Functional and Structural Intermediate Vascular Phenotypes and Biomarkers Related to Long-Term Cardiovascular Risk in Kawasaki Disease

Katherine Chen[1], Nagib Dahdah[6,7] Roch Maurice [7], Jessica Miller[1], Nigel Curtis[1, 3, 4], Michael Cheung[1, 2, 3], David Burgner[1, 3, 5]

[1]Murdoch Childrens Research Institute, [2]Department of Cardiology, [3]Department of Paediatrics, The University of Melbourne and [4]Infectious Disease Unit, Department of General Medicine, The Royal Children's Hospital Melbourne, Parkville, Victoria [5]Department of Paediatrics, Monash University, Melbourne, Victoria, Australia,[6]Division of Pediatric Cardiology, [7]CHU Ste-Justine Research Centre, University of Montreal, Qc, Canada

Introduction

Kawasaki disease (KD), an acute vasculitis of unknown aetiology, is the commonest cause of acquired heart disease in children in industrialised countries.[1] Predictive modeling suggests that there will be an increasing population of adults who have significant coronary artery disease following KD.

Whether KD increases later cardiovascular risk, even in those with no identified coronary artery (CA) changes or with regressed CA lesions, is an important clinical issue.

There have been numerous studies addressing the vascular sequelae of KD, mostly using intermediate phenotypes extrapolated from studies of atherosclerotic cardiovascular risk.[2] The results to date, especially in KD patients with no CA changes or regressed aneurysms, are conflicting. Here we report an interim analysis of cardiovascular intermediate phenotypes following KD.

Methods

Patients at least 2 years post-KD and healthy controls had blood pressure, anthropometric measurements, carotid-femoral pulse wave velocity (PWV), carotid intima-media thickness (cIMT), abdominal aorta intima-media thickness (aIMT), retinal vascular calibre, carotid and aortic elastography (analysis ongoing) performed using standardised methods during one study visit. Plasma glucose, lipid profile, and high sensitivity C-reactive protein (hsCRP) were performed on a fasting blood sample. Data analysis using standard linear regression was performed in Stata 13.0 (Stata Corp, College Station, TX). High sensitivity C-reactive protein was log transformed.

Melbourne Children's
Excellence in clinical care, research and education

Results

To date, 48 patients with KD and 54 controls have been studied. (Table 1)

	Number	Age (years) Mean +/- SD	Male: Female	Time since KD (years) Mean +/- SD
Controls	54	15.49 +/- 6.54	23:31	-
KD always normal CA	24	14.02 +/- 5.13	12:12	9.91 +/-5.31
KD with history of CA abnormality	24 (10 persistent)	17.18 +/- 5.35	15:9	12.85 +/- 6.12

Table 1: Participant characteristics

Compared to controls, KD patients did not differ in traditional cardiovascular risk factors; blood pressure, body mass index, waist-to-hip ratio, glucose, cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, and smoking history. The mean PWV in KD patients overall (4.69 +/- 0.68 m/sec) was slower compared to controls (4.80 +/- 0.92 m/sec), especially in those with a history of CA abnormality (4.66 +/- 0.63 m/sec).

45 KD patients (age 15.32 +/- 7.40 years) and 36 controls (age 16.94 +/- 7.30 years) have had cIMT and aIMT analysed.(Table 2) The mean aIMT in KD patients (0.53 +/- 0.12mm) was greater than controls (0.51 +/- 0.095mm), with the most marked difference in those KD patients with a history of CA abnormality (0.56 +/- 0.11mm). After adjusting for age (the only significant confounder), the mean aIMT in KD patients with a history of CA abnormality was **0.054mm (95% CI 0.001, 0.11 p=0.046) larger** than controls. There were no detectible differences to date in cIMT and retinal vascular calibre between KD patients and controls. Carotid IMT and aIMT were poorly correlated in KD patients (r=0.13) and controls (r=0.15).

	KD normal CA Adjusted*difference (95% CI)	KD with history of CA abnormality Adjusted* difference (95% CI)
Pulse wave velocity (m/sec)	-0.071 (-0.44, 0.30) p=0.7	-0.44 (-0.81, -0.06) p=0.023
Mean cIMT(mm)	0.0092 (-0.024, 0.042) p=0.6	0.0091 (-0.026, 0.044) p=0.6
Mean aIMT (mm)	0.018 (-0.040, 0.077) p=0.5	0.058 (-0.002, 0.12) p=0.060
Mean aIMT (mm) *adjusted for age only*	0.016 (-0.033, 0.066) p=0.5	0.054 (0.0010, 0.11) p=0.046
Retinal arteriolar equivalent (mm)	9.31 (-0.77, 19.38) p=0.069	1.63 (-7.84, 11.10) p=0.7
Retinal venular equivalent (mm)	7.86 (-8.34, 24.05) p=0.3	6.81 (-7.90, 21.52) p=0.4
Arteriole to venule ratio (AVR)	0.032 (-0.0084, 0.072) p=0.1	0.0014 (-0.037, 0.039) p=0.9

Table 2: Differences in structural and functional vascular phenotypes between KD patients and controls

**Pulse wave velocity was adjusted for age, sex, systolic blood pressure, body mass index, log hsCRP, LDL and HDL cholesterol*
** cIMT and aIMT measurements were adjusted for the minimum diastolic diameter of respective vessels, age, sex, systolic blood pressure, log hsCRP, LDL and HDL cholesterol.*
**Retinal vascular calibre was adjusted for age, sex, height, systolic blood pressure, LDL and HDL cholesterol.*

Patients with a history of CA abnormality had a non-significant trend towards higher hsCRP compared to controls with a geometric mean increased of 1.73 mg/L (95% CI 0.91, 3.32, p=0.096).

Discussion

In this interim analysis of a larger study, traditional cardiovascular risk factors were similar between KD patients and controls. Intermediate cardiovascular phenotyping showed a potentially adverse change in the structure of the abdominal aortic wall in KD patients with CA abnormalities. However, these patients had a more favourable marker of arterial stiffness. There was a non-significant trend towards increased markers of inflammation in KD patients with CA abnormality who were more than 5 years since the acute KD illness.

Conclusions

Compared to carotid artery characteristics, changes in the abdominal aorta may be a more discriminating marker of long-term cardiovascular risk in KD. Longitudinal studies are warranted.

Acknowledgements:
Participating families
Meg Kaegi
Greta Goldsmith
Jane Koleff
Diana Zannino
Kawasaki Disease Foundation, Australia
Funding support from the National Heart Foundation, Australia and National Health and Medical Research Council

Contact details:
Dr. Katherine Chen
Email: Katherine.Chen@mcri.edu.au

REFERENCES

1. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. Journal of Epidemiology 2012; 22(2): 79-85.
2. Cheung YF. Vascular health late after Kawasaki disease: implications for accelerated atherosclerosis. Korean Journal of Pediatrics 2014; 57(11): 472-8.

FOR MORE INFORMATION ON THESE AND OTHER STUDIES PLEASE VISIT **WWW.MCRI.EDU.AU**