Prospective Follow-Up Cardiac Evaluation of Children With Kawasaki Disease in Northern India Using the Japanese Echocardiography Criteria

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Abstract

Objectives. There is no information available on the follow-up of children with Kawasaki disease (KD) in developing countries. This prospective study was undertaken to evaluate the cardiac abnormalities in a cohort of children with KD from a tertiary care centre in Northern India.

Methods. Twenty children with diagnoses of KD and followed-up for at least 3 months in the Pediatric Rheumatology and Immunology Clinic of the Advanced Pediatric Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh were evaluated between July 2002 to January 2006. Age of onset of disease ranged from 12 months to 10 years. The male: female ratio was 4:1. All patients had received intravenous immunoglobulin (IVIG) administration in the acute stage. Chest radiography showed no abnormalities in the 15 patients in whom it was done. Electrocardiographic abnormalities were seen in 3 patients in the form of T wave inversion in 3, ST segment changes in 2, and prolonged PR interval in 1 patient which normalized on follow-up. The mean time interval between the diagnosis of KD and first follow-up echocardiography was 7.9 ± 3.5 months (range 4.4–11.4 months), which was repeated at 1 year and 2 years follow-up in patients who had abnormal findings. When we analyzed coronary artery diameters using Japanese Ministry of Health criteria, none of our patients could qualify for a diagnosis of coronary aneurysm. However, 3 had coronary artery diameters more than +2 SD when the body surface area adjusted coronary dimensions were used.

Results. One of our patients also had increased left ventricular dimensions but also had normal ejection fraction and shortening fraction, and there were no regional wall motion abnormalities. Mitral valve was thickened in 2 patients and trivial mitral regurgitation was noticed in 1 patient. Repeat echocardiography done 1 year and 2 years later on follow-up, showed persistence of thickening of the mitral valve leaflet in one of these but there was no regurgitation. None of our patients had evidence of cardiac failure, arrhythmia or myocardial infarction. There was no mortality in this series. Thallium scans were carried out during follow-up on 14 patients in this cohort and 2 patients showed perfusion defects in anterior wall, septum and posterior wall of lateral ventricle.

Conclusions. We conclude that significant myocardial dysfunction and coronary artery changes due to KD were uncommon in our cohort. We speculate that this can be attributed to the IVIG given to the patients during the acute phase of the illness. To the best of our knowledge, this is the first study on detailed cardiac follow-up of children with KD from a developing country.

Key Words

- Kawasaki disease (India, developing country)
- Immunologic factors (immunoglobulin)
- Echocardiography (cardiac evaluation)
INTRODUCTION

Kawasaki disease (KD) is a generalized vasculitis of unknown etiology, first described by Dr. Tomisaku Kawasaki in 1967 in Japan, which affects predominantly the medium vessels and is the commonest vasculitic disorder of childhood. It is a leading cause of acquired heart disease among children in developed countries, and has now been reported from all over the world including India. Although this acute febrile illness involves multiple organ systems, the major complication is the development of coronary artery aneurysms in as many as 20–30% of patients who are not offered treatment. Some cases of coronary artery disease and myocardial infarction in young adults have been attributed to missed childhood KD. A survey of 21 survivors of childhood KD concluded that childhood KD should be included in the differential diagnosis of coronary artery disease in young adults.

The use of intravenous immunoglobulin (IVIG) during the first 10 days of the illness has been shown to significantly reduce the risk of coronary artery abnormalities. Other cardiac manifestations include conduction disturbances, mitral valve regurgitation and pericardial effusion which are usually transient.

We undertook this prospective follow-up study for the evaluation of cardiac function using echocardiography in a cohort of children with KD in Northern India. Computer assisted analysis of M-mode echocardiography has been shown to accurately assess myocardial function and two-dimensional echocardiography is sensitive for identifying proximal coronary artery aneurysms. No information is available on the follow-up of children with KD in developing countries. The present study aims to bridge this gap in the literature.

SUBJECTS AND METHODS

Patients and methods

The present study was conducted jointly in the Departments of Pediatrics, Cardiology and Nuclear Medicine of the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh from July 2002 to January 2006.

