

Kawasaki disease in childhood

Dr Emily Kiernan, MB BCH, Department of Paediatric Cardiology and Dr Colin J McMahon, MB MRCPI MRCP (UK) FAAP, Consultant Paediatric Cardiologist, Our Lady's Hospital for Sick Children, Crumlin.

Introduction

Kawasaki disease is an acute, self-limited systemic vasculitis of childhood first described in the Japanese paediatric population in 1967 by Dr Tomisaku Kawasaki.¹ It was originally called mucocutaneous lymph node syndrome, but was soon given the title Kawasaki disease.

The disease is known to occur worldwide and cases are reported in children of all races. Studies in Japan, North America and Western Europe have shown that Kawasaki disease has surpassed acute rheumatic fever as the leading cause of acquired heart disease in childhood.^{2,3}

Typical features of Kawasaki disease include fever, bilateral non-exudative conjunctivitis, extremity changes and ultimate periungual desquamation, oropharyngeal erythema, polymorphous rash and non-suppurative cervical lymphadenopathy. The most serious complication of Kawasaki disease is the development of coronary artery aneurysms, ectasia and coronary artery dilatation, which have prevalence in untreated patients of 15-25%.⁴

Subsequent myocardial ischaemia secondary to thrombotic or stenotic occlusion of these aneurysms is the leading cause of death due to Kawasaki disease. The priority in trying to prevent morbidity and mortality from Kawasaki disease lies in the early diagnosis and initiation of specific treatment, the early diagnosis of coronary artery involvement and adequate long-term follow-up after the resolution of the acute illness. This article aims to inform the reader of the diagnostic criteria, natural history, treatment and outcomes of children with Kawasaki disease.

Epidemiology

Since it was first described in 1967, Kawasaki disease has been most prevalent in Japan and in infants and children of Japanese origin. In the United States in 2000, there were an estimated 4,248 hospital admissions due to Kawasaki disease.⁵ World wide, the annual incidence reported varies significantly from 3.4 to 100/100,000.⁶ Japanese immigrant children have higher rates compared to the native population of the new country, supporting the idea of a genetic involvement.⁷

In Western Europe and the United States, Kawasaki Disease

is more common in the winter and early spring months. The diagnosis is more common in boys than girls by 1.5-1.7:1.5. At time of diagnosis, 76% of children are less than five years old, with a peak incidence at 9-11 months.^{5,6,8} Children younger than six months of age at time of diagnosis are more likely to have incomplete presentation, late diagnosis and therefore late treatment, coronary involvement and a relatively poorer outcome.

Aetiology

The exact aetiology of Kawasaki disease remains unknown, however, the clinical and epidemiological features all direct us towards an infectious cause, possibly related to a bacterial superantigenic toxin. Ongoing attempts to identify a causative infectious agent in Kawasaki disease have, however, failed with conventional bacterial and viral cultures and serological methods.

The lower incidence in the first few months of life suggests an agent from which infants are protected by passive maternal antibodies.⁴ The increased disease prevalence in Asian children suggests a possible genetic influence in certain individuals. This is supported by reports of siblings of index cases in Japan having an increased incidence of up to 9%.⁹ Another possible theory is that Kawasaki disease results from an immunologic response triggered by specific microbial agents.⁴

Pathology

Even though coronary artery involvement and aneurysm formation is the most important and serious pathological feature of Kawasaki disease, one must remember that it is by definition a generalised systemic vasculitis, affecting blood vessels throughout the body. Aneurysm formation is reported in femoral, iliac, renal, axillary, brachial, celiac and mesenteric arteries. During the first 10 days after the onset of fever, a multisystem vasculitis develops, which has the greatest significance on the coronary arteries. Other pathological findings include hydrops of the gallbladder and severe lymphadenitis with necrosis.

Diagnosis

Most centres worldwide use specific guidelines of clinical criteria for diagnosing Kawasaki disease. Laboratory investigations, along

with other diagnostic tools such as echocardiography, are helpful in confirming the clinical diagnosis and guiding treatment and follow-up. It is important to remember that, although relatively uncommon, children less than six months who have Kawasaki disease tend to present with atypical or incomplete symptoms and signs and, therefore, the following diagnostic criteria do not apply to them.

