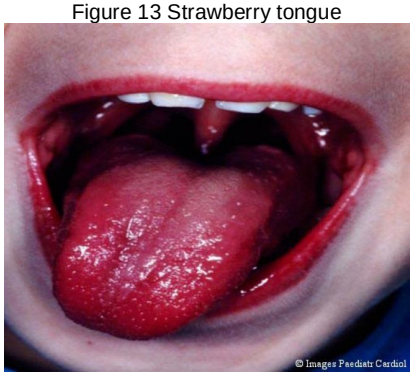

Figure 14 Erythematous polymorphous rash over trunk and genitalia

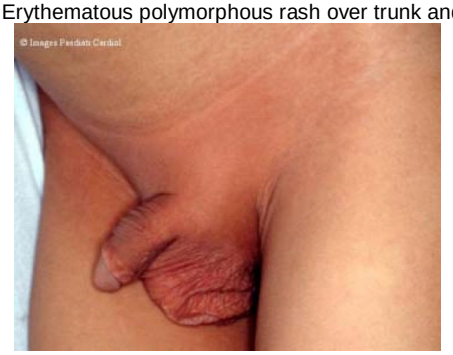

Figure 15 Cervical lymphadenopathy

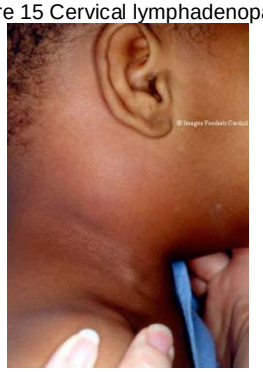

Figure 16 Peeling and membranous desquamation around genitalia

Patients with fever and < 4 principal criteria can be diagnosed as having *Atypical or Incomplete Kawasaki Syndrome* when coronary artery abnormalities are identified.

Clinical course
The clinical course of KD can be broadly classified into 3 stages:

1. **Acute febrile phase:** Characterized by high remittent fever and features mentioned above in various combinations. Cardiac involvement in the form of myocarditis is common during this time and pericardial inflammation with pericardial effusion can occur. Acute inflammation of the coronary arteries--'coronary arteritis' may be seen echocardiographically as broadening of the wall or perivascular brightness. This stage usually lasts for 1-2 weeks.
2. **Subacute phase:** Fever, rash, and lymphadenopathy resolve and desquamation of extremities is noted (Figure 16). Coronary artery aneurysms usually develop during this time, and the risk for sudden death is highest during this stage.[6] This stage generally lasts 1-2 weeks.
3. **Convalescent stage:** Begins when all clinical signs of illness have resolved and continues until the ESR returns to normal, usually 6 to 8 weeks after the onset of illness.

