Long-term Cardiac Sequelae of Kawasaki Disease

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Kawasaki disease is the leading cause of acquired heart disease in childhood. Despite treatment with intravenous gamma globulin, 2% to 4% of patients have coronary abnormalities. Those with giant aneurysms are at risk for stenosis and myocardial ischemia/infarction, and require aggressive anticoagulation with frequent follow-up, including stress testing and coronary angiography. In rare cases, patients will have coronary artery bypass grafting. Those with less severe coronary involvement need antiplatelet therapy and infrequent noninvasive testing. Patients with normal echos after the acute phase are not treated, but the future impact of the disease is not certain particularly in the setting of adult onset coronary artery disease.

Introduction

Kawasaki disease (KD) is the most common cause of acquired heart disease in children. Subsequent to the first report in 1967 in Japan, several hundred cases have been identified and treated [1]. A decade later, KD was diagnosed sporadically in the US; over the last 20 years, it has been recognized with greater awareness with an estimated 3000 to 5000 new cases yearly [2]. Prior to routine utilization of intravenous gamma-globulin (IVIG) therapy, the frequency of coronary artery abnormalities was approximately 20%; however, treatment with single dose IVIG in the first 10 days of the illness has reduced the degree of involvement in the acute phase of the illness to 2% approximately [3••]. This expanding population of individuals with coronary artery disease identified by echocardiography has future long-term implications for adult care providers.

Cardiac Sequelae Following Early and Subacute Phases

The late outcome of KD is determined by the degree of involvement of the coronary arteries, myocardium, or mitral/aortic valves.

Coronary arteries

Abnormalities of the coronary arteries may be identified by echocardiography as early as 7 days after the onset of fever. The Japanese Ministry of Health defines coronary abnormalities as an internal lumen diameter greater than 3mm in children of less than 5 years old or greater than 4mm in children of older than 5 years; the presence of a segment diameter 1.5 times that of an adjacent segment or a clearly irregular lumen [4]. Multiple reports have shown that coronary artery ectasia or aneurysms occur in 15% to 25% of children with KD not treated with (IVIG) in the acute phase [5–7]. A later US multicenter study of patients treated with high-dose IVIG within the first 10 days of illness has shown abnormalities in only 2% to 4% of patients 7 weeks after the onset of illness [3••]. Angiographic resolution of coronary artery aneurysms identified within 2 months from the onset of KD has been observed in approximately 50% of affected vessels [5,8••,9]. Several reports suggest that the likelihood for aneurysm resolution is associated with the initial size of the aneurysm; smaller aneurysms having a greater potential for regression [9,10]. Other factors identified with regression of aneurysms include onset of illness in infants less than 1 year, saccular morphology, and distal coronary segment location. When aneurysms do not resolve, stenosis or occlusion may result.

Myocardium

Myocarditis is suggested in the early phase of the illness by physical signs or echocardiography [10]. Myocardial inflammation, diagnosed by abnormal Gallium-67 citrate scans in 50% to 70% of cases [11] or technetium-99m labeled white blood–cell scans [12], resolves rapidly after IVIG infusion [13]. However, late myocardial biopsy studies of the right ventricle have demonstrated myocardial abnormalities, including fibrosis, as well as disarray, abnormal branching, and hypertrophy of myocytes, in all time periods after disease onset [14]. Electron microscopic examination of endomyocardial biopsies has demonstrated similar histologic abnormalities late after KD [15]. Reports regarding left ventricular function among children without coronary artery lesions have been variable with some noting complete resolution of dysfunction within 2 years of disease onset [16,17], whereas abnormalities of both left ventricular size and of systolic and early diastolic function have been noted to persist [18].

Aortic/Mitral Valves

Found far more frequently than aortic regurgitation, mitral regurgitation may result from transient papillary muscle dysfunction, myocardial infarction, or valvulitis. Onset of insufficiency after the acute stage is generally related to myocardial ischemia, although late-onset valvulitis has been reported [19]. Aortic regurgitation has been documented angiographically and echocardiographically; however, hemodynamically significant aortic regurgitation is rare [8••,19].

Course of Kawasaki Disease

Given the divergent populations of coronary artery disease following the subacute course of the illness, the approach to the individual patient varies depending upon underlying cardiac involvement. The ability to predict late outcomes in patients with KD is limited because the oldest affected population has not exceeded the fifth decade of life.