The diagnosis of Kawasaki disease is based on the presence of five or more days of fever (typically spiking up to 40°C/104°F) and four or more of the five following principal clinical features:⁴

- Extremity changes
Acute: erythema of palms and soles, oedema of hands and feet
Subacute: periungual peeling of skin on the fingers and toes. (typically weeks two and three)
- Polymorphous exanthema; usually appears within five days of onset of fever
- Cervical lymphadenopathy, usually unilateral and >1.5cm diameter
- Bilateral, non-exudative, conjunctivitis
- Changes to peri-oral region and oral cavity; erythema, lips cracking, strawberry tongue, diffuse infection of oral and pharyngeal mucosa.

The typical clinical diagnostic features may occur at different stages of the disease and all may not be present at any one time. Also, it is good practice to keep Kawasaki disease in mind in the differential diagnosis for any child with a fever for five or more days associated with any of the above five diagnostic criteria. This is of particular importance when dealing with children less than six months old and in adolescents who regularly have an atypical presentation, the diagnosis often being missed.

A diagnosis of Kawasaki disease can be made in any patient with a typical fever for five or more days and four or more of the principal features, once coronary artery disease has been revealed on echocardiography or coronary angiography. If four or more of the above principal criteria are present by day four, the diagnosis of Kawasaki disease may be made and appropriate treatment commenced.

The classical fever associated with the disease is high, spiking frequently above 40°C/104°F. If not treated, the fever may last for a mean of 11 days, but has been known to remain for up to four weeks. Appropriate treatment has a good effect on reducing the fever associated with Kawasaki disease.

Extremity changes are typical and distinctive. Initial erythema of the palms and soles and oedema of the hands and feet is followed later in the disease course by desquamation, usually starting in the periungual region and spreading to the palms and soles. Deep transverse grooves across the nails (Beau's lines) have been described as appearing one to two months after the onset of the fever.

The polymorphous rash associated with the disease is very

non-specific and can take on various forms. The most common appearance is a diffuse maculopapular eruption, but it may take on various different forms, including an erythema-multiforme-like appearance or a micropustular eruption. However, bullous and vesicular eruptions have not been reported. The rash is usually widespread, affecting the trunk and limbs with accentuation in the perineal region, where early desquamation has been described.

Eye involvement is bilateral and usually begins shortly after the onset of fever at the start of the illness. It typically gives a non-exudative conjunctivitis confined to the bulbar conjunctiva. This is not associated with conjunctival oedema or corneal ulceration and is usually painless.

Changes of the lips and oral cavity are very varied, but are not associated with oral ulceration or pharyngeal exudates. They include erythema and dryness leading to subsequent fissuring, peeling, cracking and bleeding of the lips. It is also associated with a 'strawberry tongue' not unlike that seen in streptococcal scarlet fever.

Cervical lymphadenopathy is usually unilateral, confined to the anterior cervical triangle and the criteria includes one or more lymph node that is >1.5cm in diameter. The lymph nodes are typically firm, non-fluctuant and with minimal tenderness.

Other non-cardiac findings may be observed in children with Kawasaki disease. The musculoskeletal system can be involved, giving arthritis and arthralgia, involving multiple small and large joints. Approximately one-third of patients experience gastrointestinal symptoms, including diarrhoea, vomiting and abdominal pain.⁴ Rarely, Kawasaki disease can present as an acute surgical abdomen.¹⁰ Hepatic enlargement and jaundice can occur during the acute disease. Gallbladder hydrops occurs in approximately 15% of patients, typically in the first two weeks of the illness.¹¹

Central nervous system involvement includes extreme irritability compared to children with other febrile illnesses and aseptic meningitis. Transient high-frequency sensorineural hearing loss can occur during the acute illness, but persistent sensorineural hearing loss is rare.¹² Genito-urinary system symptoms include urethritis and scrotal swelling in males, and an early desquamating rash in the groin area.

Laboratory findings in acute Kawasaki disease

The characteristic laboratory finding is an elevation of acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These usually return to normal by six to 10 weeks after the onset of the illness.

In the later stages of the illness, thrombocytosis is typical, with platelet count often >500,000/mm with a mean peak platelet count of 700,000/mm. Platelets rarely rise before week two of the illness. Thrombocytopenia is seen rarely in the acute phase and may be a sign of disseminated intravascular coagulation. A low platelet count at illness presentation is a

risk factor for coronary aneurysms.

