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REVIEW ARTICLE

An update on Kawasaki disease II: Clinical features, diagnosis, treatment and outcomes

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Abstract: This is the second of two updates on Kawasaki disease. The first review focused on epidemiology and aetio-pathogenesis. Here, we review the clinical features and diagnosis of Kawasaki disease, as well as recent evidence on treatment, follow-up and cardiovascular outcomes.

Key words: diagnosis; Kawasaki disease; outcome; treatment.

Introduction

Kawasaki disease is an important childhood systemic vasculitis with potentially major cardiovascular implications, especially if the diagnosis is missed, or if timely and appropriate treatment is not given. In part I of our review, we highlighted important research advances in epidemiology, proposed aetiologies, host susceptibility and pathogenesis.[1] Here, we review the clinical features, diagnosis, treatment, recommended follow-up and long-term cardiovascular outcomes of Kawasaki disease.

Key Points

1 Kawasaki disease is characterised by prolonged fever plus four of the five cardinal clinical diagnostic criteria; a polymorphous rash, non-exudative conjunctivitis, mucosal changes, erythema or desquamation of extremities and cervical lymphadenopathy.
2 Infants may present with a prolonged fever and fewer clinical features; the diagnosis should therefore be considered in any infant who has a fever for longer than 1 week, for which no aetiology is found.
3 Treatment in the acute phase with intravenous immunoglobulin has been shown to reduce the risk of coronary artery complications from up to 25% to 2–4% and should be given to children even after day 10 of illness if systemic inflammation persists.

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Clinical Features and Diagnosis of Kawasaki Disease

The typical presentation of Kawasaki disease is an infant or young child who has a high swinging fever (often >39°C) for 5 or more days that often persists despite antibiotic and/or antipyretic treatment. Without treatment, the fever lasts a median of 11 days but may persist up to 3 weeks.[2] The child is irritable and usually looks unwell. Parents frequently comment that the child is much more irritable than with previous febrile illnesses.

The absence of any laboratory test with sufficient specificity or sensitivity for Kawasaki disease means that the diagnosis is made by the presence of a constellation of clinical features. Thus, Kawasaki disease is more correctly described as a syndrome,[3] although this distinction has not gained much traction in the literature. The consistent phenotype in different ethnic groups has allowed broadly similar diagnostic criteria to be adopted worldwide, with some minor variations. Given the largely preventable but potentially life-threatening coronary artery damage that may occur, timely diagnosis and treatment are essential.

The classical diagnostic criteria include prolonged fever plus at least four of the five principal or cardinal clinical diagnostic criteria (Table 1).[2] The presence of fever is universal (with the exception of a single case report[4]) and the onset of fever is considered the first day of the illness. Definitions for the length of fever necessary to fulfil diagnostic criteria vary; in the United States and Europe, at least 5 days of fever is standard, unless four principal criteria are present, in which case the diagnosis can be made on day 4 of fever. The Japanese Ministry of Health criteria include fever (which need only be present for 4 days if shortened by treatment for Kawasaki disease[5]) as one of the six principal diagnostic criteria, of which at least five must be present.[6] It is important to remember that the diagnostic features often appear sequentially and may be transient and therefore may have resolved by the time the child presents to a

Table 1 Diagnostic criteria for Kawasaki disease

Fever (>39°C) for at least 5 days:
plus at least four of the following five diagnostic features
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity:
Erythema, fissured cracked lips, strawberry tongue or diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
Changes in extremities:
Acute: Erythema of palms and soles; oedema of hands and feet
Subacute: Periungual peeling of fingers and toes (in the second and third week)
plus exclusion of other diseases with similar clinical features

doctor. A focused history is therefore important, and it may be reasonable to wait for additional features to appear if the child presents relatively early in the illness, as treatment is usually started after day 5 and before day 10. Not surprisingly, delayed diagnosis is more likely in those whose features are spread over a longer period[7] and in those who fall outside the typical age range of 6 months to 4 years.[8]

Kawasaki disease should still be considered in infants and children who do not fulfil the formal diagnostic criteria. It is also important to appreciate that the diagnostic criteria were designed to maximise specificity (for research studies) rather than to maximise sensitivity (which is more important in clinical practice, so that the diagnosis is not overlooked). They therefore do not include the many non-specific clinical features that are also commonly present in Kawasaki disease, such as vomiting, cough, poor intake, diarrhoea, rhinorrhoea, and abdominal and joint pain.[9] A microbiologically diagnosed infection is present in approximately one-third of children with Kawasaki disease, which may make the diagnosis more difficult. A concurrent infection does not alter the coronary artery outcomes.[10]

Other characteristic features of Kawasaki disease include perineal desquamation and erythema, which occurs during the acute phase of the illness. In contrast, periungual desquamation of the fingers or toes (and occasionally also of the palms and soles) occurs in the subacute phase (weeks 2 and 3) and is therefore not helpful in making a timely diagnosis. Mild reactivation of clinical features such as re-desquamation may also occasionally be seen beyond the convalescent phase. Inflammation and crusting of a recent Bacille-Calmette-Guérin (BCG) injection site is a specific feature of Kawasaki disease,[11] although BCG is no longer part of the standard immunisation schedule in Australia and New Zealand, unlike Japan.

