Fatal Kawasaki disease caused by early occlusive coronary artery disease

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In Kawasaki disease severe coronary artery narrowing may develop at an early stage despite treatment with gammaglobulin and in the absence of prominent aneurysm formation or thrombosis. Vaso-occlusive disease may not be clinically or echocardiographically apparent until very severe.

Two children with Kawasaki disease (KD) died from severe fibrocellular proliferation of the coronary arteries causing fatal myocardial infarction within four months of presentation. They received intravenous gammaglobulin (IVIG) on days 8 and 10 from the onset of illness and in neither was prominent aneurysmal dilatation or intramural thrombus present.

**CASE 1**
A previously well 6 month old white boy developed fever, abdominal distension, vomiting, rash, irritability, redness of lips, and cervical lymphadenopathy. KD was diagnosed and treated with 2 g/kg of IVIG and aspirin 80 mg/kg/day on day 8. Echocardiograms on admission and day 10 showed no coronary artery dilatation.

On day 20 further IVIG 2 g/kg was given because of continued irritability. Hb remained approximately 80 g/l; platelets peaked at 2316×10⁹/l (day 16) falling only to 964×10⁹/l (day 46) when aspirin was reduced to 5 mg/kg/day. C reactive protein (CRP) peak was 84 mg/l (day 12) declining to 28 mg/l (day 46). Echocardiogram on day 50 showed mild left coronary artery dilatation to 3 mm diameter and normal right coronary artery.

On day 95 he was readmitted with cardiac failure and shock. Biochemical, ECG, and echocardiographic features indicated myocardial infarction. He deteriorated rapidly and arrangements were made for transport to the national paediatric cardiac centre, but he died before transfer.

Postmortem findings showed pallor of the endocardium of the left ventricular free wall and interventricular septum. There was prominent segmental mural thickening and luminal stenosis affecting all three main coronary arteries and branches, with a mild degree of aneurysmal dilatation of proximal left anterior descending (LAD) and right coronary arteries. Further small local aneurysmal dilatations, 2–3 mm luminal diameter, were found in the right coronary artery 10 and 20 mm from the ostium and on a side branch at 15 mm.

Histological examination revealed extensive patchy acute subendocardial myocardial infarction. Multiple epicardial coronary artery branches showed circumferential mural fibrosis replacing both intima and media, often with notable luminal stenosis. The mural fibrous tissue contained patchy, generally mild, chronic inflammatory cell infiltrate, and the latter was also present in surrounding congested epicardial tissue (fig 1). No luminal thrombi were seen.

**CASE 2**
A previously healthy 4 year old white boy presented with three days of fever, lethargy, and irritability. He had bright red cheeks and lips, truncal rash, bilateral conjunctivitis, and perungual desquamation. Hb was 105 g/l, WBC 24.4×10⁹/l, and erythrocyte sedimentation rate 42 mm/h. On day 10 of his current illness KD was diagnosed and treated with 2 g/kg IVIG and high dose aspirin. Echocardiography showed diffuse dilatation of the left and right coronary arteries to 4 mm and 5 mm diameter respectively and a possible left ventricular regional wall abnormality. Two days later he received another 2 g/kg dose of IVIG for persistent fever and was discharged the next day, afebrile.

Over the next 10 weeks he remained unwell with haemolytic anaemia, arthritis, abdominal pain, and intermittent fever. Repeated echocardiography showed 4–5.5 mm diameter coronary arteries. He developed unstable angina with ST elevation on ECG and was admitted to the national paediatric cardiology centre.

Echocardiography showed significantly impaired left ventricular function. The left main coronary artery and proximal LAD remained uniformly 4 mm and there appeared to be a giant aneurysm 8 mm in diameter just proximal to the first septal branch. The circumflex was possibly occluded but no thrombi were seen. A heparin infusion was started and 16 hours later, when considered to be more haemodynamically stable, he was taken for catheterisation. After induction of general anaesthesia he became pulseless with complete heart block, and died despite intensive resuscitation efforts.

**Abbreviations:** CRP, C reactive protein; IVIG, intravenous gammaglobulin; KD, Kawasaki disease; LAD, left anterior descending.
There is no reliable way of identifying children at risk of developing aggressive vaso-occlusive disease beyond speculating that they may share risk factors for more severe cardiac disease in general and aneurysm formation in particular. These are: young or relatively old age of onset, delayed diagnosis and treatment, and more laboratory evidence of increased inflammatory markers at diagnosis or after treatment.

Some authorities advocate that all children with KD receive coronary angiography at the eighth week following diagnosis; our cases support such an approach. However, the procedure is not without risk and there is no evidence that such an approach alters long term management or outcome.

KD remains a clinical diagnosis without specific markers predictive of coronary vascular outcome. In most instances early administration of IVIG will prevent serious cardiovascular sequelae. When abnormalities develop they can usually be adequately diagnosed and followed by echocardiography. Clearly there exists a small group of children with KD who, despite conventional therapy and normal or unremarkable echocardiographic appearances, have progressive coronary arteritis. This may cause very severe luminal stenosis which does not become clinically apparent until overt ischaemia or infarction results. The challenge remains to identify those children at risk, and to develop effective therapy to arrest or reverse coronary artery narrowing.

ACKNOWLEDGEMENTS

We thank Drs Bruce Smith, Taranaki Base Hospital, New Plymouth; Simon Stables, Auckland Hospital; and Louise Calder, Green Lane Hospital Auckland, for the pathology reports and illustrations, and also for providing valuable clinical discussion of the cases.

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Arch Dis Child 2002 87: 145-146
doi: 10.1136/adc.87.2.145

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