Twenty children with diagnoses of KD were followed-up for at least 3 months in the Pediatric Rheumatology and Immunology Clinic of the Advanced Pediatric Centre. The diagnosis of KD was based on standard criteria viz. Fever of at least 5 days duration; presence of four of the following principal features, changes in extremities, presence of four of the following principal features, changes in extremities, desquamation usually beginning periungually, non vesicular polymorphous exanthema, predominant truncal, bilateral conjunctival injection, erythematous, dry fissured lips, strawberry tongue, cervical lymphadenopathy; and exclusion of diseases which mimic KD such as Stevens Johnson syndrome, measles and other febrile exanthemata, scarlet fever and drug reactions.

Study design

The following investigations were carried out in the study group. Electrocardiography was recorded in all leads including long lead II, V₃₆. These were interpreted according to normative age-based standards for children. Chest radiography was performed. Echocardiography was done initially in the acute phase within 2–3 weeks of illness, and was subsequently repeated after an interval of 7.9 ± 3.5 months (range 4.4–11.4 months) from the onset. Patients with abnormal echocardiographic findings were reexamined at 1 year and 2 years of follow-up. Two-dimensional echocardiography was performed by a standard echocardiographic machine with sector scanning instruments (General Electrical), Vivid 5, phased array probe of 5 MHz, 84-degree sector angle with color flow monitoring, motion mode (M-mode), pulse wave Doppler, continuous wave Doppler, and two-dimensional octave mode with tissue harmonic imaging facility. Two-dimensional echocardiographic examination included all standard planes including parasternal long- and short-axis views, apical four-chamber view, apical long-axis view and subcostal four-chamber view. During echocardiography, a standard precordial short-axis view of the great vessels was recorded. Once the aortic and tricuspid valve leaflets were identified, slow superior angulation of the transducer was performed until the tricuspid leaflet echoes were lost and the tricuspid valve ring was recognized. This method produced the characteristic linear echoes of the right main and proximal third of the right coronary artery. The distal third of the right coronary artery was recorded from the standard four-chambered apical view and by angling the transducer either superiorly or with appropriate clockwise or counterclockwise rotation. The left main coronary artery

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was recorded from the parasternal short-axis view of the aorta. The bifurcation was visualized by moving the transducer from the standard short-axis view of the aorta and directing the transducer inferiorly and medially. Left ventricular short-axis contraction patterns were evaluated to detect asymmetric contraction at three levels: mitral leaflet, chordae, and papillary muscle. Valvular involvement (aortic regurgitation, mitral regurgitation) was examined. Doppler imaging was used to detect the direction of flow and flow disturbances.

M-mode echocardiography was done according to standard performance techniques. Parameters included left atrial and ventricular dimensions, and left ventricular function by ejection fraction and shortening fraction. Pericardial thickness was measured and we looked for evidence of pericardial fluid. M-mode echocardiograms were interpreted in accordance with normal values established in children. We judged myocardial abnormalities to be present if the ejection fraction was < 63%, shortening fraction < 27%, and ratio of left ventricular pre ejection time to left ventricular time was increased for the heart rate.

Two-dimensional echocardiography evaluated the proximal portions of the left main coronary artery, left anterior descending coronary artery, circumflex artery, and origin and course of right coronary artery according to standards published by the Japanese Ministry of Health11 on which current statistics of prevalence of coronary dilation are based. Coronary artery aneurysms were diagnosed if the internal diameter was greater than 3 mm in children younger than 5 years of age or 4 mm in children at least 5 years of age; if the internal diameter of the segment measured was 1.5 times that of adjacent segment; or if the coronary artery lumen was clearly irregular. In addition, we also calculated coronary artery dimensions adjusted for body surface area,6,14 which provide a more accurate assessment of the size of the proximal right coronary artery or left anterior descending coronary artery as compared with expected population norms. Any evidence of thrombus inside the dilated coronary arteries was assessed. Tissue Doppler imaging was used to detect ischemic myocardium.

