

Kawasaki syndrome

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Kawasaki syndrome is an acute, self-limited vasculitis that occurs in children of all ages and presents a challenge for the clinician: the disorder can be difficult to recognise; there is no diagnostic laboratory test; there is an extremely effective therapy; and there is a 25% chance of serious cardiovascular damage if the treatment is not given early in the course of the disease. This review includes discussion of the history of the syndrome, the diagnostic challenges, epidemiology, aetiology, pathology, immunopathogenesis, therapy, genetic influences, and the long-term cardiovascular sequelae.

Introduction

Tomisaku Kawasaki saw his first case of an unusual illness with rash and fever in a 4-year-old child at the Red Cross Hospital in Tokyo, Japan, in January, 1961. During the next 6 years, he saw 50 similar patients, and he published first reports on the disorder in Japanese in 1967¹ and in English in 1974.² An English translation of the 1967 paper became available only in 2002.³ Reports from Japan from the 1950s described similar patients.⁴ However, no published reports could be found of Japanese patients with the symptom complex of Kawasaki syndrome before the 1950s. To address the question of when the syndrome first appeared in Japan, researchers reviewed the records of 7618 children admitted to the Tokyo University Hospital between 1940 and 1954 for 15 different rash/fever diagnoses. They found 144 patients with one of these rash/fever diagnoses, of whom only five met all the clinical criteria for Kawasaki syndrome.⁵ None of these patients was seen before 1950. That study coupled with other historical inquiry suggests that cases of the disorder were not seen in Japan before the 1950s.

The most important issue about the syndrome in the 1960s in Japan was whether the illness described by Kawasaki was connected to subsequent cardiac complications noted in some cases. Noboru Tanaka, a pathologist, and Takajiro Yamamoto, a paediatrician, disputed Kawasaki's early assertion that the syndrome had no long-term sequelae.⁴ The controversy was resolved in 1970 when a nationwide survey in Japan identified ten autopsy cases of children who had died from complications of coronary-artery aneurysms after Kawasaki syndrome.⁶ By the time Kawasaki's paper was published in English in 1974, the link between the syndrome and coronary-artery vasculitis was well established.

Kawasaki syndrome was independently recognised as a new and distinct disorder in the early 1970s by Melish and Hicks at the University of Hawaii.^{4,7,8} Different features of the same complex of signs and symptoms were emphasised by these investigators, who focused on the urethritis and sterile pyuria and the inflammation of small and large joints that accompanied the illness in almost a third of patients. In 1973, Larson and Landing retrospectively diagnosed a 1971 autopsy case as Kawasaki syndrome. The similarity between fatal

Kawasaki syndrome and infantile polyarteritis nodosa was apparent to these pathologists, as it had been to Tanaka earlier.⁹

Case reports of infantile polyarteritis nodosa from western Europe extend back to the 19th century.¹⁰ What remains unknown is the reason for the simultaneous recognition of fatal and non-fatal Kawasaki syndrome around the world in the 1960s and 1970s.¹⁰ Several hypotheses have been proposed. The syndrome could have newly emerged in Japan and emanated elsewhere through Hawaii, where the disease is most prevalent among Asian-American children. Alternatively, Kawasaki syndrome and infantile polyarteritis nodosa could be part of the continuum of the same disease, and clinically mild Kawasaki syndrome masqueraded as other diseases such as measles or scarlet fever before the advent of vaccines and antibiotics.

Diagnosis

Kawasaki syndrome is self-limited; the signs and symptoms evolve over the first 10 days of illness then gradually resolve spontaneously in most children, even in the absence of specific therapy (figure 1). Coronary-artery aneurysms develop in 20–25% of cases; their development is clinically silent in most cases and may be recognised only years later at the time of sudden death or myocardial infarction.^{11,12} Treatment with high-dose intravenous immunoglobulin (IVIG) within the first

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Search strategy and selection criteria

We reviewed translations of early Japanese articles on Kawasaki syndrome, polyarteritis nodosa, and fatal infantile periarteritis nodosa. JCB was a member of a research team that undertook extensive interviews in Japan with key figures involved in the recognition of the syndrome as a distinct clinical entity. We reviewed relevant abstracts from the seven international symposia held since 1984. We reviewed selected publications from the PubMed database identified by searches with the keywords "Kawasaki syndrome", "Kawasaki disease", and "mucocutaneous lymph node syndrome", which included 2853 publications on the subject since 1975; we placed emphasis on citing relevant papers from the past 3 years. We did not restrict the language of publication.

