Long-Term Outcome of Kawasaki Disease

Hideaki Senzaki, MD

Kawasaki disease was first reported in 1967 by Japanese pediatrician Tomisaku Kawasaki as an acute febrile syndrome mainly affecting the skin, mucosa, and lymph nodes. Although initially recognized as benign, this syndrome was subsequently acknowledged to have a serious complication of coronary artery aneurysm, and it has gained the worldwide interest of pediatricians and pediatric cardiologists. The importance of and interest in this disease can be seen in the existence of the unusual publication of the English translation of the first report in Japanese. Because Japan is the country where the disease was first observed and the largest numbers of new patients are diagnosed each year, researchers there have been making outstanding efforts to uncover the mystery of this disease. Scientists from other countries have also contributed greatly in this regard despite the underlying difficulties in conducting research due to the limited number of cases compared with Japan. The present review article covers such longstanding efforts and their fruits, with a special focus on the long-term outcome of Kawasaki disease. Although data on the epidemiology, origin, pathophysiology, and treatment of this disease are important for a better understanding of the outcome, they have been reviewed extensively by several previous publications. Nevertheless, key data on these topics are summarized briefly herein.

Overview of Kawasaki Disease

Epidemiology

Kawasaki disease is most prevalent in Japan and in children of Japanese ancestry. A neighboring country, Korea, has the second-largest number of patients, which indicates apparent racial factors in the origin of this disease. The most recent published data indicate that the annual incidence of Kawasaki disease in Japan is nearly 140 cases per 100,000 children younger than 5 years of age, which is approximately 10 to 20 times higher than that of the United States (≈17 cases per 100,000) and the United Kingdom (≈8 cases per 100,000). Administrative data in the United States also indicate a race-specific difference in the incidence, with the highest incidence rates noted in Americans of Asian descent, followed by blacks, Hispanics, and non-Hispanic whites, in that order. Table 1 summarizes other epidemiological features of Kawasaki disease.

Origin

Although the origin of Kawasaki disease remains unknown, the epidemiological features listed in Table 1 provide important clues regarding its cause. This aspect of the disease is well summarized in a review article by Burgner and Harnden. The striking age distribution, with male predominance and seasonal variation, and the endemic nature of the disease, with a clear epicenter and geographic spread, strongly suggest infection as the underlying cause of Kawasaki disease. The racial variability and the higher incidence in siblings of affected children suggest the important role of genetic factors in susceptibility to this disease. Environmental factors may also contribute to the development of this disease. Extensive research has thus far failed to identify a microbiological cause. A superantigen theory has been proposed and attracted great interest, but no convincing evidence supporting this hypothesis has been established. Recent investigations appear to support an alternative theory that immune response in Kawasaki disease is oligoclonal (as observed in response to a conventional antigen) rather than polyclonal (as observed in response to a superantigen). Using synthetic IgA antibodies, Rowley et al demonstrated the presence of an antigen-driven IgA response in the inflamed tissues of acute Kawasaki disease and noted that the antigen targeted by the IgA response is present in cytoplasmic inclusion bodies in the ciliated bronchial epithelium. Identification of nucleic acids and proteins in the inclusion bodies could provide important information about the causative agent for Kawasaki disease. Studies examining the genetic determinant(s) of susceptibility to Kawasaki disease have been performed but have not yielded conclusive results. International collaborative studies using standardized phenotypic definitions and large samples of patients would facilitate the delineation of the genetic background of patients affected by Kawasaki disease. Given the mounting data on its epidemiology, pathophysiology, and treatment, the consensus that Kawasaki disease is due to 1 or more widely distributed infectious agents that evoke an abnormal immunologic response in genetically susceptible individuals still appears to be valid, and it appears that the day of discovery of the exact cause of Kawasaki disease, including genetic factors, is close at hand.