Incomplete Kawasaki Disease

The diagnostic criteria for Kawasaki disease are potentially useful in reducing over-diagnosis but may result in children with incomplete forms of the condition being missed. Children with at least 5 days of fever and two or three of the cardinal diagnostic criteria are described as having 'incomplete Kawasaki disease'. These cases account for 15–20% of children eventually diagnosed with Kawasaki disease in most case series. Children with incomplete Kawasaki disease may develop coronary artery changes, but these usually develop in the sub-acute phase, from about day 10 onwards. As treatment is ideally given before day 10, coronary artery changes are of little use for diagnosis in the clinical setting. If coronary artery dilatation is seen on echocardiography, then the diagnosis of Kawasaki disease is confirmed, even if less than four principal features are present. Treatment with intravenous immunoglobulin (IVIG) should be given if incomplete Kawasaki disease is suspected, irrespective of the echocardiographic findings. It is likely that additional children with fewer features and/or without overt coronary artery changes on echocardiography are never diagnosed. The term 'incomplete' Kawasaki disease is more accurate than 'atypical', which should be reserved for those who have less typical features, such as renal impairment or shock.[2]

The diagnosis of incomplete Kawasaki disease is particularly challenging, as it is commoner in those younger than 6 months and older than 5 years of age, with the younger age group more likely to present with fewer clinical features and therefore less likely to fulfil the full diagnostic criteria. These children are consequently at greater risk of delayed diagnosis, have lower rates of timely and appropriate treatment and are at the highest risk for coronary artery complications.[12,13] It is imperative to consider incomplete Kawasaki disease in any infant, irrespective of age, who has a fever for more than 7 days with systemic inflammation for which no aetiology has been found.[2] The American Heart Association guidelines recommend that infants less than 6 months of age with fever for 7 or more days without an obvious cause, and laboratory evidence of systemic inflammation, should be assessed for possible Kawasaki disease and referred for echocardiography.[2] Although positive findings of coronary artery involvement on echocardiography are grounds to institute treatment, a negative echocardiogram does not exclude the diagnosis and should not be used as a rule-out diagnostic test.

The American Heart Association has formulated an algorithm to provide a structured approach to the child over 6 months of age with suspected incomplete Kawasaki disease, which is available online (http://circ.ahajournals.org/content/110/17/2747.full).[2] These guidelines are currently being updated. Children over 6 months of age with prolonged fever of at least 5 days and two or three principal diagnostic criteria are assessed for the presence of additional clinical and laboratory features, which may lead to echocardiographic assessment and/or treatment in those who have other suggestive features. The performance of the algorithm has been assessed retrospectively in children in the United States with coronary artery abnormalities; at least 97% of patients would have been appropriately referred for IVIG treatment if the guidelines were followed, compared with only 70% if the usual clinical diagnostic criteria were used.[14] Given the lack of a diagnostic test, the study could not address the specificity of the algorithm and therefore how many children were investigated and/or treated unnecessarily. A smaller prospective study found that the American Heart Association guidelines, especially the early use of echocardiography, increased the diagnostic sensitivity and treatment rate.[15]

Less Typical Presentations

There are myriad reports of unusual clinical presentations in Kawasaki disease, including acute abdomen,[16] upper airway obstruction due to massive lymphadenopathy,[17] meningoencephalitis,[18] blindness,[19] transient deafness (either due to the disease itself[20] or as a consequence of salicylate toxicity[21]) and cranial nerve palsies.[22] Frequently, the atypical clinical and laboratory features lead clinicians down blind-ending diagnostic paths. For example, lymphadenopathy, a feature more commonly seen in older children, may be mistaken for pyogenic lymphadenitis. The presence of leucocytes in urine or cerebral spinal fluid (CSF) may lead to an erroneous diagnosis of urinary tract infection or aseptic meningitis.