Cardiovascular involvement in KD
Cardiovascular involvement is the most serious manifestation of KD and is responsible for the morbidity and mortality associated with this disease. It can be in the form of:
Myocarditis: Myocardial inflammation during the acute stage has been demonstrated in 50-70% of patients.[7] The severity of myocarditis seems unrelated to coronary artery abnormalities. Clinical findings include sinus tachycardia, gallop rhythm, cardiomegaly, prolonged PR interval and non-specific ST and T changes on EKG during the 2nd and 3rd weeks and usually disappear by the end of 4th week. Pericardial inflammation with effusion can occur. Clinical or echocardiographic ventricular dysfunction improves rapidly after IVIG therapy, although ultra structural abnormalities have been noted to persist for years. The long-term implications of these abnormalities remain to be seen.
Valvular regurgitation: Valvulitis in the acute stage can result in mitral or aortic regurgitation, but late onset regurgitation that may or may not be related to myocardial ischemia has been reported.
Aortic root dilation: mild aortic root dilation has been reported to be common.[8]
Coronary artery involvement: Coronary ectasia or dilatation is recognized in 50 % of patients during the acute stage. An aneurysm is defined as a segment whose internal diameter is ≥ 1.5 times the adjacent segment. About 15 to 20 % of untreated patients and 5% of those treated with IVIG develop coronary artery aneurysms.[9] They usually occur within 1 to 3 weeks (mean 10 days) and if they are not involved during this period, it is extremely unusual for them to be affected subsequently. They are classified (American Heart Association) based on their internal diameter as small (< 5 mm), medium (5-8 mm) or giant (≥ 8 mm).[10] The Japanese Ministry of Health considers coronary arteries as abnormal if the internal lumen diameter is > 3mm in children < 5 years old or > 4 mm in children ≥ 5 years old, or if the lumen is irregular. They are called *fusiform*, when they have a dominant longitudinal dilation and *saccular*, when their transverse axial and lateral diameters are nearly equal. The most frequent site for aneurysm formation is the proximal LAD and proximal RCA, followed by the left main coronary artery (LMCA), the left circumflex artery (LCX), and finally the distal RCA and the junction between the RCA and the posterior descending coronary artery.[11] Giant coronary aneurysms occur in less than 1% of cases and are usually associated with a greater morbidity and mortality due to increased risk of rupture, thrombotic occlusion or stenotic obstruction leading to myocardial infarction. In a 10- to 21- year follow-up study by Kato et al,[9] 46% of giant coronary aneurysms developed stenosis or complete obstruction and 67% experienced myocardial infarction, with a 50% mortality rate. Fusiform aneurysms tend to have a better outcome than the saccular ones.
There is no definitive way to predict which patients will develop coronary aneurysms, but certain risk factors have been identified that are listed in Table 2.[12–14]

Table 2 Risk Factors for development of coronary artery aneurysms

• Male gender
• Very young infants, particularly <6 months, where the disease is often atypical
• Older age (> 5 years), partly because of the delay in the recognition and treatment
• Prolonged fever (> 16 days) and fever despite IVIG treatment
• Recurrence of fever after an afebrile period of at least 48 h
• Anemia
• Thrombocytopenia early in the disease process and thrombocytosis at a later stage
• Peripheral leucocyte count > 30,000/ mm2
• ESR > 101 mm/hr and high CRP
• Elevated ESR or CRP beyond 30 days or recurrent elevations
• Low serum albumin and age-adjusted serum IgG levels

Scoring systems based on these factors however, have not been sensitive enough to allow patient selection for angiography or IVIG treatment. Duration of fever has been identified as the most important predictor of aneurysms in various studies.

Laboratory findings
Leukocytosis is common; anemia can occur. Acute phase reactants like ESR, CRP are elevated which normalize in 6-10 weeks. Thrombocytopenia can rarely occur in the acute phase, but thrombocytosis is frequent usually during 2nd and 3rd weeks. An alteration in lipid profile is seen with decreases in cholesterol, high-density lipoprotein and

apolipoprotein. Mild to moderate elevation in liver transaminases and bilirubin with hypoalbuminemia may occur. Urine analysis shows sterile pyuria due to urethritis and mononuclear cells are seen in cerebrospinal fluid in 50% of patients due to aseptic meningitis. Elevation of cardiac troponin I, a marker of myocardial damage has been reported.
Echocardiography is the initial screening test to evaluate cardiac involvement in KD and a baseline study should be performed as soon as the diagnosis is suspected. Imaging should be supervised by a trained pediatric cardiologist and high frequency transducers should be used for detailed evaluation of coronary arteries. Serial echocardiographic follow-up is very important and is indicated at 2 weeks and 6 to 8 weeks after the onset in uncomplicated cases. In presence of coronary abnormalities, LV dysfunction, or valvular regurgitation, imaging should be repeated at more frequent intervals. Evidence suggests that repeat echocardiography at 1 year after the onset of the illness is unlikely to reveal coronary artery abnormalities if the initial echocardiogram at 4 to 8 weeks was normal.[15] Limitations of echocardiography include difficulty in identifying thrombi and coronary artery stenosis and difficulty in visualization of distal coronary artery segments. Magnetic resonance angiography provides accurate delineation of coronary artery aneurysms, including those in the peripheral arteries, coronary stenosis and occlusions. Ultrafast computed tomography has also been used to assess aneurysms.
Cardiac catheterization and coronary angiography may be necessary in certain cases for detailed evaluation of coronary artery anatomy, to detect coronary stenosis or occlusion and to define extent of collateral formation. Indications and timing vary between institutions, but in general is indicated in complex coronary lesions and when non-invasive studies suggest myocardial ischemia.
Cardiac stress testing by exercise echocardiography, dobutamine echocardiography, magnetic resonance stress imaging or nuclear perfusion scans is indicated to evaluate myocardial perfusion and may guide clinical decision to perform invasive evaluation or intervention.