As the disease progresses, a normochromic, normocytic anaemia is often seen. At present, there is only conflicting evidence on the value of measuring serum cardiac troponin I, a marker specific to myocardial damage, to predict myocardial cell injury in acute Kawasaki disease.^{13,14} Urinalysis shows intermittent mild-to-moderate sterile pyuria in approximately 33% of patients and, if lumbar puncture is carried out, approximately 50% show evidence of aseptic meningitis.¹⁵

Cardiac findings and diagnosis

Cardiac involvement can be present in the acute phase of Kawasaki disease, highlighting the importance of accurate early diagnosis and appropriate treatment to try and prevent long-term cardiac morbidity and mortality. In the acute phase, the pericardium, myocardium and endocardium valves, as well as the coronary arteries, may be involved. It is important that a thorough examination of the cardiovascular system is performed on a child showing possible features of Kawasaki disease, in particular looking out for signs of cardiac failure secondary to depressed myocardial contractility or clinical evidence of pericardial effusion.

In the majority of cases of Kawasaki disease, there is a typical pancarditis, involving the AV conduction system (which can produce AV block), myocardium (causing myocardial dysfunction), pericardium (pericardial effusion) and endocardium (associated with AV valve involvement). Coronary artery aneurysms typically develop during day 10 to day 40 of the illness. Late changes after 40 days consist of healing and fibrosis in the coronary arteries, with thrombus formation and stenosis in the post-aneurysmal segment. Myocardial fibrosis may be seen as a result of small areas of old myocardial infarction.¹⁶

Coronary artery aneurysm formation is the most serious complication of Kawasaki disease, being reported in 15-25% of untreated cases and up to 4% of treated patients. They can occur in any of the coronary arteries, but are described most often in the following decreasing order, left main, left anterior descending, left circumflex, right and posterior coronary arteries.

Aneurysms are described as taking one of two forms, saccular if the lateral and axial diameters are approximately equal and fusiform if symmetrical vessel dilatation is seen with proximal and distal tapering. Guidelines published by the American Heart Association in 1994 classify aneurysms into the following three groups; small if <5mm internal diameter, medium if 5-8mm internal diameter and large if >8mm internal diameter.¹⁷

Due to its relatively easy accessibility and non-invasive nature, 2-D echocardiography is the ideal initial and subsequent follow-up imaging modality for assessing cardiac involvement. Once diagnosis is made, or strongly suspected, a detailed echocardiogram should be carried out by an experienced operator.

This initial study is important for establishing the baseline extent of cardiac involvement to which future images can be compared to assess the effect of treatment and also deterioration in cardiac function in subsequent years after the acute illness. For this reason, it is important that images are carefully stored for future review.

Extensive imaging with the transducer in multiple different planes should be carried out to ensure that all the major coronary artery distributions are visualised. As well as thorough examination of the coronary arteries, the initial echocardiogram should determine baseline left ventricular function, left ventricular end-diastolic and end-systolic volumes, and ejection fraction; examination for signs of myocarditis and pericardial effusion is also important. Aortic root dilatation has been documented as being associated with Kawasaki disease, therefore the aortic root size calculated on echocardiogram should be compared to the norm for age and body surface area.¹⁸

Valvular regurgitation, in particular involving the mitral or aortic valves, has been reported after the acute illness; the most likely cause for this is inflammation of the valve tissue, causing a valvulitis, or secondary or myocardial ischaemia.

Other diagnostic techniques used to assess cardiovascular involvement in patients with Kawasaki disease include magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and cardiac computed tomography (CT; see Figures 1 and 2).¹⁹ Due to the relatively non-invasive nature and the ability to detect coronary and peripheral artery aneurysms, MRI and CT prove very useful in the diagnosis and follow-up of patients, however, limited availability and cost mean that 2-D echocardiogram remains the primary diagnostic tool used in our centres.

One imaging technique, which may prove very useful in Kawasaki disease to evaluate myocardial perfusion, is cardiac single photon emission CT (SPECT). This evaluates myocardial perfusion and ischaemia secondary to coronary artery stenosis both at stress and rest following administration of tetrahydrofosmin. Intravenous Persantine acts as an agent to induce pharmacological stress and increase myocardial blood flow.

