Endothelial dysfunction in a cohort of North Indian children with Kawasaki disease without overt coronary artery involvement

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Summary
Objective: Kawasaki disease (KD) is a diffuse necrotizing vasculitis with predominant involvement of coronary arteries. Endothelial dysfunction has been implicated as an important event in the pathogenesis of arteriosclerosis, coronary vasoconstriction, hypertension, and myocardial ischemia. We examined the presence of endothelial dysfunction in North Indian children (of Caucasoid ethnicity) with KD without overt coronary artery involvement.

Methods: Twenty children (mean age 8.4 ± 2.3 years; range 4.5—12.1 years) in the convalescent phase of KD were studied. All had received intravenous immunoglobulin during the acute phase of the disease. The interval between acute episode and enrolment ranged from 3 to 78 months (mean 25.3 ± 20.1 months). High-resolution ultrasonography was used to analyze brachial artery responses to reactive hyperemia (with increased flow causing endothelium-dependent dilatation) and sublingual nitroglycerine (causing endothelium-independent dilatation). Flow-mediated dilatation was also studied in an equal number of healthy age- and sex-matched controls. Carotid artery stiffness index (SI) was calculated and compared in all subjects using previously published equations.

Results: Significant differences were observed between the percent flow mediated dilatation in children with KD (5.7 ± 9.2%) compared with controls (12.2 ± 8.9%, p = 0.017). Sublingual nitroglycerine-mediated dilatation in children with KD was 28.5 ± 12.3%. Carotid artery SI was higher in children with KD (2.81 ± 0.77 U) when compared to controls (2.32 ± 0.80 U), but it failed to meet statistical significance (p = 0.058).
Introduction

Kawasaki disease (KD) is a diffuse necrotizing vasculitis with predominant involvement of coronary arteries. While some children with KD develop large aneurysms, others may have more subtle changes. There has been considerable research interest in diagnostic assays for the assessment of endothelial dysfunction and pre-clinical detection of arteriosclerosis in children with KD [1—3]. Besides pathogenesis of arteriosclerosis, endothelial dysfunction has also been implicated as an important event in coronary vasoconstriction, hypertension, and myocardial ischemia [4]. It has been postulated that KD may predispose to early arteriosclerosis and this is a topic of ongoing study [5—8]. There have also been reports of deranged lipid profiles in patients with KD [9,10].

Most of the published studies pertain to endothelial function in children with echocardiographic evidence of coronary artery abnormalities (CAA). However as KD is being increasingly recognized early and promptly managed with Intravenous immunoglobulin (IVIG) therapy, overt CAA are becoming less common [9,11]. In our own institute, CAA were detected in only 5 of the 69 patients diagnosed during the period 1994—2004 [12,13]. The results of similar studies in children without obvious coronary artery involvement have been conflicting. Also, to the best of our knowledge, there has been no similar study in children with KD from a developing country [5,6].

Diminished flow-mediated dilatation (FMD) and increased carotid artery stiffness index (SI) have been used as surrogate markers of premature arteriosclerosis. Both of these indices have been shown to correlate with late cardiovascular events and/or mortality in adults [4]. Because of their non-invasive nature these parameters have recently been studied in children as well [3].

There is paucity of data on KD from developing countries. The clinical presentation of KD reported from India appears to be somewhat different from that in the west [14—16]. We have previously reported that more than one-third of children with KD in our cohort were above 5 years of age [16]. Further, the periungual desquamation (so characteristic of KD) appears to occur earlier in Indian children compared to their counterparts in the west [15,16]. Whether these differences are limited only to the clinical presentation of KD or are also applicable to the complications of the disease is open to question. The present study is an attempt to answer some of these questions while adding Indian data pertaining to endothelial function post KD.