Management
Intravenous gamma globulin (IVIG) at a dose of 2mg/kg should be administered to all patients at diagnosis, preferably within 7 days of onset of illness. In 10% of patients who fail to defervesce within 36 hours of IVIG treatment (“non-responders”) a second dose of IVIG at 2 g/kg is recommended. It should also be offered to patients in whom diagnosis is missed and present after 10 days with persistent fever, coronary aneurysms or elevated acute phase reactants. The exact mechanism of action of IVIG is not known, but it is thought to exert an anti-inflammatory reaction. There is ample evidence that it reduces the prevalence of coronary artery abnormalities.[16,17] Aspirin is used during the acute phase at high doses (80 to 100 mg/kg/day), for anti-inflammatory effect. This must be continued at least 48 – 72 hours after the patient defervesces, and some centers continue for 14 days. Subsequently, low- dose aspirin at 3-5 mg/kg/day is used for its anti-platelet effect, which is continued until 6-8 weeks, in the absence of coronary artery abnormalities.
The role of steroids in treatment of KD is controversial; some studies suggest detrimental effect on coronary artery disease,[18] while some others report shortened duration of fever and hospital stay with either no effect[19] or lower prevalence of coronary artery disease.[20] The committee on KD, in its recent statement[11] recommends that steroid treatment be restricted to children who do not respond to ≥ 2 infusions of IVIG. Pentoxifylline appeared to have a beneficial effect on coronary aneurysms in one study.[21] Use of abciximab, a platelet Iib/IIIa receptor, in acute or subacute stages has been shown to have a favorable effect in patients with large coronary aneurysms.[22] Other treatments like plasma exchange, ulinastatin, a human trypsin inhibitor been reported to be effective in patients refractory to IVIG in uncontrolled clinical trials. Monoclonal antibodies against pro-inflammatory cytokines and certain cytotoxic agents may have some role in treatment of refractory KD.

Management of coronary artery disease in patients with KD
Recommendations for the management of coronary disease in KD are based on the severity and extent of coronary involvement. Anti-platelet agents play a critical role in the prevention of thrombosis in all patients and anticoagulant therapy is added in severe cases. Asymptomatic patients with mild and stable disease may be managed on aspirin alone. Other antiplatelet agents such as clopidogrel or dipyridamole (adenosine -5-diphosphate inhibitor) may be used as the extent of involvement increases. Patients with giant aneurysms are at highest risk for developing thrombosis owing to stasis within the aneurysm in combination with turbulence at the aneurysm inlet and outlet which activates endothelial and platelet cascades. These patients require warfarin therapy with a target INR of 2.0 to 2.5 in addition to aspirin therapy. Twice daily subcutaneous low-molecular weight heparin in combination with aspirin is an alternative.
Lacking randomized controlled trials in children with KD, the treatment of thrombotic coronary occlusion is based upon recommendations from treatment of adults with acute coronary syndromes. Thrombolytic therapy consists of use of streptokinase, urokinase or tissue plasminogen activator in combination with aspirin and heparin (unfractionated or low-molecular weight). The Research Committee of the Japanese Ministry of Health recommends that catheter interventions including balloon angioplasty, rotational ablation, and stent placement should be considered in patients presenting with ischemic symptoms, patients without ischemic symptoms but with reversible ischemia on stress test, and patients without ischemia but with more than 75% stenosis in the LAD.[23]
The indications for surgical revascularization in children have not been established in clinical trails but should be considered in presence of reversible ischemia, demonstrable by stress- imaging, or when there is severe occlusion of LMCA, proximal LAD or severe occlusion of > 1 major coronary artery.[24] Coronary bypass grafting is best accomplished with the use of internal mammary arterial grafts, which grow with the child and have better patency rates than saphenous venous grafts. Heart transplantation should be considered for patients with severe, irreversible myocardial dysfunction with coronary lesions that are not amenable to interventional or bypass graft procedures.[25]