Persistent coronary artery abnormalities

Although aneurysm size tends to diminish over time, in contrast, stenotic lesions often progress related to myointimal proliferation [20]. Of those who develop stenoses, lesions are found in about 50% of patients within 2 years from onset of disease; the prevalence of stenosis continues to increase almost linearly over time [8••,21]. Giant aneurysms (maximum diameter more than 8 mm) pose an increased risk for thrombosis from stasis, as well as vessel stenosis at either end of the aneurysm. The lesions are thought to rarely regress in size, although the majority progress to stenosis or complete obstruction within years from onset of disease [22]. In a Japanese natural history series, 12 of 26 patients with giant aneurysms diagnosed at initial angiography had progression to stenosis or complete obstruction between 10 and 21 years later. Myocardial infarction occurred in eight of these 12 patients, four of whom died. The remaining 14 patients continued to have coronary aneurysms without significant coronary artery stenosis [8••].

The principal cause of death in KD is myocardial infarction caused by thrombotic occlusion of an aneurysmal or stenotic vessel. [23]. A Japanese nationwide survey of 195 patients with myocardial infarction showed that the initial event occurred in the first year after disease onset in 142 (72.8%) children, 77 of these within 3 months of onset [24]. Symptoms, present in 122 patients (63%), included shock, crying, chest pain (occurring in 17% of children under age 4 years and in 83% of those older), abdominal pain, vomiting, dyspnea, and arrhythmia. The presentation occurred during sleep or at rest in 63% of patients, whereas only 14% experienced myocardial infarction during activity. Few children had symptoms of angina pre-dating the actual event. Mortality percentage from the first myocardial infarction was 22%. Most fatal attacks were associated with obstruction of the left main coronary artery, or both the right main and left anterior descending coronary arteries; whereas survivors generally had single vessel obstruction, often in the right coronary artery.

The clinical course after myocardial infarction is variable depending on the extent of myocardial damage. Kato reported 41% of survivors doing well without cardiac symptoms. Suzuki [20] found that decreased left ventricular ejection fraction at the first angiogram following myocardial infarction often improved at follow-up angiography. Of 152 survivors of a first myocardial infarction in Kato's experience [24], 24 (16%) had a second myocardial infarction, with an associated mortality of 62.5%. A third attack occurred in six of the nine survivors, with only one patient surviving. As the population with chronic coronary artery disease increases, it is likely that the percent of cases with late myocardial infarction and chronic ischemic heart disease will increase.

Serial stress tests and myocardial imaging are essential in managing patients with significant coronary artery disease, to guide the need for coronary angiography and surgical or transcatheter intervention [24–26]. Hijazi [27] found that the majority of patients with coronary aneurysms had normal regional coronary flow reserve, as assessed by myocardial perfusion imaging, and even giant coronary aneurysms were associated with normal coronary flow reserve and preserved regional function during stress. Hamaoka [28] evaluated flow velocity dynamics and flow reserve in patients with coronary aneurysms using an intracoronary Doppler flow guide wire. Abnormalities in flow dynamics and a reduction in coronary flow reserve were present in coronary artery aneurysms of intermediate to large size as well as in stenotic lesions, even of mild to intermediate severity. Abnormalities in the coronary microcirculation, as well as epicardial lesions, contributed to the pathophysiologic responses.

Although most serious disease is identified in childhood, late cardiac sequelae may become evident initially in adulthood. Burns [29] identified 74 patients with onset of KD in childhood, in which the first presentation with coronary artery disease occurred in young adulthood [29]. In adults with coronary aneurysms, a careful history should explore the possibility of a preceding prolonged febrile illness in childhood.

Spontaneous regression of aneurysms

Approximately 50% of vascular segments with coronary artery aneurysms show angiographic regression [10,14,23]. Examination of healed aneurysms has shown fibrous initial thickening, supported by intravascular ultrasound showing marked symmetric or asymmetric myointimal thickening [30]. These histologic abnormalities in arteries with aneurysm regression have raised concerns that such segments may be at risk for accelerated atherosclerosis [9,14].

In addition, arteries with regressed aneurysm show reduced vascular reactivity during diastole [31], as well as during pharmacologic vasodilatation with intravenous

dipyridamole [32] or nitroglycerine [33]. Sugimura [34] assessed coronary artery diameter reactivity to intracoronary isosorbide dinitrate during coronary angiography. Arterial segments that had never been of abnormal caliber were somewhat similar in their vascular reactivity in affected patients to those of control patients, whereas arterial segments with regression of earlier coronary artery aneurysms had vascular reactivity, which decreased progressively from illness onset. Vascular reactivity of arterial segments with aneurysms and stenosis had vascular reactivity comparable with that found in regressed coronary artery segments. These changes suggest that arterial segments with regressed aneurysms may be developing early atherosclerotic changes and may manifest decreased responsiveness during increased myocardial metabolic demands with exercise [9,32].