Patients and methods

Study population

The study was carried out jointly in the Departments of Pediatrics and Cardiology of the Postgraduate Institute of Medical Education and Research (PGIMER) during the period July 2005 to June 2006. Our institute serves as a tertiary care teaching and referral hospital for North West India. Twenty North Indian children (of Caucasoid ethnicity) diagnosed to have KD at least 3 months earlier were randomly selected from the Pediatric Rheumatology Clinic. An equal number of age- and sex-matched controls were also enrolled. Parents of controls were asked for any history suggestive of KD, heart disease, smoking, and abnormal lipid profile. The controls lived in the same geographical area and were of the same ethnicity as the cases. The same cohort was also studied for the presence of QT interval dispersion and data related to that are being published elsewhere.

Data were obtained by direct questioning and review of the records maintained in the unit and included the date of birth, date of diagnosis, clinical features leading to diagnosis, therapy received, duration between the onset of fever and administration of IVIG, and other therapy received, if any. The study protocol was approved by the Institutional Ethics Committee.

All cases had fulfilled the American Heart Association guidelines for diagnosis of KD and had received IVIG in doses of 2 g/kg in a single infusion as the primary therapy for KD. In addition, aspirin was given in a dose of 75—80 mg/kg/day for the first 3—5 days followed by a lower antiplatelet dose (3—5 mg/kg/day) for the next 4—6 weeks. None of our patients had received dipyridamole. The duration between the acute episode and enrolment in the study ranged from 3 to 78 months (mean
25.3 ± 20.1 months; median 21 months). The mean duration between onset of fever and receipt of IVIG was 11.4 ± 5.3 days (median 11 days). Standard echocardiography criteria were used for the purposes of this study [13].

High resolution ultrasound and Doppler study of brachial and carotid artery imaging was carried out by a single observer (RMK) for all 40 subjects. The operator has vast experience in performing echocardiographic and Doppler examinations in children. Nitroglycerine-mediated dilatation was not studied in the controls because of ethical considerations and for this reason the sonographer could not be blinded. Similar methods have been used earlier in previous studies on the subject [1—3].

B-mode ultrasound images of brachial arteries in longitudinal section were obtained 2–3 cm above the right elbow for all the 40 subjects using ultrasound system for 2D imaging fitted with an internal ECG and a vascular transducer operated at 10 MHz (Vivid Five, GE Vingmed Ultrasound, Horten, Norway). The depth and gain settings were set to optimize the images of lumen-intimal interface. When a satisfactory transducer position was found, the skin was marked and the arm was kept in the same position throughout the study. The machine-operating parameters were not altered during the study. The study was conducted in supine position at controlled room temperature of 20–25 °C.

A baseline scan was obtained after 10 min of rest. The brachial artery was imaged in the longitudinal axis and diameter was measured from one intimal surface to the other in three cardiac cycles incident with the R wave on ECG and the average of the three was used for analysis. A pneumatic tourniquet was then applied proximal to the arterial segment imaged and inflated 50 mmHg above systolic blood pressure for five minutes. The cuff was then deflated rapidly. A second scan was recorded from 30 to 90 s after cuff deflation. Mean diameter of the vessel was calculated at rest and during reactive hyperemia (45–60 s after cuff deflation) from three cardiac cycles incident with the R wave on ECG and the average of the three was used for analysis. Dilatation was expressed as percentage of baseline [(diameter after cuff deflation – baseline diameter)/baseline diameter] × 100.

A 10-min rest was provided after this scan for vessel recovery and one sublingual nitroglycerine puff (400 microgram per puff) was administered. A second scan was then recorded after 3–4 min and brachial artery diameter was measured as in the resting scan. The dilatation was expressed as percentage of baseline similar to FMD.