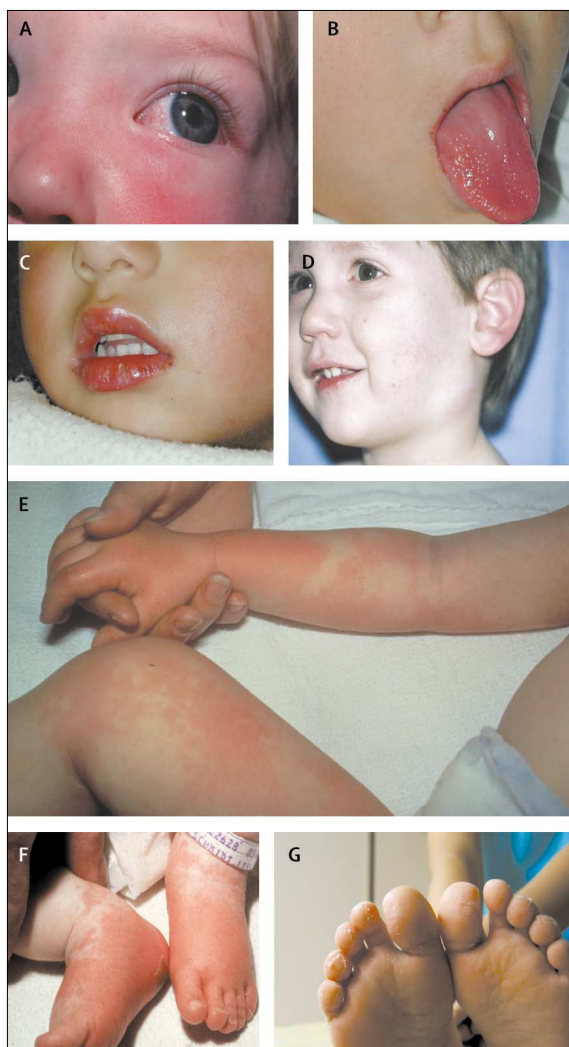


Figure 1: Features of Kawasaki syndrome

A: Bilateral, non-exudative conjunctival injection with perilimbal sparing. B: Strawberry tongue with loss of filiform papillae and persistence of fungiform papillae ("seeds" of strawberry). C: Erythematous, fissured lips. D: Unilateral enlarged left jugulodigastric nodes. E: Erythematous rash. F: Erythema of soles, swelling of dorsa of feet. G: Periungual desquamation of toes in convalescent phase.

Panel 1: Diagnostic criteria for Kawasaki syndrome

The diagnosis is confirmed by the presence of fever for at least 5 days and of four of the five criteria below, and by the lack of another known disease process to explain the illness.

- Bilateral conjunctival injection
- Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue
- Polymorphous rash
- Changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation
- Cervical adenopathy

10 days of fever onset reduces the risk of coronary-artery aneurysms.^{13,14} The syndrome is currently diagnosed by use of a case definition created for epidemiological surveys in Japan (panel 1). Concern has been raised about the appropriateness of this case definition as a clinical tool to identify children who must be treated to prevent coronary-artery sequelae of the vasculitis.^{15–18} Thus, a broader definition must be used to ensure the identification of all children who would benefit from IVIG treatment.

In many cases, the clinical criteria for Kawasaki syndrome are not all present on any given day. Experienced clinicians use crucial elements of the history and physical examination in the differential diagnosis of a rash/fever syndrome (figure 2). The lack of a specific and sensitive diagnostic test remains a major obstacle to correct identification of all patients with the syndrome. The clinical challenge lies in the ability to exclude diseases that resemble Kawasaki syndrome but require different treatment (eg, diseases mediated by staphylococcal or streptococcal toxins). There have been many attempts to identify discriminating clinical features and tests that could distinguish Kawasaki syndrome from other illnesses with rash and fever.^{19–23} Although the greatest concern is that the syndrome is underdiagnosed, there is also likely to be some degree of overdiagnosis. In clinical practice, physicians use laboratory markers of inflammation (eg, high white-blood-cell count, C-reactive protein, and erythrocyte sedimentation rate) to support the diagnosis of Kawasaki syndrome in patients with rash/fever syndromes (figure 3).

The concept of "incomplete" (atypical) Kawasaki syndrome has emerged in recent years.^{24,25} This term should be used for patients with fever for at least 5 days, at least two of the clinical criteria for Kawasaki syndrome, no other reasonable explanation for the illness, and laboratory findings consistent with severe systemic inflammation. Many experienced clinicians have encountered patients with an inflammatory disorder who did not meet the clinical case definition, but in whom an echocardiogram documented coronary-artery abnormalities, thus confirming the diagnosis of Kawasaki syndrome. We should bear in mind that five of the patients in Kawasaki's original series of 50 would not have satisfied the current clinical case definition.³

The recognition that IVIG therapy is highly effective for Kawasaki syndrome has placed a substantial burden on physicians to consider this diagnosis in children with unexplained illness that includes rash and fever. Specific features of Kawasaki syndrome that can mislead physicians include sterile pyuria misdiagnosed as urinary-tract infection,⁸ cerebrospinal-fluid pleiocytosis misdiagnosed as aseptic meningitis or partially treated bacterial meningitis,²¹ rash misdiagnosed as viral or drug eruption, and cervical lymphadenopathy misdiagnosed as bacterial adenitis.^{26,27} Research should