Aside from coronary artery involvement, children may develop myocarditis and/or pericarditis as part of the acute inflammatory process. This may lead to ventricular dysfunction, valvular regurgitation or pericardial effusion. Although rare, cardiac tamponade can occur, and late-onset severe aortic or mitral regurgitation necessitating valve replacement has been reported.[23–25] Diffuse myocarditis and microvascular inflammation uncommonly leads to conduction system abnormalities, which occur independently of coronary artery involvement.[26,27] Sinus node and atrioventricular node dysfunction can manifest with clinical arrhythmias such as heart block, ventricular tachycardia or ventricular fibrillation.[26,28]

There are case reports of patients who fulfil criteria for both toxic shock syndrome and Kawasaki disease, although the incidence of this subset of patients is unclear.[29] Shock is not usually a feature of Kawasaki disease, despite the overlap in clinical features between Kawasaki disease and toxic shock syndrome. Recently, children with 'Kawasaki disease shock syndrome' have been described in the United States[30] and Australia.[31] This syndrome is characterised by hypotension, haemodynamic instability, disease refractory to IVIG infusion and more severe coronary artery abnormalities. It occurs in children older than is typical for Kawasaki disease. These patients have been found to require intensive haemodynamic support and have significant coronary artery involvement.[29] The syndrome may represent a more virulent trigger and/or a particular genetic susceptibility.

Investigations

Laboratory tests

Kawasaki disease is characterised by marked acute inflammation and laboratory investigations reflect this. Raised C-reactive protein (CRP) (>35 mg/L) is seen in approximately 80% of cases and a raised erythrocyte sedimentation rate (ESR) (>60 mm/h) in 60%. Once IVIG has been given, the ESR becomes uninterpretable due to the increased plasma viscosity.[3] Common haematological features include leucocytosis with a predominant neutrophilia (in approximately 50%), often with left shift and toxic granulation, and a normocytic normochromic anaemia. Thrombocytosis (usually >500 000 $\times 10^9$/L) is also common, but the platelet count peaks 2–3 weeks after disease onset and is therefore not helpful diagnostically in the acute phase to guide treatment decisions. Leucopaenia or thrombocytopaenia are unusual, but do not preclude the diagnosis; the latter is associated with non-response to initial IVIG treatment.[32]

Biochemical abnormalities such as hyponatraemia have also been observed and may reflect inappropriate antidiuretic hormone secretion.[33] A plasma sodium level less than 135 mol/L has been associated with worse coronary artery outcomes, although this cut-off had a poor positive predictive value.[34] Approximately half of children have at least one (usually mildly) abnormal liver function test, which has been reported to be moderately predictive of subsequent IVIG resistance.[35] Dyslipidaemia is common in acute Kawasaki disease, with a pro-atherosclerotic profile (i.e. increased low density lipoprotein (LDL) and decreased high density lipoprotein (HDL)).[36] Whether these lipid abnormalities persist or are important in longer term cardiovascular risk remains unclear.[37] Cardiac troponin levels may be elevated in acute Kawasaki disease,[38] but its measurement is not part of routine clinical management and interpretation is difficult.[2]

Data on a variety of novel biomarkers are reported, but none are yet in clinical practice. Brain natriuretic peptide (BNP) and its N-terminal moiety (NT-proBNP) increase during the acute and subacute phases of Kawasaki disease and a significant increase in pre-IVIG NT-proBNP levels may become a useful adjunct in the diagnosis of incomplete Kawasaki disease where there is myocardial damage.[39,40] Damage-associated molecular pattern molecules, such as S100 proteins, which are expressed by myeloid cells, are important pro-inflammatory factors. Various S100 protein isoforms (particularly S100A12) are increased in Kawasaki disease and they may have a pathogenic role in vascular inflammation by recruiting leucocytes to sites of inflammation.[41] Urinary levels of 8-iso-prostaglandin F2alpha may be a useful marker of vascular oxidative stress in acute Kawasaki disease and its levels may reflect the effectiveness of initial IVIG treatment.[42]

Echocardiography

The main aim of echocardiography is to assess the presence of coronary artery dilatation or aneurysm formation (Fig. 1), as well as valvular regurgitation, ventricular (dys)function or a pericardial effusion, suggestive of pericarditis and/or myocarditis. Myocarditis may lead to ventricular dilatation, characterised by an increased left ventricular end-diastolic dimension, as well as wall motion abnormalities in 50–70% of patients in the acute phase.[27] A schematic diagram showing the various aneurysm types and ectatic dilatation is shown in Figure 2. The main sites of coronary involvement (in order of decreasing frequency) are the proximal left anterior descending artery, proximal right coronary artery, left main coronary artery, left circumflex branch, distal right coronary artery and the junction of the right and posterior descending coronary artery.[2]

Transthoracic echocardiography should be performed in all suspected cases of Kawasaki disease at initial presentation. Use of sedation should be considered if the child is too irritable to tolerate a detailed echocardiographic study. However, a normal study does not exclude the diagnosis of Kawasaki disease and, as emphasised previously, the results should not delay or dictate initial treatment. The presence of coronary artery abnormalities on echocardiography may suggest incomplete Kawasaki disease