**OBSERVATIONS AND RESULTS**

Among the 20 patients followed-up in this cohort, the age of onset of KD ranged between 12 months and 10 years (mean 5.4 ± 2.96 years). The male to female ratio was 4: 1. Laboratory investigations revealed thrombocytosis (5.0 – 7.5 × 10^4 µl) in 10 patients. Two patients who had thrombocytopenia at admission showed recovery of platelet counts following administration of IVIG. Sixteen of the 20 patients had an erythrocyte sedimentation rate of more than 20 mm in the first hour.

All 20 patients enrolled in the study had received therapy with IVIG 2 g/kg body weight in the acute phase except one patient who had received 1.5 g/kg. Eight patients received the therapy within 10 days of onset of illness, and others within 2–3 weeks after the onset of illness as they reported late to our hospital. All patients responded dramatically with resolution of fever following administration of IVIG. One patient had recurrence of fever which spontaneously subsided after 3 days. None of the cases in this cohort had required a second course of IVIG. In addition, all patients had received high dose aspirin 80–100 mg/kg in the acute phase and this was reduced to 5 mg/kg/day once the fever subsided. None of the 20 patients were clinically symptomatic at the time of inclusion in the study. Chest radiography in 15 of our patients during follow-up showed no abnormalities.

Electrocardiograms (ECGs) were judged according to age comparative standards for children (Table 1).13 The PR interval ranged from 0.12–0.2 sec (mean 0.14 ± 0.023 sec), which was normal for age related upper limits except in one patient (Case 4) who had PR interval of 0.2 sec indicating delay in conduction. T wave inversion was found in 3 patients and ST segment changes in 2 patients. None of our patients had significant Q wave or conduction abnormalities. Repeat ECG 1 year later showed normalization of previous abnormalities in all 3 patients.

Echocardiography in the acute phase, within 2–3 weeks of onset of illness, and in the convalescent phase revealed no aneurysms according to the criteria of the Japanese Ministry of Health (Table 2).11 However, when these diameters were assessed according to the body surface area,6,14 3 patients had increased coronary diameters (Cases 7 and 14 could be classified as having increased right coronary artery diameter [more than 2SD] and Cases 2 and 7 as having increased left coronary artery diameter). However, left anterior descending coronary artery diameters were normal in all patients. When we repeated the echocardiography according to the protocol, coronary artery diameters normal-
ized in one patient (Case 7). In the other 2 patients (Cases 2, 14), the coronary artery diameters remained above $+2SD$. No patient had regional wall motion abnormalities at the level of chordae, papillary muscle or mitral leaflet.

All patients underwent M-mode echocardiography according to the procedure described in methodology section (Table 2). One patient (Case 14) had increased left ventricular dimensions [left ventricular end-systolic dimension (LVES) = 28 mm, left ventricular end-diastolic dimension (LVED) = 37 mm] compared with the age related normal parameters. However, she had normal ejection fraction and shortening fraction, which are indicators of normal ventricular function. Ejection fraction ranged from 60–83% (mean 68.2 ± 6.1%) and shortening fraction ranged from 30–52% (mean 38.4 ± 5.7%). None of our patients had evidence of pericardial effusion in the acute or convalescent phase of the disease. When echocardiography was repeated, Case 14 continued to have increased LVES and LVED, though the dimensions were less than before.

The mitral valve was thickened in 2 patients, and trivial mitral regurgitation was noticed in another patient. Repeat echocardiography showed the mitral valve remained thickened in 1 patient (Case 2) but was not associated with any regurgitation, and normalized in the remaining 2 children. No other valvular involvement was seen in any of the study patients. Tissue Doppler imaging did not reveal any ischemic changes in the myocardium.

As part of the unit protocol for follow-up of patients with KD, dobutamine stress induced thallium scintigraphic cardiac scans were also done during follow-up. Of the 14 patients who underwent this investigation, 2 had perfusion defects in the anterior wall, septum and inferior wall of the left ventricle.