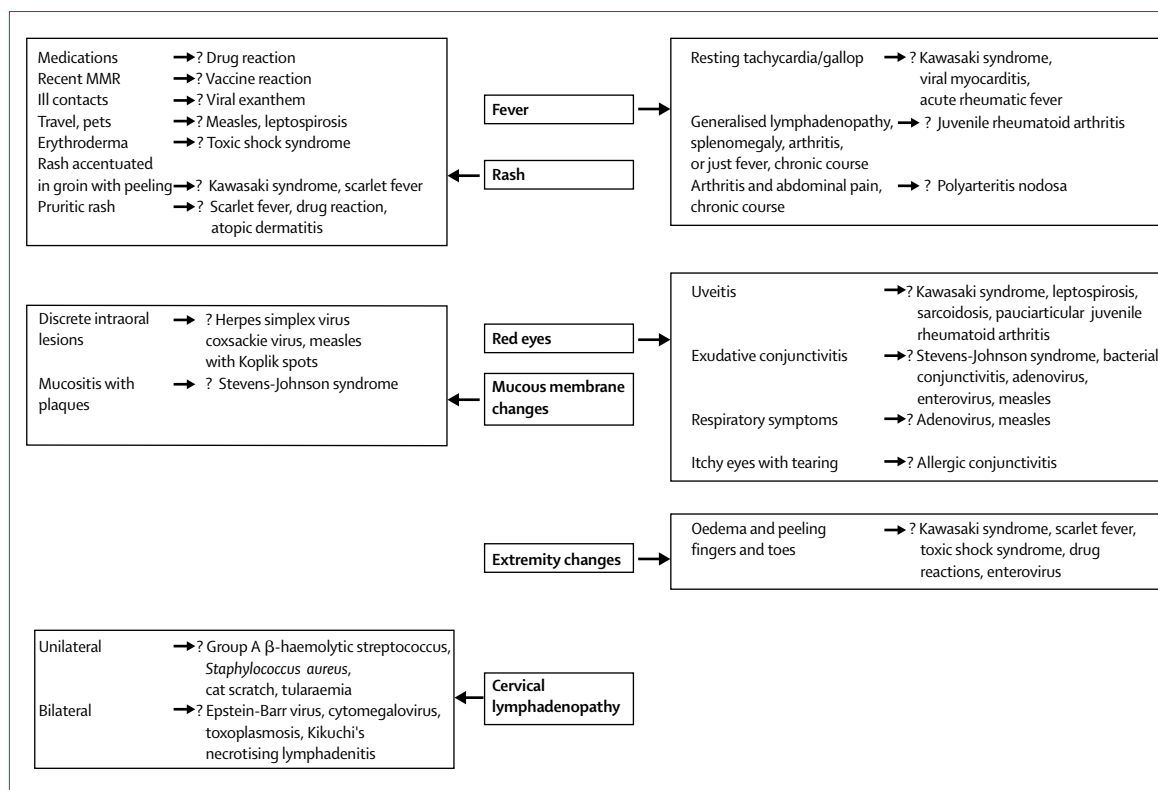


Figure 2: Approach to investigation of children with suspected Kawasaki syndrome
MMR=measles, mumps, rubella vaccine.

focus on unique features of this vasculitis that might serve as a diagnostic test, even if the underlying cause remains unknown.

Epidemiology

Kawasaki syndrome has been reported in all racial and ethnic groups and across the entire paediatric age range, although in most series 85% of patients are younger than 5 years. Patients younger than 6 months or older than 8 years are encountered infrequently but might be at increased risk of coronary-artery aneurysms.^{28–31} The reported annual incidence rates of the syndrome per 100 000 children under 5 years of age by country range from 3 in South America to 134 in Japan, although the reliability of these data is uncertain (figure 4).³² The annual incidence per 100 000 children under 5 years in the UK has doubled during the past decade and is now reported to be 8.1, compared with a recently reported US rate of 17.1.^{33,34} In Japan, about one child in 150 develops Kawasaki syndrome during childhood (Hiroshi Yanagawa, personal communication). In Hawaii, the annual incidence for Japanese Americans is 135 per 100 000 children under 5 years, which is similar to that for Japanese living in Japan (Marian Melish, personal communication). Many studies have sought environmental risk factors for Kawasaki syndrome. Investigations have linked the syndrome to exposure to

freshly cleaned carpets, humidifier use, and residence near a body of water, but these findings have not been consistently replicated in other studies.^{35–39}

Aetiology

The cause of Kawasaki syndrome remains unknown, although an infectious agent is suspected in view of the following evidence. There is a seasonal peak in the winter and spring months in most geographical areas, and geographically focal epidemics occurred in the 1970s and 1980s. The peak incidence in the toddler age-group with only rare cases in infants under 3 months of age and in adults suggests a role for transplacental antibodies conferring protection and development of protective immunity as a result of asymptomatic infection in most individuals. The diagnosis of recurrent cases in 3–5% of children in Japan suggests either failure to mount a protective immune response in a subset of patients after the first exposure to the causative agent or exposure to multiple agents that cause the same syndrome.⁴⁰ Finally, many of the clinical features are similar to those of other infectious diseases, such as adenovirus infection and scarlet fever.

A long list of discarded pathogens is all that remains after 30 years of searching for the aetiological agent of Kawasaki syndrome. Initially, standard microbiological methods to isolate pathogens from body fluids and

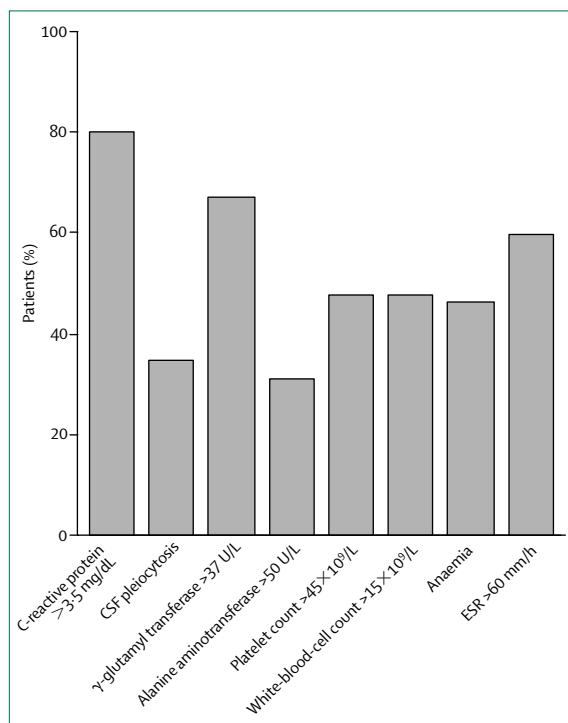


Figure 3: Laboratory findings in acute Kawasaki syndrome

Proportion of patients with laboratory abnormalities when investigated within 10 days of fever onset. Anaemia is defined as haemoglobin concentration <2 SD below the mean for age. Cerebrospinal-fluid (CSF) pleiocytosis is defined as >10 white blood cells per high-power field. ESR=erythrocyte sedimentation rate. Derived from references 19, 21, and 22, and JCB, unpublished.