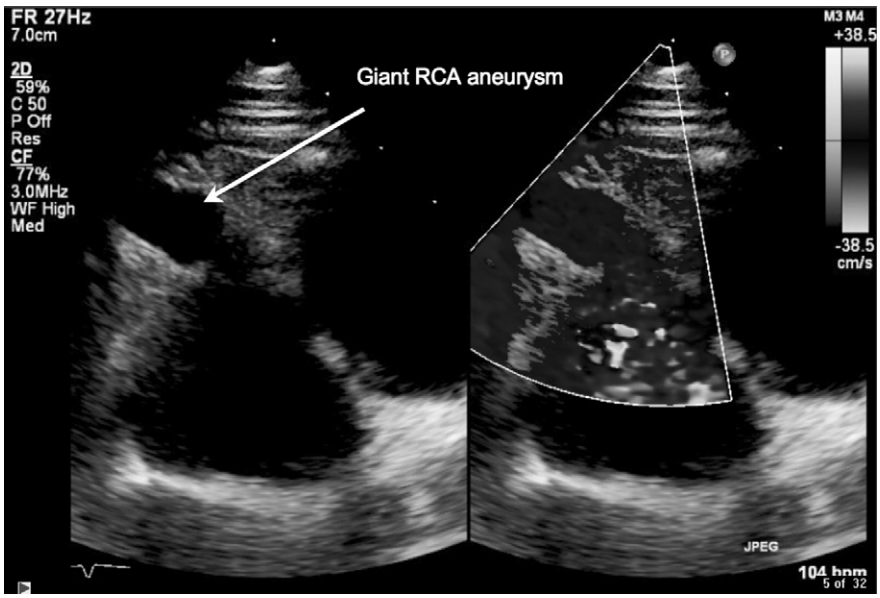

Fig. 1 Parasternal short axis echocardiographic image showing a giant right coronary artery (RCA) aneurysm.

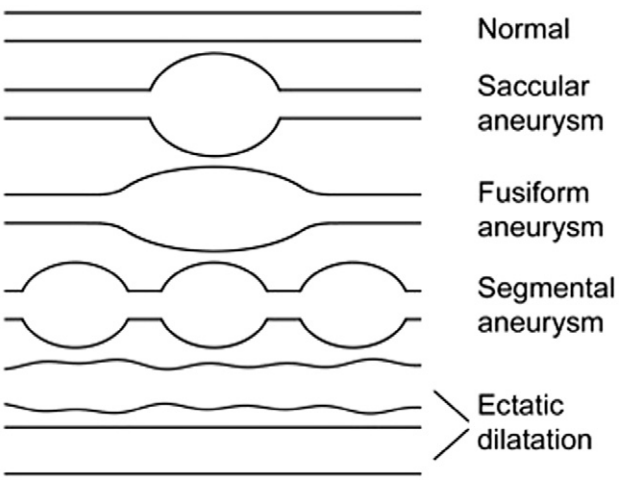

Fig. 2 Illustrative example of coronary artery abnormalities.

and its selected use as a diagnostic adjunct is part of the American Heart Association management algorithm.[2]

Evaluation using *z*-scores of coronary artery aneurysms

Assessment of the internal diameters of the coronary arteries is central to determining if there is pathological dilatation. The original classification schema from the Japanese Ministry of Health used absolute values for coronary artery dimensions[33] and did not account for patient size nor for the differences in calibre of coronary artery branches. The 2004 American Heart Association guidelines accounted for body surface area by incorporating coronary artery *z*-scores into the current classification.[2] If the coronary artery has an intra-luminal diameter *z*-score of $\geq$2.5, then it is considered to be dilated. Minor differences in coronary artery measurements, however, can lead to large changes in calculated *z*-scores; hence, this method of classifying coronary artery sizes to determine ongoing anticoagulation and management should be interpreted with care.[43] Moreover, height is not necessarily routinely recorded on hospital admission in Australia, and may have to be inferred from weight centiles, reducing the confidence in body surface area estimates and hence in coronary artery *z*-scores.