This has particular use in identifying patients who have coronary artery involvement with significant stenosis in whom ischaemic symptoms are not reported. This may allow for early intervention, either surgical or via cardiac catheterisation techniques, before any possible major ischaemic events.

Classical stress testing using either exercise or pharmacologically induced stress is used to identify reversible ischaemia and to prioritise patients needing further, more detailed invasive investigation, cardiac catheterisation or angiography, or those requiring intervention due to the extent of their coronary stenosis. The use of pharmacologically induced stress compared to exercise depends on patient age, activity levels and compliance.

Recently, MRI has allowed detection of the vascular inflammatory process within the vessel wall using triple inversion recovery (STIR) techniques (see Figures 3 and 4). This may have clinical utility in allowing evaluation of resolution of inflammation following medical therapy.

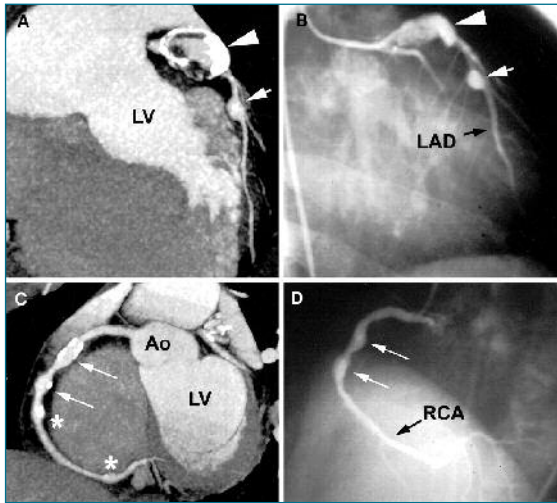


Figure 1. Multiplanar reconstructed CT image of the left anterior descending artery reveals a giant aneurysm (large arrowhead) with calcified wall (the eggshell-shaped high density area), thrombi (the low density area inside) and irregular residual lumen. A smaller aneurysm in the middle segment is also noted (small arrowhead). Angiography is presented adjacent to the CT images.

Reproduced with permission from Wu MT et al. Evaluation of coronary artery aneurysms in Kawasaki disease by multislice computed tomographic coronary angiography. *Circulation* 2004; 110 (14): e339.

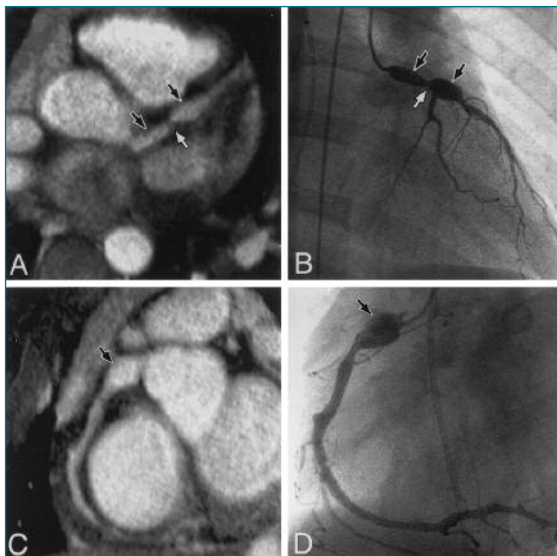


Figure 2. Multiplanar reformatted image of the left and right coronary arteries using MRI, demonstrating aneurysmal disease in the left and right coronary arterial systems. Reproduced with permission from Greil et al. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki Disease. *Circulation* 2002; 105 (8): 908-11.