Pathophysiology

The undetermined cause of Kawasaki disease leads directly to the lack of a suitable animal model, which hinders the study...
of the pathophysiology of this disease. The inability to obtain samples of affected tissues in living bodies and the limited availability of autopsy specimens are further obstacles to the study of the pathophysiology of this disease. Despite such difficulties, extensive efforts have been made to uncover the pathophysiology of Kawasaki disease. Briefly, mononuclear cells and platelets activated by a yet-unknown inflammatory stimulus (possibly by infectious agents) interact with vascular endothelial cells, which in turn express several adhesion molecules and a family of selectins, which further attracts inflammatory cells (monocytes, neutrophils, and macrophages), and induce vascular endothelial growth factor, which increases vascular permeability. The inflammatory cells then infiltrate the intima and media with excess production of proinflammatory cytokines, matrix metalloproteinases, and neutrophil elastase. The latter 2 appear to be intimately involved in the destruction of arterial wall, which leads to aneurysm formation and intimal thickening due to proliferation of migrated smooth muscle cells through the damaged internal elastic lamina. Importantly, IgA-secreting plasma cells are also found in the vessel wall during the inflammatory process, a finding that potentially links pathophysiology with cause.

### Treatment of Kawasaki Disease During the Acute Stage

Treatment is the only area in Kawasaki disease in which evidence derived from randomized clinical trials is established. Studies by Newburger et al. contributed greatly to this achievement, and a single infusion of high-dose (2 g/kg) γ-globulin is currently the standard therapy for the acute stage of Kawasaki disease. Antifibrinolytic doses of aspirin are also recommended in conjunction with γ-globulin, although there is no evidence of its efficacy to prevent the development of coronary abnormalities. Newburger et al. also conducted an important study recently to address the longstanding controversy about the efficacy of steroid therapy and demonstrated that methylprednisolone, administered at a single dose of 30 mg/kg immediately before intravenous γ-globulin, does not improve coronary outcome or reduce the total number of days of fever and of hospitalization. However, the efficacy of other steroid regimens for primary treatment or that of steroid rescue therapy for children who are resistant to conventional primary treatment remains to be elucidated in future prospective studies. Other treatment options that are potentially beneficial are listed in Table 2, but the efficacy of these treatments has not yet been confirmed.

### Outcome of Kawasaki Disease

An expert panel of the American Heart Association has recently listed Kawasaki disease as a disease with a high-risk pediatric setting in which clinical cardiovascular events could occur in childhood and very early adult life and has presented a scientific statement, endorsed by the American Academy of Pediatrics, that particularly emphasized the importance of cardiovascular risk reduction in patients with this disease. Although a full picture of the outcome of Kawasaki disease remains unclear, there is no doubt that coronary lesions are the predominant determinants of its outcome. There are also other cardiovascular sequelae that could potentially affect the outcome. The following section will discuss important aspects related to the outcome of this disease.

### Morphological (Angiographic) Changes in Coronary Artery Lesions

The foundation work of Kato et al. followed by several other studies that examined the angiographic outcome of coronary aneurysms in Kawasaki disease, has led to the current understanding that coronary artery lesions change markedly with time into a variety of forms. As outlined in Figure 1, these lesions may regress, stay unchanged, progress to stenotic or obstructive lesions with or without recanalization/collateral vessels, and, on very rare occasions, rupture, develop new lesions, or expand. These changes show apparent size and time dependency. Small lesions (<5 mm) have a higher likelihood of angiographic resolution and rarely progress to stenotic lesions. Large coronary aneurysms show a wide range of remodeling processes, with virtually all of the changes described in Figure 1. Regression and obstruction typically occur within the first 2 years after onset of the disease, whereas stenotic changes may occur after a longer period of time. Calcifications generally develop 5 or more years after disease onset and become more noticeable after 1 decade. There is also a crossover of the changes in the