animal inoculation of these specimens were used in attempts to isolate an agent.^{1,8} Later, molecular methods to detect agent-specific nucleic acid in samples from patients were used without success.⁴¹ The hypothesis

that bacterial toxins acting as superantigens could trigger the cascade of events that lead to Kawasaki syndrome has been widely debated.⁴² Most recently, a multicentre, prospective study detected no difference in the rates of isolation of superantigen-producing bacteria between patients with the syndrome and febrile controls.⁴³ However, in a subset of patients there was a difference in rates of isolation of bacteria producing toxins that cause clonal expansion of T cells bearing Vβ2 receptors. Other investigators have found evidence for an oligoclonal antibody response, suggesting a conventional antigen.⁴⁴

New molecular techniques in proteomics and nucleic acid detection might be useful in the search for the agent. Have any classes of microorganisms been overlooked in the search for the causative agent? Since most human infectious diseases arose from a zoonotic reservoir, perhaps we are overlooking such a clue in Kawasaki syndrome.

Pathology

Our understanding of the pathological changes of the vasculitis of Kawasaki syndrome has been impeded by the paucity of clinical material available for study. The low mortality rate coupled with primary involvement of medium-sized extraparenchymal muscular arteries, particularly the coronary arteries, which cannot be sampled during life, has precluded a comprehensive understanding of how the pathological changes in the vessel wall evolve. Although both Kawasaki syndrome and adult-type polyarteritis nodosa can cause coronary-artery aneurysms, the histopathology differs in important ways.⁴⁵ First, in Kawasaki syndrome there is a strong predilection for the coronary arteries. Second, the pattern of inflammation in Kawasaki syndrome involves striking oedema and infiltration of CD8-positive T cells and macrophages with little or no fibrinoid necrosis and few polymorphonuclear cells. Increased vascular permeability mediated by high concentrations of vascular endothelial cell growth factor (VEGF) could be the cause of the oedema in the vessel wall.⁴⁶⁻⁴⁸

The earliest pathological change in the vessel wall is the subendothelial accumulation of mononuclear cells, primarily T cells, monocytes, and macrophages (figure 5).⁴⁹ Transmural inflammation results when inflammatory infiltrates from the lumen and from the adventitia meet in the media. IgA-secreting plasma cells are also found in the vessel wall as the inflammation progresses.⁵⁰ Finally, there is destruction of the media and aneurysm formation. A role for matrix metalloproteinases (MMPs) in this process is suggested on the basis of high serum concentrations of these enzymes during acute Kawasaki syndrome and immunolocalisation of MMP9 and MMP2 in the arterial wall of the lesions.^{51,52} Autopsy studies of the arteries show thrombus formation with or without recanalisation, myointimal proliferation and thickening of the

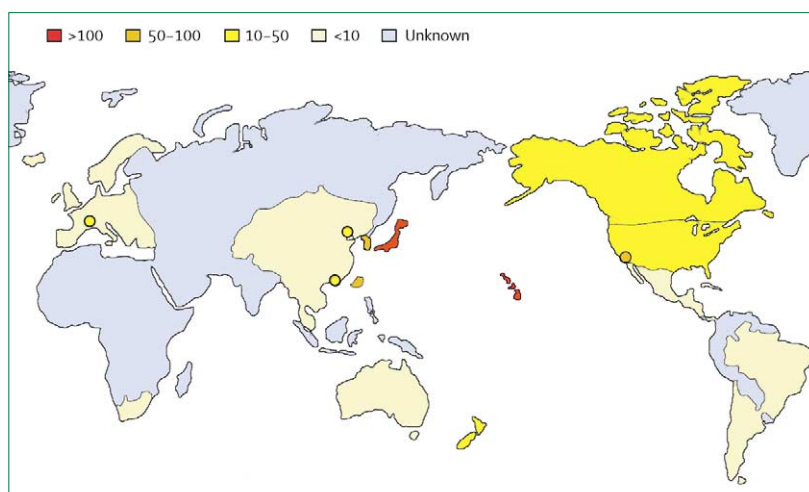


Figure 4: Cases of Kawasaki syndrome per 100 000 children younger than 5 years

Only Japan and Hawaii have rates higher than 100 per 100 000 children <5 years of age. The rate for Hawaii is for children of Japanese descent only. Areas with high endemic rates cluster around the Pacific basin. Los Angeles, CA, with a large Asian population, has the highest rate for the continental USA (67 per 100 000). Rates are based on data presented at the 7th International Kawasaki Disease Symposium, Hakone, Japan, 2001.³²