A single observer (JSG) measured systolic (SBP) and diastolic (DBP) blood pressure three times at intervals of 3 min. Average of the 3 records was used for analysis. B-mode ultrasound images of carotid artery were obtained with the subject in supine position with head turned slightly to the left. Images were obtained in longitudinal sections 1–2 cm proximal to carotid bulb. Carotid artery diameter was measured during systole (D_s) and diastole (D_d). The diastolic diameter (D_d) was measured coincident with the R wave on the electrocardiogram. Carotid artery wall SI was calculated as SI = ln (SBP/DBP) × (D_s/ΔD) where D = (D_s + D_d)/2 and ΔD = D_s − D_d.

Data analysis

Conventional distance statistics were employed for calculating the mean and standard deviation for each of the parameters included in the study. Data were expressed as mean ± standard deviation. Statistical analysis for differences in mean value was performed using Student t-test and a p value < 0.05 was considered to be significant. For comparison of two groups of non-parametric variables, the Mann–Whitney U test was used. Spearman’s correlation analysis was used to assess for a possible relation between endothelial dysfunction and the time since the acute illness as well as duration between onset of symptoms and IVIG administration. Statistical Package for the Social Sciences version 13 with default settings (SPSS Inc., Chicago, IL, USA) was used for analyses.

Results

Baseline characteristics of participants are presented in Table 1. There were no statistically significant differences between any of the baseline parameters amongst cases and controls. None of the subjects had history of smoking, hyperlipidemia, congenital heart disease, arrhythmias, hypertension, obesity, or diabetes mellitus.

Two patients had mild stress-induced reversible perfusion defect on thallium scintiscanning of the myocardium which normalized on follow up. The coronary arteries in these patients were, however, found to be normal on echocardiography and they had received IVIG on days 15 and 11 of fever, respectively. Another patient had ectasia of left main coronary during the acute phase which normalized on follow up. He had received IVIG on day 7 of fever. The remaining 17 cases had no evidence of involvement of coronary arteries.
Table 1  Baseline characteristics of study participants.

<table>
<thead>
<tr>
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<th>Cases (n = 20)</th>
<th>Controls (n = 20)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>8.4 ± 2.3</td>
<td>8.6 ± 2.6</td>
<td>0.802</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>65</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>92.3 ± 5</td>
<td>90.3 ± 5.2</td>
<td>0.221</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>66.2 ± 4.3</td>
<td>68.1 ± 3.9</td>
<td>0.147</td>
</tr>
<tr>
<td>Heart rate</td>
<td>91.8 ± 24.6</td>
<td>104.6 ± 22.8</td>
<td>0.096</td>
</tr>
<tr>
<td>Months since diagnosis</td>
<td>25.3 ± 20.13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Onset of fever-IVIG (days)</td>
<td>11.4 ± 5.29</td>
<td>—</td>
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</table>

Significant differences were observed between the percent FMD (% FMD) in children with KD (5.7 ± 9.2%) compared with controls (12.2 ± 8.9%, p = 0.017). Sublingual nitroglycerine administration mediated dilatation (%NTG) in children with KD was 28.5 ± 12.3%. Carotid artery SI was higher in children with KD (2.81 ± 0.77 U) when compared to controls (2.32 ± 0.80 U), but it failed to meet statistical significance (p = 0.058).

There was no correlation between delay in IVIG therapy or time since diagnosis and either of the carotid artery or brachial artery parameters. Details of endothelial function assessment are presented in Table 2.

Discussion

KD is a medium vessel vasculitis with predominant involvement of coronary arteries. Up to 15–20% of untreated children develop coronary artery abnormalities detectable on echocardiography. It stands to reason that a child who has CAA is likely to have a more severe disease and possible subclinical involvement of arteries other than the coronaries. Histopathology of coronary arteries in KD has revealed fibrosis in coronary artery walls, even in absence of visible dilation or stenosis [17]. The less distensible carotid artery wall in patients with KD is likely to be the result of a diffuse vasculitis involving noncoronary arteries [8].