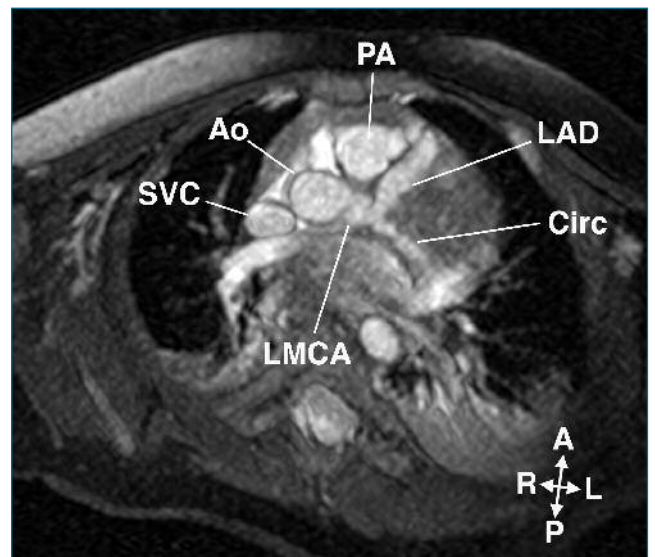


Figure 3. Local maximum intensity projection of left coronary system from three-dimensional gradient echo navigator images. Note coronary artery dilation. TE = 2.3ms. TR = 6.9ms. PA = main pulmonary artery. LAD = left anterior descending coronary artery. Circ = circumflex coronary artery. LMCA = left main coronary artery. SVC = superior vena cava. Ao = aorta. A = anterior. L = left. R = right. P = posterior.

Reproduced with permission from McMahon CJ et al. Detection of active coronary arterial vasculitis using magnetic resonance imaging in Kawasaki disease. *Circulation* 2005; 112 (19): e315-6.

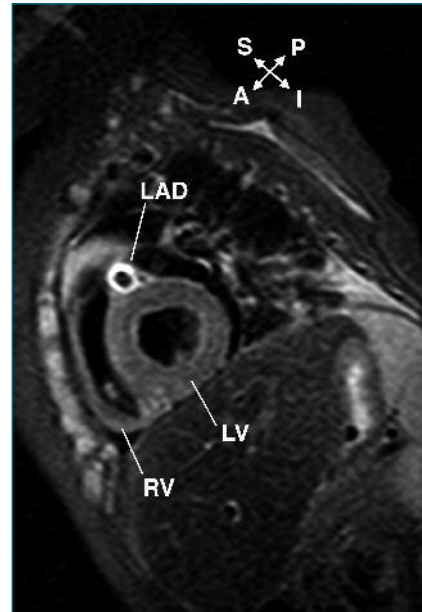


Figure 4. Fat suppressed double inversion recovery short-tau inversion recovery (STIR) - turbo spin echo image (or TIR sequence). Note high signal intensity in cross-section of the left anterior descending coronary artery (LAD). LV = left ventricle. RV = right ventricle. S = superior. I = inferior. P = posterior. A = anterior. TE = 80ms. TR = 1,500ms.

Reproduced with permission from McMahon CJ et al. Detection of active coronary arterial vasculitis using magnetic resonance imaging in Kawasaki disease. *Circulation* 2005; 112 (19): e315-6.

Table 1. Risk Stratification⁴

Risk	Pharmacologic Rx	Physical activity	Follow-up	Invasive tx
I	None after eight weeks	Normal	Risk assessment	None
II	None after eight weeks	Normal	Risk assessment	None
III	Low dose aspirin (3-5mg/kg/day) until aneurysm regression	<11yrs >11yrs biennial ST guides activity	Annual echo, ECG Biennial ST	Angio if +ST
IV	Long-term anti-platelet therapy and warfarin (INR 2-2.5) or LMWH (Factor Xa 0.5-1.0 IU/mL) in giant aneurysms	No contact or high impact sports, other activity depends on ST	Biannual ECHO/ECG Annual ST or perfusion scan	Angio six months
V	Long-term low dose aspirin Warfarin or LMWH +/- β -blockers	No contact/high impact sports, other activity depends on ST/perfusion study	Biannual ECHO/ECG Annual ST or perfusion scan	Angio for surgical RX

Abbreviations: Angio: angiogram; ECG: electrocardiogram; ECHO: echocardiogram; ST: stress test; tx: treatment; LMWH: low molecular weight heparin.

Risk classification: I; no coronary involvement at any stage, II; transient coronary artery ectasia disappearing within six to eight weeks, III; One small-to-medium coronary artery aneurysm/major coronary artery, IV; ≥ 1 large or giant coronary artery aneurysm or multiple or complex aneurysms in same coronary without obstruction, V; coronary arterial obstruction.

Treatment of Kawasaki disease

The treatment of Kawasaki disease is based around two goals, the reduction of inflammation within the coronary arteries and myocardium, and preventing thrombosis developing by inhibiting platelet aggregation. Treatment classically involves the use of two agents, aspirin and intravenous immunoglobulin (IVIG).²⁰ Treatment should be initiated as soon as the diagnosis is made and should not be delayed if diagnosis is highly suspected but echocardiography is not available immediately.