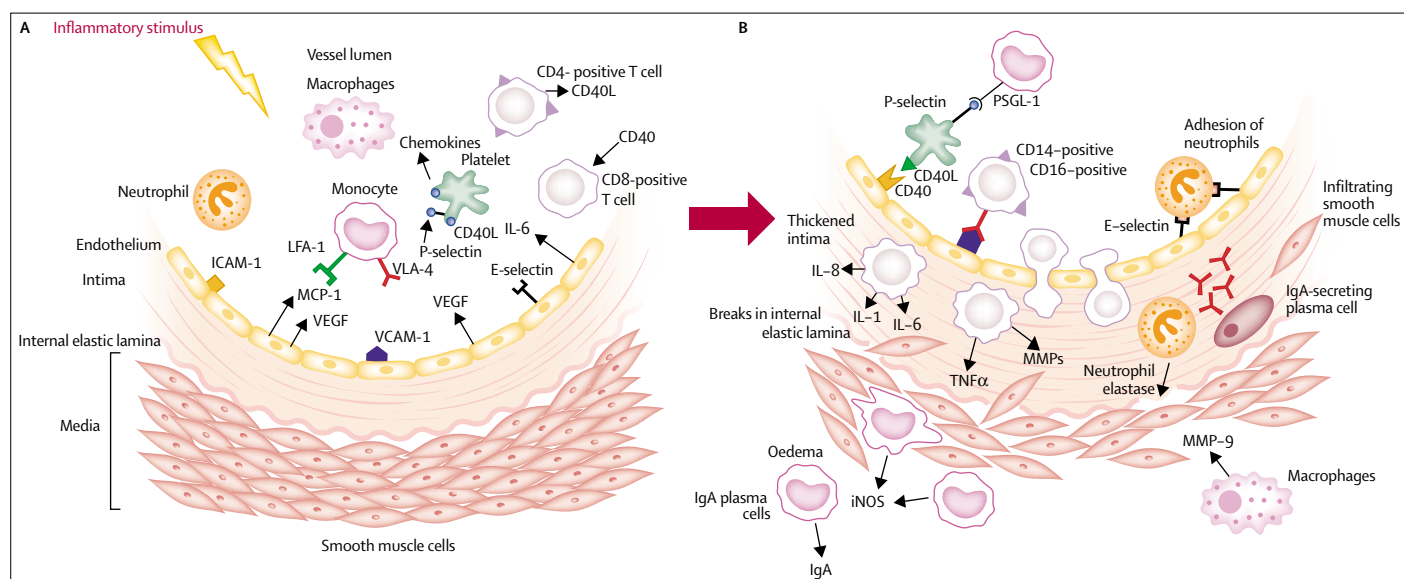


Figure 5: Proposed events in the evolution of vasculitis in Kawasaki syndrome

An unknown inflammatory stimulus sets in motion a cascade of events that in genetically predisposed individuals leads to inflammatory-cell infiltration, myointimal proliferation, destruction and thinning of the media, and aneurysmal dilation of the vessel. **A:** Initially, activated circulating mononuclear cells and platelets interact with endothelial cells that express surface adhesion molecules intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1), E-selectin, P-selectin, leading to margination of activated monocytes, platelets, and neutrophils. Activated endothelial cells also secrete monocyte chemoattractant protein 1 (MCP-1), which further attracts monocyte/macrophages, and vascular endothelial-cell growth factor (VEGF), which increases vessel permeability. **B:** Later, platelets adhere to the vascular wall elements. Inflammatory cells cross the endothelium, accumulate in the intima, and liberate proinflammatory molecules including interleukins (IL) 1, 6, and 8, tumour necrosis factor α (TNF α), and matrix metalloproteinases (MMPs). Neutrophils release neutrophil elastase, which damages the internal elastic lamina and contributes to destruction of the extracellular matrix. Activated macrophages secrete the inducible form of nitric oxide synthase (iNOS). Oligoclonal IgA-secreting plasma cells infiltrate into the media. Thickening of the intima results from infiltration and proliferation of smooth-muscle cells.

intima, and thinning and fibrosis of the media.⁵³ A recent study highlighted the accumulation of eosinophils in coronary microvessels.⁵⁴

A fundamental unresolved issue is the long-term effect of the acute, self-limited vasculitis of Kawasaki syndrome on the structure of the arterial wall in children with normal coronary arteries by echocardiography. Histological examination of tissues from children who die of unrelated causes after Kawasaki syndrome could address this issue, but capture of this rare population of children has proven difficult.

Immunopathogenesis

Activation of the immune system is a central feature of Kawasaki syndrome, and concentrations of many proinflammatory cytokines and chemokines, including tumour necrosis factor α (TNF α), interleukins 1, 6, and 8, are higher than normal during the acute phase of the disease.^{55–60} Activated monocytes/macrophages seem to have an important role in Kawasaki syndrome.^{61–63} These cells have been found in the vessel walls of patients who died⁶³ and in skin biopsy samples from patients in the acute phase of the disease.⁶⁴

The most promising new insight into the pathogenesis comes from the work of Rowley and colleagues who are investigating the role of the IgA immune response in patients with Kawasaki syndrome. They propose a respiratory portal of entry for the agent, which then elicits an oligoclonal IgA response.^{44,50,65} The prominence

of CD8-positive T cells infiltrating the tissues in these patients coupled with the presence of IgA-secreting plasma cells is similar to findings in children who have died from fulminant respiratory viral infection.⁶⁵ Inflammatory pulmonary nodules have been documented in two patients by autopsy and CT, lending further support to the theory of an inhaled pathogen.⁶⁶ The specificity of IgA-secreting plasma cells detected in autopsy tissues is currently under investigation.⁶⁷