Long-term follow-up
In about 50 to 67 % of cases, coronary aneurysms regress within 1 year; regression being more likely when the age at onset of KD is < 1 year, when aneurysms are smaller in size (< 5 mm), if they are fusiform rather than saccular and when they are located in the distal segments. In patients with stenotic lesions or giant aneurysms, the stenosis is frequently progressive in nature and may result in myocardial infarction, which is the principal cause of death in KD.[5] Ischemic heart disease develops in < 3% of cases and usually occurs within the first year but fatal infarctions have been reported more than 6 years after the disease onset. Initial reports from Japan in the 1970s indicate a case fatality rate of 1 – 2%, but this has decreased to 0.08% with improved recognition and treatment. Late cardiac

sequelae include predisposition of the coronary arteries to accelerated atherosclerosis as suggested in one report based on findings of chronic thickening and loss of distensibility in carotid arteries in these patients.[26] Despite anatomical regression of aneurysms, segments of coronary arteries continue to demonstrate abnormalities in vascular reactivity, endothelial function and myocardial flow reserve[27,28]. In fact, these abnormalities have been noted even in those patients that did not have detectable coronary lesions. Long-term consequences of these findings remain to be seen.

A multidisciplinary committee of experts convened by the American Heart Association has recently issued a revised statement[11] regarding long-term management and follow-up of patients with KD and includes recommendations for medical therapy, physical activity, follow-up and diagnostic testing based on risk stratification. The group recommends aspirin therapy and physical activity restriction for the initial 6-8 weeks, with cardiovascular risk assessment and counseling at 5-year intervals for those patients that have no coronary artery involvement at any stage of illness (Risk level I). Similar recommendations but with more frequent cardiovascular risk assessment (every 3 -5 years) is suggested for those that have transient coronary artery ectasia disappearing within 6-8 weeks (Risk level II). Risk level III applies to those patients that have small-medium (3-6 mm) aneurysms involving more than one coronary artery. Antiplatelet therapy should be continued in these patients until regression of aneurysms is documented and competitive collision and high-impact sports should be discouraged during this time. Follow-up should include annual echocardiogram and ECG with stress imaging every 2 years for children > 10 years old. Coronary angiography is recommended if stress tests suggest myocardial ischemia.

Patients who have ≥ 1 large aneurysm (> 6mm) including giant aneurysm or multiple aneurysms in same coronary artery without obstruction (Risk level IV) should be treated with warfarin or low-molecular-weight heparin in addition to the long-term antiplatelet therapy. They should be evaluated with echocardiogram and ECG at 6-month intervals. Stress tests with myocardial perfusion imaging should be performed annually and should guide recommendations for physical activity. Selective coronary angiography should be performed 6 to 12 months after recovery from the acute illness. Subsequently, the decision to repeat angiography should be guided by clinical indications of the individual case. Reproductive counseling should be done for females of child-bearing age. Patients with demonstrated coronary artery obstruction fall into Risk level V and recommendations for this category include all those indicated for risk level IV plus consideration for beta-adrenergic blocking drug to decrease myocardial oxygen consumption. Coronary angiography should address therapeutic options of bypass grafting or catheter interventions.

Conclusion

Kawasaki disease has replaced acute rheumatic fever as the most common cause of acquired heart disease in children. Four decades after its recognition, there continues to be great deal of uncertainty regarding the etiology, diagnosis, treatment and follow-up of this disease. Early recognition, treatment and follow-up of these children is vital in order to decrease cardiovascular morbidity and mortality. Existing evidence pointing to persistent abnormalities in vascular function and premature atherosclerosis is certainly disturbing. The full impact of Kawasaki disease on long-term cardiovascular health remains to be seen.

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