Aspirin is used for both its proven anti-inflammatory and anti-platelet activity and its use at low doses in patients with proven coronary artery involvement continues long after the acute illness. However, it has not been proven to reduce the frequency of development of coronary artery abnormalities.^{20,21}

In the initial acute phase, the dose is 25mg/kg four times a day for 14 days, then 3-5mg/kg once daily for six to eight weeks. If coronary artery changes have been identified on echocardiogram, the patient should remain on the low dose treatment indefinitely. Patients with no evidence of coronary involvement by six to eight weeks may stop treatment at this stage.

IVIG has been proven to be very effective in reducing the incidence of coronary artery abnormalities when used early in the acute phase of Kawasaki disease.²⁰⁻²² The dose used is 2mg/kg IVIG as a single infusion, given together with aspirin. Treatment has maximum benefit if given in the first 10 days of the illness. However, treatment with IVIG before day five has been described as being no more likely to prevent the formation of coronary artery abnormalities and, for this reason, the ideal treatment period is day five to seven of the illness.²³

Patients who have a persistent or recurrent fever ≥ 36 hours after the IVIG dose may be considered for a repeat treatment at

2mg/kg infusion. Persistent fever following repeat IVIG therapy is treated with intravenous methylprednisolone. In patients with persistent fever and rapidly dilating coronary arteries, intravenous abcximab has been used.

Prevention of thrombosis in patients with proven coronary artery involvement is a major factor in reducing the long-term morbidity and mortality associated with Kawasaki disease. The thrombotic process in coronary arteries post-Kawasaki disease is mainly due to low blood flow velocities and relative flow stasis within the aneurysm, combined with turbulence in the post-stenotic region, which lead to the activation of the clotting cascade and subsequent thrombus formation.

This is a different process of coronary thrombus formation to that present in adults with atherosclerosis in whom thrombi are secondary to plaque instability or rupture. It is for this reason that thrombolytic protocols used to treat adults with atherosclerotic coronary disease may not be ideal for patients with thrombosis due to Kawasaki disease.⁴ Patients with large aneurysms considered at significant risk from thrombus formation may, in addition to their daily dose of aspirin, be commenced on warfarin (INR 2.0-2.5) or low-molecular-weight heparin.

Surgical management in Kawasaki disease

The role of surgery in Kawasaki disease lies mainly in coronary artery bypass grafting for stenotic lesions and attempts at surgical excision of coronary aneurysms are very rare and yield little success. Careful consideration should be taken when selecting patients whose extent of coronary disease necessitates coronary artery bypass grafting.

Detailed imaging studies using either angiography or very

detailed non-invasive imaging should be carried out to assess the patency and condition of the vessels distal to the graft site. The condition of the myocardium that will be perfused by the graft should be assessed using stress MRI or other detailed stress imaging to ensure the tissue is still viable. Arterial grafts (usually left or right internal mammary artery) are reported as having better long-term patency rates compared to venous (usually saphenous vein).²⁴

Cardiac catheterisation can be used in Kawasaki disease for diagnostic purposes, using angiography to assess the extent of stenosis in a vessel, collateral blood supply and also to visualise aneurysm size and morphology. Interventions can also be carried out using catheterisation. These include stent placement in both stenotic vessels and across aneurysm segments, and balloon angioplasty or rotational ablation of stenotic areas.

Long-term follow-up

Patients should be followed up closely in the initial period after diagnosis. Typically, echocardiograms are performed at two weeks, six weeks and 12 weeks after diagnosis. The extent of clinical surveillance depends on the degree of coronary involvement and risk stratification (see Table 1).

Conclusions

Kawasaki disease is the leading cause of acquired coronary artery disease in the West. Early recognition and prompt, appropriate treatment of this condition will lower the prevalence of coronary artery aneurysms and, hence, morbidity and mortality from this disease process. Clinicians should remain astute to this potential diagnosis, not only in children, but also in the adult population.

Correspondence to: Dr Colin McMahon, Consultant Paediatric Cardiologist, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Tel: 01 409 6153, Email: colin.mcmahon@olhsc.ie.

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