Treatment of Kawasaki Disease

Intravenous immunoglobulin (IVIG)

A single high-dose single infusion of 2 g/kg of IVIG within 10 days of the onset of fever as the main intervention for acute Kawasaki disease has a strong evidence base, reducing the risk of coronary artery lesions from 20–25% to 2–4%.[44] IVIG should still be given to children presenting after day 10 of illness if fever and signs of/or inflammation persist,[2] although the prognosis worsens with treatment initiated after day 10.[45] Initiation of IVIG before day 5 does not appear to improve coronary artery outcomes and may increase the need for retreatment.[46] The mechanism of action of IVIG in Kawasaki disease is unclear. Potential effects include neutralising microbial toxins and down-regulating immune responses and endothelial activation. There is limited evidence that different IVIG preparations vary in efficacy; a retrospective Canadian study showed a significant difference in coronary artery *z*-scores between children treated with two different IVIG preparations (neither of which are widely used in Australia), although there was no difference in the overall frequency of coronary artery lesions or aneurysms between the two groups.[47]

Aspirin

Aspirin has been used in the treatment of Kawasaki disease for many years, but there is no evidence that it improves outcomes[2]

and a recent Cochrane review concluded that there was insufficient evidence to support its use.[48] The treatment of Kawasaki disease without aspirin was not found to have an effect on the response rate to IVIG, or duration of fever,[49] nor did it have an effect on lowering the frequency of developing coronary artery abnormalities.[49,50] Despite these findings, the use of aspirin in Kawasaki disease continues to be a widely accepted practice, albeit with varying dose regimens, as there are no data to guide the optimal dosing regimen. Traditionally, 'anti-inflammatory' high doses (often 80–100 mg/kg/day in divided doses in the United States and 30–50 mg/kg/day in divided doses in the United Kingdom and Japan) are used in the acute phase, followed by a low 'anti-platelet' dose (3–5 mg/kg/day) following defervescence.[2] However, on the basis that there is no evidence for any additional benefit over IVIG from an anti-inflammatory doses of aspirin and that only the low dose has anti-platelet activity, many Australian centres use the lower dose of aspirin from presentation,[51] using paracetamol for symptomatic relief. There is a risk of antagonising the anti-platelet effect of low-dose aspirin by the additional use of a non-steroidal anti-inflammatory agent such as ibuprofen[52] or naproxen,[53] whereas both diclofenac and paracetamol have not been found to counteract the anti-platelet effect of aspirin.[52] The lack of interaction between diclofenac and aspirin, but not ibuprofen, may be in part due to the lower potency and shorter duration of action with diclofenac; however, more complex pharmacokinetic distinctions are also possible.[52]

Low-dose aspirin is continued for at least the first 6–8 weeks of the illness, during which time the risk of coronary artery damage is greatest. If the echocardiogram of the coronary arteries is normal at 6–8 weeks, the aspirin is usually discontinued. If mild coronary artery dilatation or small to medium aneurysm(s) (>3 and <6 mm diameter) remain after this period, aspirin should generally be continued until resolution of arterial involvement is documented, although evidence is lacking to support or refute this practice. Some experts therefore elect to continue aspirin for a longer period or even lifelong. Addition of clopidogrel, dipyridamole or low molecular weight heparin may be considered if coronary artery aneurysm(s) enlarge. Warfarin is recommended if giant aneurysms (>8 mm diameter) are present.[2] Management should be directed in consultation with a paediatric cardiologist. A multi-centre retrospective study of warfarin and aspirin combination therapy in Kawasaki disease patients with giant coronary aneurysms found that this combination had a high cardiac event-free survival, although there was an increased risk of haemorrhagic complications.[54]

Steroids

Steroids are widely and successfully used in other vasculitides and their use in Kawasaki disease has a long and – until recently – largely evidence-poor history. Many previous studies were methodologically flawed, which made interpretation of data difficult. A recent rigorous prospective North American randomised controlled trial has shown that steroids have no additional benefit in the initial management of Kawasaki disease when used as an adjunct to IVIG in unselected patients.[55] A recent meta-analysis of 11 studies reported that concurrent use of corticosteroids with IVIG as primary therapy improved the clinical course and reduced rates of treatment resistance.[56] However, primary adjunctive steroids were not shown to reduce the incidence of coronary artery complications though the number of cases requiring retreatment was shown to be less. Results from a study in Japan suggest that the small subgroup of patients at high risk of coronary artery complications despite IVIG may benefit from adjunctive steroids.[57] However, the reliability, particularly sensitivity, of the risk-scoring system used to identify high-risk patients is generally poor in non-Japanese populations and it is therefore difficult to extrapolate the findings to non-Japanese patients until further data are available.[58] Therefore, it is not currently routine practice in Australia, United States, Canada or the United Kingdom to give initial adjunctive steroids.[59] Further larger randomised controlled trials are required to evaluate the use of corticosteroid therapy for both adjunctive primary treatment in high-risk cases and for additional 'rescue' therapy in IVIG non-responsive cases.[56] There is also a need for the development of risk-stratification algorithms in non-Japanese populations that reliably identify patients at highest risk of coronary artery damage who are most likely to benefit from primary adjunctive steroid therapy.