### Table 1. Epidemiological Features of Kawasaki Disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age-specific distribution</td>
<td>&gt;80% of cases occur between ages 6 mo and 4 y</td>
</tr>
<tr>
<td>Sex predominance: male patients</td>
<td>outnumber female patients (male/female ratio: 1.2 to 1.7)</td>
</tr>
<tr>
<td>Seasonal variation: predominant</td>
<td>season varies in different countries (winter-spring in temperate climates)</td>
</tr>
<tr>
<td>Epidemics:</td>
<td>epidemics have been reported in many countries</td>
</tr>
<tr>
<td>Geographic distribution:</td>
<td>there is geographic spread</td>
</tr>
<tr>
<td>Rate of recurrence:</td>
<td>as low as 1% to 3%</td>
</tr>
<tr>
<td>Familial history: proportion of</td>
<td>cases with positive family history is increasing in Japan</td>
</tr>
<tr>
<td>Incidence rate in siblings:</td>
<td>2.1% within 1 year after onset of the first case</td>
</tr>
<tr>
<td>Occurrence in twins:</td>
<td>risk of occurrence in twins is ~13%</td>
</tr>
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</table>

### Table 2. Potentially Beneficial Treatments for Kawasaki Disease

<table>
<thead>
<tr>
<th>Agents</th>
<th>Potentially Beneficial Actions</th>
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<tr>
<td>Abciximab</td>
<td>Modulation of vascular remodeling</td>
</tr>
<tr>
<td>Urinastatin</td>
<td>Neutrophil elastase inhibition</td>
</tr>
<tr>
<td>Pentoxifylline, infliximab</td>
<td>Anti-TNF-α</td>
</tr>
<tr>
<td>Cyclosporin A, cyclophosphamide</td>
<td>Immunomodulation</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>Removal of substances causing vasculitis</td>
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Anti-TNF-α indicates anti-tumor necrosis factor-α.
later phase, as illustrated in Figure 1. Notably, recent studies have reported that new dilated or expanding lesions are also found in approximately 1% to 3% of patients with coronary aneurysms, with the time for detection of these new lesions ranging from approximately 2 to 20 years (median years). Coronary rupture occurs primarily as a result of a very rapid progressive dilation of aneurysm during the acute phase, but an intriguing case report also demonstrated that this could happen even in the late phase (>20 years after disease onset).

**Histopathology and Mechanisms**

Histopathology is one of the most difficult research areas in this condition because of the difficulty in obtaining tissue samples, and most such work has been performed in Japan on autopsy or surgical cases. The most prominent histopathological feature of late coronary artery lesions in Kawasaki disease is intimal thickening, which consists of extracellular matrix and smooth muscle cells that probably migrated through the disrupted internal elastic lamina. The degree of intimal thickening varies from 1 lesion to another, with progressive localized stenosis in the extreme case. Intimal thickening can be found in almost all forms of lesions, including regressed coronary arteries, and even in some echocardiographically normal coronary arteries. Occluded aneurysms are usually filled with organized thrombi but are characterized in some cases by accumulation of extracellular matrix or extensive intimal hyperplasia. Recanalized vessels, which are often observed in the occluded aneurysm and which typically take the form of "arteries in the artery," develop in the layer of deep intima adjacent to the media and have a thick smooth muscle cell layer that is surrounded by a layer of numerous microvessels. Representative photographs of histopathological changes together with other features of lesions of localized stenosis and recanalization after occlusion are displayed in Figure 2.

Intravascular ultrasound (IVUS) provides useful information about coronary status by linking morphology and histology. The intima of a normal coronary artery in children typically appears on IVUS as a thin, smooth lumen-vessel wall interface, the width of which is not measurable. With intimal proliferation, the intimal layer can be demonstrated by IVUS as a dense echo with a measurable symmetrical or asymmetrical thickening of the layer. This change is observed in angiographically regressed aneurysms with normal lumen diameters or sometimes even in angiographically normal coronary arteries, as well as stenotic lesions, consistent with the histopathological features of coronary lesions. A study by Tsuda et al further demonstrated that the initial diameter of the coronary artery lesion, particularly that exceeding 4 mm, as assessed by IVUS, can predict future intimal thickening with high sensitivity and specificity. Calcification can be detected by IVUS with greater sensitivity than by angiography as a line of very strong, bright echocardiographic signal with ultrasound shadowing.