Kawasaki disease without detectable coronary lesions

The long-term status of the coronary arteries in children who have never had demonstrable abnormalities is unclear. The mean variation in arterial dimension between systole and diastole in the proximal left anterior coronary artery of patients with Kawasaki disease who do not have a history of dilatation in this segment is intermediate between that of patients with resolved aneurysms in that segment and that of control patients [31]. Fujiwara [23] reviewed the coronary pathology of patients who died 9 to 22 days after disease onset, in whom there was no coronary artery dilatation, and found all with microscopic evidence of coronary vasculitis. Meaningful extrapolation is not possible because these patients may have progressed to coronary aneurysms had they survived the illness. An autopsy series of five individuals with a history of Kawasaki disease who died of unrelated causes at an interval ranging from 60 days to 2 years after illness onset showed intimal thickening and fibrosis indistinguishable from adult onset arteriosclerosis [14].

Although coronary artery aneurysm formation is the most serious sequelae of Kawasaki disease, vascular inflammation during the acute stage is diffuse. The possibility of generalized endothelial cell dysfunction has been suggested by the observation that plasma 6-keto-prostaglandin F1-α, a metabolite of prostacyclin, remained generally undetectable over an observation period of 8 weeks after onset of disease [35]. Additional biochemical evidence for endothelial cell dysfunction is supported by the observation that lipid metabolism is altered after clinical resolution of disease [36]. Further research is needed to elucidate the mechanism by which these abnormalities are produced and to assess their course over many years.

Muzik [37] used positron emission tomography to compare myocardial blood flow and flow reserve in a group of patients with normal-appearing coronary arteries following KD with that of young adult volunteers. Patients with KD had lower myocardial flow reserve and higher total coronary resistance, without evidence of regional perfusion abnormalities. The abnormal hyperemic blood flows and flow reserves suggest an impaired vasodilator capacity, postulated to have resulted from damage to the coronary microcirculation.

Mitani [38] assessed the responses of left epicardial and resistance coronary arteries following serial intracoronary infusions of acetylcholine and nitroglycerine in subjects by using quantitative angiography and a Doppler flow wire system. Normal-appearing epicardial coronary arteries showed a significant constriction in response to acetylcholine, an endothelium-dependent vasodilator, whereas responses to nitroglycerin, an endothelium-independent vasodilator, were preserved, indicating an impairment of endothelial-dependent relaxation regardless of the absence of coronary artery lesions at any time in the illness.

Dhillon [39] has suggested that abnormalities of endothelial function may be present years after resolution of acute illness, even in those patients without detectable coronary artery involvement. Endothelial function in the brachial artery was assessed using high-resolution ultrasound in patients 5 to 17 years after acute Kawasaki disease, and demonstrated marked impairment in brachial artery flow-mediated dilation compared with controls. In contrast, endothelial-independent dilation was similar in patients with Kawasaki disease and controls, suggesting that abnormalities of systemic endothelial function are present many years after resolution of acute KD, even in patients without detectable early coronary artery involvement.

From the purely clinical perspective, children without known cardiac sequelae during the first month of KD appear to return to their baseline state of health, without signs or symptoms of cardiac impairment. In Kato's natural history study, 258 of 448 children were found to have normal coronary arteries at coronary angiography. At long-term follow-up 10 to 21 years later, none of these patients demonstrated cardiac symptoms or abnormal findings [8]. We evaluate such children 1 year after recovery from the acute illness, and then every 3 to 5 years. Additional knowledge about long-term myocardial function, late-onset valvar regurgitation, and coronary artery status in this population will require careful long-term surveillance.

Therapy

Patients with persistent coronary artery abnormalities are treated with long-term antithrombotic medication preferably low-dose aspirin at 3–5mg/kg/d. Other therapeutic options, used primarily in patients with large or giant aneurysms include antiplatelet therapy with aspirin together with other inhibitors of platelet aggregation (clopidogrel), anticoagulant therapy with warfarin, or a combination of anticoagulant and antiplatelet therapy (usually warfarin with aspirin). No prospective data exist to guide the clinician in choosing an optimal regimen, and there are anecdotal reports of thrombosis occurring with each of these drug combinations. In our experience, we have used low-dose aspirin alone for patients with coronary abnor-

malities other than giant aneurysms, though our latest modification involves combining clopidogrel with aspirin for patients, in which aneurysms are in the 6–8mm range. Because the risk of thrombosis and myocardial infarction is greater in patients with giant aneurysms [22,23], low-dose aspirin in combination with warfarin is generally recommended, maintaining the INR at 2.0–2.5. Some physicians have substituted low molecular-weight heparin for warfarin, although subcutaneous injections make it less acceptable for children.