Non-responders to IVIG

Approximately 10–15% of Kawasaki disease patients have a persistent or recrudescent fever more than 36 h after the end of the initial IVIG infusion and require further treatment.[60] A variety of risk factors both before IVIG therapy and immediately following therapy have been associated with lack of response to IVIG, including initial IVIG treatment before day 5 of illness, a recurrent episode of Kawasaki disease, male sex, a low platelet count and elevated alanine transaminase (ALT) and CRP levels.[32] A white cell count of $>13.1 \times 10^9$/L and neutrophil differential of >51% 24 h after the first dose of IVIG may also predict non-response.[61] Those not responding to IVIG have an increased risk of coronary artery aneurysms, especially giant aneurysms.[32] A variety of other scoring systems have been developed in an attempt to predict IVIG resistance,[62] although none are in routine clinical use.

A further dose of 2 g/kg IVIG is recommended for patients who remain febrile or have a recrudescence of fever at least 36 h after the end of the initial IVIG infusion, although this is based mainly on recommendations from experts rather than trial data.[2] It is also important to re-evaluate the initial diagnosis of Kawasaki disease if the child is not responding to standard therapy.

The appropriate treatment for the child who has not responded to two doses of IVIG remains uncertain. Current practice varies between centres and may involve a trial of corticosteroids or anti-cytokine therapy, such as infliximab (discussed below). There is insufficient evidence on which to base further treatment recommendations, and until further studies are conducted, American Heart Association guidelines suggest the use of intravenous pulse methylprednisolone 30 mg/kg daily for up to 3 days in patients who fail to respond to two IVIG doses.[2]

Tumour necrosis factor blockade

The widespread use of 'biological' therapy to treat juvenile idiopathic arthritis and other systemic vasculitides and increased levels of the pro-inflammatory cytokine, tumour necrosis factor

(TNF) in Kawasaki disease,[63] has fuelled interest in TNF blockade in management. Infliximab, a monoclonal antibody against TNF-alpha, suppresses cytokine-mediated inflammation. However, one potential concern is the suggestion that, despite this, it may not reduce local vasculitis in IVIG-resistant disease.[64] A multi-centre, prospective phase 1 trial of infliximab for treatment of IVIG-resistant disease determined that both infliximab and a second IVIG infusion were well tolerated in Kawasaki disease patients with no severe adverse outcomes.[65] Small retrospective studies have reported a response rate (defined by a reduction of fever and CRP) of between 73 and 88% when infliximab was used as a second-line agent.[64–66] Furthermore, Korean children who received infliximab for refractory disease were found not to have any significant progression of coronary artery abnormalities after treatment.[66] Similarly, etanercept, a TNF receptor antagonist, appears safe and reduces fever in IVIG-resistant Kawasaki disease.[67] Larger multi-centre randomised controlled trials are underway to determine the role of anti-TNF blockade in refractory Kawasaki disease.

Other treatments

Various other agents have been tried as adjunctive primary therapy (with IVIG) or more commonly in refractory IVIG-resistant Kawasaki disease, although none is in routine use. A retrospective study examined the long-term results of abciximab, a platelet glycoprotein IIb/IIIa receptor antagonist, as an adjunct to conventional therapy, and found that the abciximab group had a greater reduction in *z*-scores of coronary artery aneurysms than the group who had conventional therapy alone.[68] There are preliminary data on the role of statins in the management of severe Kawasaki disease,[69] but their long-term safety in children is unclear.[70]

Follow-Up Recommendations (Short Term)

The American Heart Association recommends performing transthoracic echocardiography at diagnosis, and then 2 weeks and 6–8 weeks after the initial illness for uncomplicated cases.[2] The 2-week echocardiogram is not routinely performed in some centres. The timing of additional studies is case specific and is dictated by the severity of coronary artery involvement. In general, individual cases should be discussed in consultation with a paediatric cardiologist experienced with managing Kawasaki disease patients. Coronary aneurysms greater than 5 mm in size require close monitoring because of an elevated risk of developing stenotic lesions within the vessel.[71]

Imaging Modalities in Kawasaki Disease

Magnetic resonance angiography and multi-detector computed tomography angiography have been increasingly evaluated for coronary artery assessment in Kawasaki disease.[72,73] These techniques are particularly relevant in older patients where delineation of coronary artery anatomy is challenging. Computed tomography angiography and magnetic resonance angiography had 100 and 93% correlations, respectively, to the gold standard of conventional coronary catheterisation for aneurysm detection. Computed tomography has been reported to provide better images of the distal coronary system compared with echocardiography and magnetic resonance imaging.[74,75] The presence of regional ischaemia can be further assessed with stress echocardiography and myocardial perfusion scans.[76,77] Virtual histology-intravascular ultrasound has been use to evaluate coronary plaque composition and coronary segment morphology as part of longer-term Kawasaki disease follow-up.[78]