Treatment

Initial treatment

In 1983, Japanese investigators reported that children with Kawasaki syndrome treated with IVIG had faster resolution of fever and developed fewer coronary-artery abnormalities than historical controls.⁶⁸ A multicentre, open-label, randomised trial in the USA showed that children treated with IVIG and high-dose aspirin had significantly faster resolution of fever and other inflammatory markers than children treated with high-dose aspirin alone.¹³ Moreover, the frequency of coronary-artery abnormalities among children with normal echocardiography at study entry was significantly lower for those assigned IVIG and aspirin than for those assigned aspirin alone (3% vs 15% 7 weeks after treatment). Subsequent studies confirmed and expanded the evidence supporting the use of IVIG as the mainstay of therapy for Kawasaki syndrome.^{14,69} A single dose of 2 g/kg IVIG infused over 10–12 h is now the standard

therapy in the USA, UK,⁷⁰ Europe, Australia, and many parts of Asia.

The trial that demonstrated efficacy of IVIG included only patients diagnosed and treated within the first 10 days of illness, with illness day 1 defined as the first day of fever. Subsequent studies have suggested that the benefit of therapy is greatest when it is given early in the illness. In one retrospective analysis, treatment with IVIG on or before day 5 of illness was associated with better coronary-artery outcomes and a shorter total duration of clinical symptoms.⁷¹ Similarly, an epidemiological survey of more than 5000 patients in Japan treated with 2 g/kg IVIG showed that patients treated before day 6 of illness had fewer cardiac complications at 1 month after onset of the syndrome than those treated later in the course of the illness.⁷² A European report described a possible benefit of IVIG when given later than 10 days after onset.⁷³ Any child with Kawasaki syndrome who has evidence of persisting inflammation, including fever or high concentrations of inflammatory markers with or without coronary-artery abnormalities, should be treated even if the diagnosis is made after illness day 10. Minor adverse reactions to IVIG vary with the specific product infused and include fever, chills, and hypotension. Administration of live virus vaccines (measles, mumps, and rubella, or varicella) should be deferred for at least 11 months after IVIG administration owing to reduced immunogenicity of the vaccine related to passive antibodies in the IVIG preparation.⁷⁴

The mechanism of action of IVIG remains unknown, although theories include cross-linking of FcγII and FcγIII receptors on macrophages, induction of immune inhibitory receptors, blocking of interaction between endothelial cells and natural killer cells, selective induction of interleukin-1-receptor antagonist and interleukin 8, binding to complement fragments, and provision of specific antibody to the causative agent or a toxin.^{75–78} In-vitro findings suggest that IVIG blocks endothelial-cell proliferation and synthesis of adhesion molecules, chemokines, and cytokines.⁷⁹

Aspirin has been used to reduce inflammation and to inhibit platelet aggregation in children with Kawasaki syndrome, although it has no effect on development of coronary-artery aneurysms.^{80,81} Whether other available non-steroidal anti-inflammatory agents might be less toxic and have a greater anti-inflammatory effect has not been studied. Currently, high doses of aspirin (80–100 mg/kg daily divided into four doses) are used in the acute inflammatory stage of the disease. Once the patient has been afebrile for 3–7 days, the dose of aspirin is decreased to a single daily dose of 3–5 mg/kg. This antiplatelet dose is continued for 4–6 weeks, until the concentrations of all inflammatory markers have returned to normal and no coronary-artery damage has been noted by echocardiography. A multicentre, randomised trial comparing initial treatment with IVIG and either low-dose or high-dose aspirin found a significantly higher

frequency of persistent or recrudescence fever with the low dose.⁸² Adverse effects of aspirin include gastrointestinal irritation and liver-function abnormalities. Because antipyretic doses of aspirin (40 mg/kg daily) in conjunction with influenza and varicella viruses have been epidemiologically linked to Reye's syndrome, immunisation against influenza may be prudent in patients who need long-term aspirin therapy.

Treatment of persistent or recrudescence fever

10–15% of children diagnosed with Kawasaki syndrome and treated with high-dose aspirin and 2 g/kg IVIG will have persistent or recrudescence fever.⁸³ Many studies have shown that children who do not become afebrile after a first dose of IVIG are at increased risk of developing coronary-artery aneurysms.⁸⁴ There have been no studies that have established the efficacy of any secondary therapy for this group of children. Clinicians should first reconsider the diagnosis of Kawasaki syndrome. If it is still believed to be the diagnosis, common practice is to give a second dose of IVIG (2 g/kg).⁸³ If fever persists, other options used successfully in small series of children include pulsed intravenous methylprednisolone (30 mg/kg for 3 days), cyclophosphamide plus prednisone, ciclosporin, plasmapheresis, and monoclonal antibodies to TNFα.^{85–89} Multicentre, comparative trials of steroids and of anti-TNFα therapy are in progress to establish the safety and efficacy of these agents in Kawasaki syndrome.⁹⁰

Treatment of cardiovascular complications

The aims of therapy in patients who develop coronary-artery aneurysms are to prevent thrombosis and the myointimal proliferation that leads to stenosis. Only anecdotal experience is available to guide the choice of treatment for these children. Low-dose aspirin (3–5 mg/kg daily) has been the mainstay of therapy for children with small to medium aneurysms (<8 mm). Use of other antiplatelet agents (eg, clopidogrel and ticlopidine) alone or with aspirin may be beneficial for some patients.⁹¹ Randomised trials are needed to establish the appropriate role of low-molecular-weight heparins, monoclonal antibodies against the platelet IIB/IIIA receptor, and warfarin in the long-term management of children with giant aneurysms.^{70,92}

Any treatment administered beyond the first dose of IVIG and aspirin should be considered experimental. The only way that we will learn how to treat children in whom IVIG fails and coronary-artery complications develop is to adopt the model used for studying cancer treatments in which children would be randomly assigned to different therapy protocols through a national registry.