Despite the use of antithrombotic agents, some patients have developed myocardial infarction from thrombotic occlusion of coronary aneurysms, particularly giant aneurysms. Although the experience in children is limited, thrombolytic agents such as streptokinase, anistreplase (anisoylated plasminogen-streptokinase activator complex or APSAX), urokinase, and tissue plasminogen activator in children with coronary artery thrombosis, either intravenous or intracoronary, have been used with some success [8,40–42]. Although therapy is most effective if initiated within 4 to 6 hours after onset of symptoms, administration of thrombolytic therapy is suggested within 24 hours if there is evidence of ongoing ischemia and absence of contraindications. Adjuncts or conjuncts to thrombolytic agents include antiplatelet agents, such as antagonists to glycoprotein IIb-IIIa receptors and intravenous heparin following re-establishment of perfusion; however, the ideal antithrombotic regimen has not been determined [42]. The pediatric experience with IIb-IIIa inhibitors is extremely limited, but the successful outcomes achieved in adults with acute coronary syndromes [43] indicate that future consideration be made. Recently, for a 6-month-old infant with identified thrombi involving the right and left anterior descending coronary arteries, we achieved partial resolution of the clot using a combination of abciximab and one half the standard dose of TPA.

Surgical management

Given the size of affected patients and the absence of symptoms, the indications for intervention are not straightforward. Furthermore, pediatric patients have been shown to develop collateral circulation frequently [20]. It appears reasonable to consider surgery in circumstances, in which reversible ischemia is present on stress-imaging tests or stenosis has been progressive without arterial lesions distal to the graft site. Coronary artery bypass grafting has been used with increasing success [44,45,46••].

Initially, the surgical technique had been performed using autologous saphenous veins or veins from a living related donor [45], but frequent graft occlusion led to the use of internal mammary artery grafts in this patient group with improved outcome [46••]. The diameter and length of the arterial grafts increase with the child's somatic growth. Following surgery, patients have shown improvement of abnormalities demonstrated preoperatively during stress exercise electrocardiography or thallium scintigraphy during exercise. In children under 7 years of age, the graft patency 90 months after surgery was 70%; whereas children older than 8 years at surgery showed 84% graft patency over the long term with overall survival of 98.7%, 8 years postoperatively [47].

Table 1. Follow-up assessment in patients following of Kawasaki disease

No echocardiographic abnormalities after acute phase
Echo at 1 year
Echo every 3–5 years
Coronary ectasia or aneurysms after acute phase
Echo yearly until abnormalities regress
Echo every 3 years after lesions regress
Exercise tolerance test every 3 years preferably with nuclear perfusion scan
Cardiac cath for symptoms of angina or ischemic changes on exercise/scan
Giant aneurysm after acute phase
Echo at 1 year
Cath at 1 year (earlier with symptoms of angina)
Exercise with nuclear scan yearly
Cath every 3 years (earlier with symptoms or [+] exercise/scan)

Interventional cardiac catheterization techniques

Because the long-term outcome for surgical graft patency remains uncertain, successful interventional catheterization therapy is an appealing surgical alternative. Percutaneous transluminal coronary angioplasty (PTCA) has been used for stenotic coronary arteries [47,48•]; however, its efficacy does not approach that in adults with atherosclerotic coronary artery disease. Because the stenoses found in KD are noncompliant and often associated with marked calcifications, the relatively high balloon pressures required to achieve dilation of the involved segments have caused aneurysm formation [48•]. Intravascular ultrasound imaging has been found to be a useful tool for evaluating internal morphology before and after PTCA [47]. If calcification and stenosis are severe, rotational ablation techniques have been successful [48•]; we have had some success stenting an isolated stenotic lesion. Further studies in this limited patient population are necessary to establish the best method for an approach to the underlying pathology.

Conclusions

Kawasaki disease, a leading cause of acquired heart disease in children in the United States, results in coronary artery aneurysms or ectasia in approximately 15% to 25% of untreated children. Although treatment with intravenous gamma globulin in the acute phase reduces this risk three- to fivefold, a large population of pediatric patients exists who will require long-term follow-up.

Strategies for diagnosis and intervention need to be in place to determine individuals at risk for progressive stenosis or occlusion of coronary arteries and their subsequent therapy (Table 1). Even in patients who demonstrate angiographic or echocardiographic resolution of aneurysmal coronary segments, histologic and functional abnormalities of the vessels persist. Continued long-term surveillance in patients with and without detected coronary abnormalities is necessary to determine the natural history of Kawasaki disease.

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