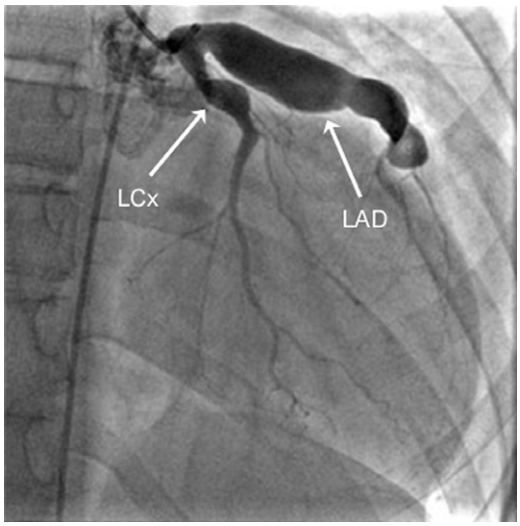

Fig. 3 Selective coronary angiogram showing a significantly dilated left anterior descending artery (LAD) and proximal left circumflex artery (LCx).

Cardiac Catheterisation

Cardiac catheterisation with selective coronary angiography is considered to be the gold standard investigation for assessing coronary artery involvement (Fig. 3) and may assist with risk stratification of patients who have complex coronary artery lesions. It is recommended that these patients undergo catheterisation and selective coronary angiography within 6–12 months after the onset of Kawasaki disease. Transcatheter interventional procedures such as balloon angioplasty, rotational ablation and stenting have been used in patients with coronary lesions due to Kawasaki disease. Although success rates greater than 90% have been reported with percutaneous rotational ablation and transluminal stenting for coronary artery lesions, the re-stenosis rate is relatively high.[79] These high-risk procedures should be performed in a centre with expertise in the field and patients should be referred on a case-by-case basis, taking into account their symptoms and the extent of coronary artery occlusion. Interestingly, arterial complications associated with arterial access in the Kawasaki disease group were observed to be 10.4 times higher than the general cardiac catheterisation group, possibly due to the systemic involvement of arterial vasculature in patients with Kawasaki disease.[80]

Surgical Management

In a study of children with giant coronary aneurysms and myocardial ischaemia, referral for earlier coronary artery bypass

grafting resulted in better post-operative results, with 95% survival rates at 20–25 years post-operatively and cardiac event-free rates that progressively declined to 60% at 25 years.[81,82]

Long-Term Outcomes

Nearly half of coronary artery lesions will show angiographic regression within 1–2 years of the illness.[83] As aneurysmal vessels remodel, however, the risk of coronary artery stenosis and thrombotic occlusion increases. Aneurysm size is a major predictor for the development of myocardial infarction.[84] A follow-up study of 48 Kawasaki disease patients with giant aneurysms reported that 74% of giant aneurysms progressed to coronary artery stenosis or occlusion, 31% developed myocardial infarction and 19% required coronary artery bypass grafting.[85] Ongoing follow-up of Kawasaki disease patients to detect at-risk coronary lesions, reversible ischaemia and cardiovascular risk assessment is necessary to detect early cardiac sequelae and referral for cardiac catheterisation or surgery if indicated.

Some studies report adverse indirect measures of possible cardiovascular dysfunction ('intermediate phenotypes') many months and years after Kawasaki disease. These include abnormal endothelial function,[86,87] increased carotid intima-media thickness[88] and increased systemic arterial stiffness,[89] with high pulse wave velocities.[90] These changes are most marked in those who have had coronary artery aneurysms. Furthermore, there is evidence of abnormal vascular endothelial function at long-term follow-up with single photon emission computed tomography imaging and altered lipid profiles in Kawasaki disease patients.[91] The clinical significance of these markers in predicting future cardiovascular risk remains uncertain.[87] A recent small study showed that Kawasaki disease individuals had significantly higher levels of total cholesterol and apolipoprotein B than matched controls,[37] but the overall contribution of Kawasaki disease to cardiovascular risk – a key issue – remains unresolved.