**DISCUSSION**

KD is a multisystem inflammatory syndrome of unknown etiology and variable clinical expression, characterized histologically by the presence of vasculitis resulting in stenosis and aneurysm of the coronary arteries. The diagnosis of KD is entirely
## Table 2  Echocardiographic findings in the convalescent phase of Kawasaki disease

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<th>BSA (m²)</th>
<th>Pericardial fluid</th>
<th>RWMA</th>
<th>Valvular abnormality</th>
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BSA = body surface area; RWMA = regional wall motion abnormalities; EF = ejection fraction; LAD = left anterior descending coronary artery; LVES(D) = left ventricular end-systolic (diastolic) dimension; Lt (Rt) MCA = left (right) main coronary artery; CX = circumflex; Echo = echocardiography; ML = mitral leaflet; L(R) CA = left (right) coronary artery; aw = anterior wall; sep = septum; iw = inferior wall; LV = left ventricle; N = normal.
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BSA = body surface area; RWMA = regional wall motion abnormalities; EF = ejection fraction; LAD = left anterior descending coronary artery; LVES(D) = left ventricular end-systolic (diastolic) dimension; Lt (Rt)MCA = left (right) main coronary artery; CX = circumflex; Echo = echocardiography; RCA = right coronary artery; MR = mitral regurgitation.
clinical and may be difficult for physicians not familiar with the disease, as there are no specific laboratory investigations to confirm it. Many of our patients with KD continue to be referred with a label of other common infectious illnesses, suggesting the lack of awareness about this condition amongst physicians in India as in other developing countries. Early diagnosis of KD is imperative to avoid the risk of acute coronary vasculitis which can occur in up to 30% of cases and which can be minimized by prompt administration of IVIG.

In our population, KD seems to affect older children, with as many as 33% of the patients above 5 years of age. Our patients also have higher percentage of rash and changes in extremities when compared to the western literature. In contrast, lymphadenopathy and conjunctivits were less commonly noted.

In this study, we found that chest radiography was not contributory in any of the 15 patients who underwent this examination. The ECG abnormalities suggestive of myocarditis were seen in 3 of 20 patients. Absence of pathologic Q waves suggested that no child had significant myocardial ischemia. There was no correlation between the ECG and echocardiogram findings. These ECG abnormalities had normalized at follow-up done 1 year later. Low incidence of these changes can be explained by the fact that all our patients had received IVIG. This is in contrast to a retrospective analysis which reported ECG abnormalities in as many as 34 of 44 patients in the first week of illness. However, none of these patients had received IVIG at that time.

A clinico-pathological study of 10 patients showed KD was correlated with pathological change in the atrioventricular node, and further reported that the abnormalities disappeared on follow-up.

In our study, echocardiography was used as a modality for cardiac evaluation which is sensitive and specific for visualizing aneurysms of proximal portions of both coronary arteries with improved technique. Sensitivity of 100% and specificity of 97% were reported for detecting coronary aneurysms in the proximal portions of both coronary arteries. When the measured coronary dimensions were compared with the Japanese Ministry of Health criteria, none of our patients had definite coronary artery abnormality (CAA). The low incidence of CAA was attributed to administration of IVIG (2 g/kg). In contrast, most older studies where the incidence of CAA was 15–40% when treatment with IVIG was not given. A meta-analysis included multicenter, randomized controlled studies performed in the United States and Japan regarding the effect of various doses of IVIG with aspirin on the prevalence of coronary artery abnormalities in KD. The prevalence of aneurysms in the subacute phase (30 days) was 25.8% without IVIG and decreased to 4.8% with therapy (2 g/kg IVIG). The corresponding prevalence in the convalescent phase (60 days) was 17.6% and 3.8%. Therefore, 2 g/kg IVIG combined with high dose aspirin provides maximum protection against coronary abnormalities in KD. These initial findings were later corroborated in several clinical trials and supported by Cochrane analysis. The potential benefits of IVIG for patients treated later than 10th day of illness are uncertain. However, a retrospective study of 16 patients with KD who received delayed treatment with IVIG (i.e., after 10 days) reported normalisation of CAA in all 7 patients compared to 4 of 7 patients not given IVIG.