Some of the published studies have detected endothelial dysfunction in children with KD and CAA. However finding children with aneurysms secondary to KD is now becoming less common as the condition is being diagnosed early and treated more readily the world over. Our study differs significantly from the many published earlier in that we have found evidence of endothelial dysfunction even in children without overt CAA [5,7,8]. We cannot explain these findings, but younger study age group and a different genetic background in the present study may partly account for some of these differences.

It may be noted that an association between coronary and carotid artery arteriosclerosis has previously been suggested [18,19]. Noto et al. and Cheung et al. have studied carotid artery stiffness as a predictor of coronary involvement in KD [5,8]. In our study the carotid artery SI was higher in children with KD when compared to controls, but it failed to meet statistical significance. However, more studies of a similar type may be needed before a definite inference can be drawn.

Brachial artery endothelial dysfunction has been assessed by non invasive means in patients with KD earlier by Dhillon et al. [7]. They concluded that FMD is impaired late after KD. They studied 20 patients of whom only 3 had received IVIG therapy. Mean % FMD in the patient group in their study was 3.1 (standard deviation 3.5) as compared to 5.7 (standard deviation 9.2) in our study. The fact that all our patients had received IVIG may explain some of these differences. It is also pertinent to note that the median age of our patients was 8.8 years as compared to a median of 13 years in the study by Dhillon et al. [7]. Further, there were methodological differences with regard to application of tourniquet in the two studies. While the tourniquet

Table 2  Comparison of endothelial function parameters of cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 20)</th>
<th>Controls (n = 20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness index (U)</td>
<td>2.81 ± 0.76</td>
<td>2.33 ± 0.80</td>
<td>0.058</td>
</tr>
<tr>
<td>% FMD</td>
<td>5.7 ± 9.19</td>
<td>12.23 ± 8.93</td>
<td>0.017</td>
</tr>
<tr>
<td>% NTG</td>
<td>28.46 ± 12.27</td>
<td>Not studied</td>
<td>—</td>
</tr>
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FMD, flow-mediated dilatation; NTG, nitroglycerine-mediated dilatation.
was applied distal to the segment being imaged by Dhillon et al., we had occluded the arterial segment proximal to the probe. The latter method arguably leads to more dilatation than the former [20]. We had not studied nitroglycerine-mediated dilatation in the control group because of ethical considerations. However, the mean percent dilatation after sublingual nitroglycerine administration was 28.5 ± 12.3 in our study which is comparable with 23 ± 9.5 in the study by Dhillon et al. [7].

Although the first study of this kind was done more than a decade ago, it is only in the past couple of years that interest in this area has revived and a number of similar looking studies have appeared in the literature. However, most of the earlier literature pertained to children with KD having CAA. In 2005, Ikemoto et al. showed that there is endothelial dysfunction after KD and that it correlates with severity of coronary involvement [21]. In a study of adults who had KD as children, Niboshi et al. concluded that percent FMD was significantly reduced in the KD group when compared with that of the control group. This was especially so in patients with coronary artery lesions [22].

Deng et al. [23] and Dalla Pozza et al. [24] have reported on a small number of children with KD, but without CAA. They reported endothelial dysfunction in such children even when there was no obvious coronary artery involvement. Our study adds weight to these findings and suggests that occurrence of KD in a given child may have lifelong consequences even when there is no discernible coronary artery involvement. The issue, however, is rather contentious because some workers [25,26] have reported virtually normal endothelial function in children with KD. We do not have an explanation for these differences, but it is possible that a completely different genetic background may explain some of the variations. It may be noted that although the North Indian population is of Caucasoid ethnicity, many anthropologists consider it to be genetically distinct. Further, methodological differences in ultrasound assessment may also account for some of the observed differences.

The present study is the first of its type from a developing country. Our results suggest that children with KD may have long-term sequelae even when there is no overt coronary artery involvement in the acute stage of the disease. Affected children should, therefore, be kept on long-term follow-up. The advent of multi-slice computed tomography may further facilitate the prognosis of such patients [27].

References