Significant behavioural sequelae have also been observed in 40% of children following Kawasaki disease, with higher rates of internalising behaviours such as somatic problems or withdrawn behaviour compared with hospital or sibling control groups.[92] It is therefore important for clinicians to identify and address any behavioural difficulties during medium- to long-term follow-up and referral to a clinical psychologist should be considered. Reassuringly, the same study did not find a significant difference in relation to social interaction, participation or school performance.[92]

Follow-Up Recommendations (Long Term)

The impact of Kawasaki disease on future cardiovascular risk is undetermined; hence, current recommendations by the American Heart Association suggest risk assessment and counselling at 3–5 yearly intervals for patients with no or transient coronary artery involvement and more frequent follow-up (annually or 6 monthly) in those with higher grade coronary artery lesions.[2] The American Heart Association suggests that an ECG and echocardiogram should be performed on each visit and exercise testing with myocardial perfusion imaging is recommended yearly or biennially depending on the level of risk stratification. This recommendation is based on expert opinion and many Australian and European centres do not routinely follow-up Kawasaki disease patients without coronary artery involvement on initial or 6-week echocardiography. It is certainly prudent however to discuss minimisation of known and modifiable risk factors for cardiovascular disease in children who have had Kawasaki disease. This includes avoidance of obesity and smoking and maintaining regular physical activity in childhood and adolescence. Many cardiologists will also recommend regular monitoring of blood pressure, fasting plasma glucose and lipids from early adulthood.[93]

Kawasaki Disease Presenting in Adulthood

There are a growing number of case reports of acute Kawasaki disease in young adults, mostly between 18 and 30 years of age.[94] The diagnostic criteria are generally present, despite the lack of validation outside the childhood age group. Adults are more likely to present with cervical adenopathy, arthralgia and abnormal liver function tests than children, whereas meningitis, cheilitis and thrombocytosis are more prevalent in children.[95] Incomplete cases of Kawasaki disease in adults are also observed relatively frequently.[94] Interestingly, a Kawasaki disease-like syndrome has been reported in HIV-positive adults.[96,97] Despite a frequent delay in diagnosis and treatment, adults have a better overall prognosis with less cardiovascular complications and no reported deaths.[98]

Conclusion

Kawasaki disease is an important and common systemic vasculitis of childhood. The timely administration of IVIG significantly reduces the risk of echocardiologically defined coronary artery lesions in the majority of patients. There have been significant advances in our overall understanding of the condition, although the aetiology remains unknown, which frustrates the development of diagnostics and biologically based treatment. The possible contribution of Kawasaki disease as a risk factor for adult coronary artery disease, irrespective of coronary artery involvement during the acute illness, remains unclear. Further research into aetiology, pathogenesis and long-term outcomes are required, together with translational research to improve diagnosis and management.

Review Questions

1 Which is not a characteristic feature of Kawasaki disease?
   A) Perineal desquamation
   B) Periungual desquamation
   C) Widespread arthritis of multiple joints
   D) Crusting of the BCG inoculation site
   E) Reddened pharynx and strawberry tongue

Answer: C. Joint pains are a non-specific clinical feature, but are not specific to, Kawasaki disease. Baker *et al*. found that of 198 patients with Kawasaki disease, irritability was present in 50%, vomiting in 44%, diarrhoea in 26%, rhinorrhoea in 19%, weakness in 19%, abdominal pain in 18% and joint pain (arthralgia or arthritis) in 15% of cases.[9]

2 Regarding incomplete Kawasaki disease, which of the following statements are false?
   A) Incomplete Kawasaki disease accounts for up to 20% of cases
   B) Echocardiography should be used to diagnose incomplete Kawasaki disease
   C) Infants less than 6 months of age are more likely to have fewer clinical features and a higher incidence of coronary artery abnormalities.
   D) The American Heart Association consensus guidelines are likely to increase treatment rate of incomplete Kawasaki disease
   E) Kawasaki disease should be considered in infants who are persistently febrile with evidence of systemic inflammation and without a clear focus

Answer: B is false. Transthoracic echocardiography should be performed in all suspected cases of complete or incomplete Kawasaki disease; however, the diagnosis should be made on clinical grounds and a normal study does not exclude the diagnosis. Although echocardiography may be used as a diagnostic adjunct, it should not be used as the determinant of whether a patient should be treated.

3 When treating Kawasaki disease, which of the following statements are false?
   A) A single high-dose infusion of IVIG has been shown to reduce the risk of coronary artery lesions
   B) IVIG should be given to children with active inflammation presenting beyond day 10 of illness
   C) Aspirin has been found to improve the outcomes in Kawasaki disease by reducing thrombosis risk
   D) The use of corticosteroids with IVIG was found by meta-analysis to improve the clinical course and decrease treatment resistance
   E) Cases who remain febrile or have a recrudescence of fever at least 36 h after initial IVIG should usually be retreated with a further dose of IVIG

Answer: C is false. Although aspirin is widely used in the acute and subacute phase, there is no evidence that aspirin improves cardiovascular outcomes. A Cochrane systematic review concluded that until good quality randomised controlled trials are performed, there is insufficient evidence to support its use.[40]

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