Genetic influence

A genetic influence on disease susceptibility is suspected because Kawasaki syndrome is over-represented among Asian and Asian-American

populations. Furthermore, the frequency is higher than in the general population among siblings of an index case. In Japan, the relative risk for siblings of developing the syndrome is 10.⁹³ No sibling statistics are available for the USA or western Europe. The frequency of the disorder was two times higher than predicted in parents of children with Kawasaki syndrome, and the frequency of recurrent disease and cases in siblings was five to six times higher in these multigeneration families than in other families with Kawasaki syndrome.⁹⁴

There is growing recognition of Kawasaki syndrome pedigrees both in the USA and Japan.^{94–98} There have been attempts to link susceptibility to Kawasaki syndrome or disease outcome to allelic variations.^{99–109} To date, only small cohorts of children have been analysed in association studies in which the frequencies of the alleles of interest have been compared between Kawasaki syndrome and control individuals. The insufficient sample sizes in these studies preclude any general conclusions, and further studies are needed. The limitations of these studies include: a limited number of alleles in each study; the possibility of silent, undiagnosed cases in the control group (particularly in Japan, where the incidence is high); population stratification that leads to differences between the control and study populations (particularly in US studies, with a very heterogeneous population); and small sample size. Another approach to association studies is the transmission disequilibrium test, which detects preferential transmission of an allele from a heterozygous parent to the affected child. A transmission disequilibrium study of 260 families affected by Kawasaki syndrome in the USA and the UK is analysing 107 alleles representing 67 different genes involved in endothelial-cell function, lipid metabolism, platelet adhesion, and immune activation.¹¹⁰ Large-scale studies involving hundreds of families and sibling pairs from Japan and other countries will be necessary for full investigation of candidate alleles.

Cardiovascular complications and long-term sequelae

Large series of patients from Japan and North America have established the following features of the natural history of Kawasaki syndrome. Coronary-artery aneurysms occur as a sequela of the vasculitis in 20–25% of untreated children.¹¹¹ Other cardiovascular complications of the syndrome include myocarditis, pericarditis with effusion, and valvulitis, which occurs in about 1% of patients and most commonly involves the mitral valve.¹¹² Echocardiography is a sensitive and reliable method to detect coronary-artery aneurysms in the acute and subacute stages of the syndrome.^{113,114} Patients with no coronary-artery aneurysms detected by echocardiography during the acute and subacute phases are clinically asymptomatic at least 10 years later.¹¹⁵

About 20% of patients who develop coronary-artery aneurysms during the acute disease will develop coronary-artery stenosis¹¹⁵ and might subsequently need treatment for myocardial ischaemia, including percutaneous transluminal angioplasty, rotational atherectomy, coronary-artery stenting, bypass grafting, and even cardiac transplantation.^{116–119}

Although depressed myocardial function and abnormalities of left-ventricular contractility are common during the acute phase of Kawasaki syndrome,¹²⁰ myofilament destruction does not seem to be the major mechanism because cardiac troponin I concentrations are not raised.¹²¹ Instead, myocardial dysfunction secondary to cellular infiltration and oedema or circulating myocardial depressants (eg, proinflammatory cytokines) has been postulated.¹²²

Many studies have attempted to identify predictors of coronary-artery aneurysms.^{123–129} Consistent risk factors across these studies include persistent fever after IVIG therapy, low haemoglobin concentrations, low albumin concentrations, high white-blood-cell count, high band count, high C-reactive protein concentrations, male sex, and age under 1 year. Thus, laboratory evidence of increased inflammation combined with demographic features (male sex, age under 6 months or over 8 years) and incomplete response to IVIG therapy create a profile of a high-risk patient with Kawasaki syndrome.

To find out the long-term outcome for children after Kawasaki syndrome, the Japanese Ministry of Health has established a registry of about 6500 children with a history of the disorder, who are being investigated longitudinally.¹³⁰ Thus far, no excess mortality has been attributed to the syndrome in the late convalescent phase. No similar registry of patients has been established in the USA or Europe, where a-priori risk of atherosclerotic cardiovascular disease in adulthood is much higher than in Japan and different environmental, cultural, and genetic factors may influence the outcome after the coronary-artery vasculitis associated with Kawasaki syndrome.

Children with coronary-artery aneurysms in acute phase

The natural history of coronary-artery aneurysms depends on the size and shape of the aneurysm. The best prognosis is associated with fusiform aneurysms of less than 8 mm in diameter and the worst with giant aneurysms (>8 mm). In a longitudinal study over 10–21 years in Japanese children with coronary-artery aneurysms, Kato and colleagues noted regression of aneurysms in about 50%, stenosis in 20%, and persistence of aneurysms without stenosis in 40%.¹¹⁵ Of patients with giant coronary-artery aneurysms, roughly half developed stenosis or complete obstruction, which resulted in myocardial infarction in two-thirds of the patients. Thrombotic occlusion of aneurysms can occur owing to stagnation of flow and the sudden reduction of shear stress in the aneurysm.¹³¹ Coronary-artery stenosis

and hypodistensibility are potential long-term complications of aneurysm remodelling over time.¹³² A study in Japan comparing transthoracic echocardiography and selective coronary-artery angiography for detection of coronary-artery stenosis found that echocardiography had sensitivity of only 85% (right coronary artery) and 80% (left anterior descending) for detection of stenotic lesions.¹³³ Thus, patients must be assessed with imaging studies of the coronary arteries as well as functional assessments of ischaemia under stress conditions (panel 2).^{134–138} Patients with silent myocardial ischaemia documented by thallium-201 scintigraphy can have normal angiograms, so stress imaging is an important component of the long-term management of these patients.^{139,140}