Currently there is no consensus regarding the norms of coronary artery diameter in children. We used the Japanese Ministry of Health criteria as well as age related norms for defining coronary artery abnormalities. The definition of coronary artery abnormalities were revised as coronary artery dimensions have been shown to increase with indices of body size, such as body surface area or body length in normal children. In particular, coronary artery dimensions adjusted for body surface area provide a more accurate assessment of the size of the proximal right coronary artery or left anterior descending coronary artery as compared with expected population norms. A z score ≥ 2.5 (i.e., a coronary dimension that is 2.5SD above the mean for body surface area) in one of these arterial segments would be expected to occur in 0.6% of the population without KD, and a z score ≥ 3.0 in one of these segments would be expected to occur in 0.1% of the population without KD. Echocardiography in convalescent phase revealed coronary artery diameters > 2SD above normal in 3 patients (Table 2). In our study, we found that 15% of patients classified as having normal coronary arteries by the Japanese Ministry of Health criteria would have had at least one coronary artery abnormality if the body surface area adjusted coronary dimensions were used. More recently, the body surface area-adjusted coronary dimensions of some
patients with KD whose coronary arteries were considered "normal" were shown to be larger than expected in the acute, convalescent and late phases when compared with references established for body size. Because use of the Japanese Ministry of Health criteria may result in both underdiagnosis and underestimation of the true prevalence of coronary dilation, coronary vessel measurements adjusted for body surface area should be compared with those of the population without KD. None of our patients had significant myocardial involvement. Our findings are in agreement with a study of 135 patients with KD, all of whom had received IVIG. None of the patients had myocardial abnormalities. We attribute the low incidence of myocardial involvement in our patient population to the administration of IVIG during the acute phase of illness.

The incidence of valvular regurgitation differs among reports. Transient valvar disease that develops in the acute phase is usually attributed to pancarditis. However, persistent valvular disease can occur due to sequelae of valvulitis and papillary muscle dysfunction secondary to coronary stenotic lesion. The mitral valve was thickened in two of our patients, and trivial mitral regurgitation was noticed in another patient. One of these patients also had myocardial perfusion defects on thallium scintigraphy. None of them had a past history of rheumatic heart disease. No other valvular involvement was seen in any of the study patients. Valvular regurgitation in KD has also been reported by other workers. A study of 1,215 patients found that 13 patients (1.1%) had valvular disease, 12 patients with mitral regurgitation and 1 patient had aortic regurgitation.

When we repeated echocardiography in the follow-up according to the study protocol, coronary artery diameters had normalized in one patient (Case 7). In the other 2 patients (Cases 2, 14), the corresponding coronary artery diameters remained at more than 2SD. Resolution of coronary dilation is similar to that noticed in other studies. However, these children need to be followed-up for longer as such patients are known to develop intimal thickening and endothelial dysfunction.

Two-dimensional echocardiography is less sensitive for distal coronary artery aneurysms and this is not sensitive to detect coronary artery stenosis and microangiopathy. Persistent perfusion defects could represent interstitial fibrosis from myocarditis or scars from obstructive lesions due to small vessel coronary vasculitis in which echocardiography and angiography may be normal. Thus thallium scintigraphy is required for detecting myocardial perfusion and areas of ischemia.

Two of the 14 patients (Cases 5 and 8) who underwent thallium scintigraphy had impaired perfusion defects in the septum, anterior wall and inferior wall of the left ventricle. One patient (Case 8) also had thickened mitral valves with normal myocardial function and coronary arteries. Echocardiography showed no corresponding regional wall motion abnormalities of the left ventricle. The second patient (Case 5) did not have any echocardiographic abnormalities. Similar findings have been previously reported. Four of 16 children with KD had normal coronary angiography but showed persistent and/or transient perfusion defects on thallium scintigraphy which indicated a lack of correlation between these modalities. Therefore, echocardiography and angiography may not identify all KD patients at risk of future myocardial ischemia. We recommend that patients with abnormal scintigraphy should be followed-up closely even if no definite coronary lesion is found on echocardiography or angiography.

CONCLUSIONS

Our study demonstrates that high dose IVIG administered early in the course of KD is effective in reducing the prevalence of CAA and myocardial dysfunction. However, 15% of patients classified as having normal coronary arteries by the Japanese Ministry of Health criteria had at least one coronary artery abnormality if the body surface area adjusted coronary dimensions were used. Two of our patients also had perfusion defects on thallium scintigraphy. Our study suggests that children with KD need long term follow-up.

References


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