A history of a clinical illness in childhood compatible with Kawasaki syndrome should be sought in all young adults presenting with myocardial infarction or sudden death. A questionnaire administered to adult cardiologists in Japan on myocardial infarction in young adults and a review of Japanese and US case reports suggest that coronary-artery aneurysms after Kawasaki syndrome can remain entirely silent until the third or fourth decade of life, when patients present with an acute cardiac event.^{11,12}

The question remains whether Kawasaki syndrome is a risk factor for accelerated atherosclerosis in adulthood. In a study of 20 adolescents with coronary-artery aneurysms after Kawasaki syndrome, measurements of intima-media thickness and carotid arterial wall stiffness by B-mode ultrasonography found thicker and less distensible carotid arteries in patients than in matched controls.¹⁴¹ In an autopsy study of six patients (aged 15–39 years) with coronary-artery aneurysms consistent with Kawasaki syndrome, histology of the non-aneurysmal arteries revealed thinning of the media and new thickening of the intima in seven of ten arterial segments examined.¹⁴² Arterial segments with aneurysms had a range of abnormalities including thrombosis, intimal thickening, foamy macrophage infiltration, and calcification.

Panel 2: Modalities for long-term follow-up of coronary-artery lesions

Structural imaging techniques

X-ray angiography¹¹⁵

Intravascular ultrasonography¹³⁴

Magnetic resonance angiography¹³⁶

Electron-beam CT¹³⁸

Functional imaging techniques

Dobutamine stress echocardiography¹³⁷

Transthoracic doppler ultrasonography¹³⁵

Positron emission tomography¹⁴⁴

Dipyridamole stress thallium-201 single-photon emission CT¹³⁹

Children without coronary-artery aneurysms in the acute phase

The clinical significance of the following findings in patients without coronary-artery aneurysms during the acute disease is uncertain: myocardial fibrosis on endomyocardial biopsy as long as 11 years after disease;¹⁴³ impaired vasodilatory capacity of coronary^{144–146} and peripheral arteries¹⁴⁷ as long as 15 years after Kawasaki syndrome; higher diastolic and systolic blood pressure, increased adiposity, and higher triglyceride concentrations than controls about 11 years after disease onset;¹⁴⁸ decreased global left-ventricular function at 2 years or later after Kawasaki syndrome as compared with baseline;¹⁴⁹ persistent aortic-root dilatation at least 1 year after acute Kawasaki syndrome with mild aortic regurgitation in 4% of the study population;¹⁵⁰ decreased fibrinolytic response to venous occlusion due to decreased release of tissue plasminogen activator at least 10 years after acute Kawasaki syndrome;¹⁵¹ and abnormal electrocardiograms in 10% of Japanese high-school students with a history of Kawasaki syndrome compared with 3% in students without a history of the syndrome (odds ratio 3.30 [95% CI 2.65–4.05]).¹⁵² Right axis deviation and incomplete right bundle-branch block accounted for 57% of the abnormalities in the Kawasaki syndrome group. The biological significance of these changes is unknown.

Thus, identification of the appropriate follow-up of these children is difficult because no clear picture has yet emerged of the potential sequelae of the syndrome without coronary-artery aneurysms. Autopsy studies of young adults who had Kawasaki syndrome in childhood without coronary-artery aneurysms and who subsequently die of unrelated causes will help to show whether the vasculitis leads to unique changes in the arterial wall or to accelerated atherosclerotic changes.

A registry and structured follow-up study should be established in each country, modelled after the Japanese registry, so that investigators can begin to collect data to address the unanswered questions about long-term outcome for these children. Improvements in non-invasive imaging techniques for functional assessment of the myocardium are needed.

Obstacles to success

Why in the 37 years since the first description of Kawasaki syndrome as a unique clinical entity has there not been better progress in elucidation of the nature of this disease? Some impediments may include the following. The lack of a clear aetiological agent has made the classification and thus the sources of research funding unclear. Is this disease the responsibility of agencies or institutes that fund cardiovascular research, rheumatological research, or infectious diseases? To obtain sufficient statistical power for research, expensive, complex, multicentre studies are necessary. Over the years, small, inadequately powered and

controlled studies that have been misleading have been published. Research has been hampered by difficulties in collecting clinical research samples from children. The lack of a diagnostic test has hindered understanding of the burden of disease in any given population, which in turn affects research priorities.

Conclusion

Although great strides have been made in the treatment of Kawasaki syndrome and in our understanding of the natural history of the disease, major questions remain unanswered. The extent to which the syndrome may eventually contribute to the burden of adult cardiovascular disease is of growing concern. Until a diagnostic test is devised, children will continue to be misdiagnosed and suffer preventable morbidity and mortality. Priorities for research should focus on devising a diagnostic test so that all children who need treatment can be identified. The ultimate goal of preventing Kawasaki syndrome must await the elucidation of the causative agent.

Conflict of interest statement

None declared.

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