Understanding the mechanisms of coronary artery remodeling, especially neoangiogenesis and progressive localized stenosis as a result of intimal proliferation, is particularly important for the design of future therapeutic modalities aimed at reducing the risk of late sequelae of this disease. A series of elegant studies using the most recent advances in immunohistochemical technology were conducted by Suzuki et al and provided important information in this regard. They demonstrated that the area of smooth muscle cells in the thickened intima at stenotic sites and at recanalized new vessels in formalin-fixed specimens from patients with Kawasaki disease expresses a variety of vascular growth factors, including transforming growth factor-β, platelet-derived...
growth factor A, basic fibroblast growth factor, and vascular endothelial growth factor. Platelet aggregation and increased laminar shear stress, both of which are strongly suspected to exist in the aneurysm, are known to activate transforming growth factor-β and transforming growth factor-β, together with basic fibroblast growth factor and platelet-derived growth factor A, induces the accumulation of extracellular matrix and promotes migration and proliferation of smooth muscle cells in injured vessels. Furthermore, vascular endothelial growth factor and basic fibroblast growth factor have been shown to play pivotal roles in promoting angiogenesis in experimental and clinical studies. Thus, these data strongly suggest that growth factors play important roles in the active remodeling process of coronary arteries in Kawasaki disease and that the process is considerably different from that of adult atherosclerosis. One laboratory has examined coronary artery remodeling from the viewpoint of vascular senescence. These researchers studied the tissues of coronary aneurysms obtained from children who underwent surgery for coronary artery bypass and reported that coronary aneurysms in children with Kawasaki disease exhibit the phenomenon of vascular senescence, similar to that observed in adult atherosclerotic plaques, such as decreases in endothelial nitric oxide synthase and increases in β-galactosidase activity, vascular adhesion molecules, or chemokines. Although these studies have provided important information, further studies are required to explore the mechanism of coronary arterial remodeling in Kawasaki disease patients.

Function of Coronary Arteries
Adopted atherosclerotic coronary arteries exhibit functional abnormalities in addition to morphological and histopathological abnormalities. Accumulating evidence also suggests abnormal function of coronary arteries in Kawasaki disease. For example, studies examining the function of epicardial coronary arteries, which are vulnerable to aneurysm formation, have shown that both endothelium-dependent and -independent vasodilatory responses are decreased in patients with aneurysms and even those with regressed aneurysms. Patients could also suffer from impaired coronary microcirculation caused by the decreased myocardial flow reserve induced by ATP. On the other hand, there are conflicting data regarding coronary physiology in patients free of documented coronary artery dilation: Some showed normal epicardial endothelial-dependent and -independent vasodilatory responses, whereas others showed impaired endothelial function in epicardial arteries but normal function of resistance arteries, and still others showed abnormal function in resistance arteries. Thus, the currently available data appear to suggest that coronary function could be impaired in some patients with history of Kawasaki disease, but data are still controversial, and this area requires further investigation in future studies.

Treatment of Coronary Artery Lesions
Once the coronary artery lesions develop, the prevention of ischemic events is a major challenge and goal of any treatment. Progress in surgical and catheter intervention
techniques has contributed greatly to better management of patients with Kawasaki disease who are at high risk of coronary events.

Coronary artery bypass grafting was first conducted with autologous saphenous vein grafts by a Japanese cardiac surgeon, Dr. Kitamura, in 1974. Subsequent studies showed poor patency of the vein graft and led to the use of internal thoracic artery grafts since the early 1980s. A nationwide Japanese survey conducted in 2002 indicated a favorable outcome for internal thoracic artery grafts placed in patients older than 12 years, with patency rates at 1, 5, and 15 years of 95%, 91%, and 91%, respectively. On the other hand, the results for grafts used in patients younger than 12 years were less satisfactory, with the respective values being 93%, 73%, and 65%. A recent analysis has demonstrated that the use of balloon angioplasty for anastomotic stenosis greatly improves graft patency for young children (<12 years of age), raising the 10-year patency rate to ~94%. Because competitive flow from the native coronary artery appears to be an important factor causing progressive anastomotic stenosis, the application of an appropriate operative indication (ie, evidence of ischemia or severe stenosis >75%) might further contribute to the achievement of better graft patency. Studies have also demonstrated that a graft with good patency serves sufficiently as a source of blood flow to meet myocardial oxygen demand during exercise.

Catheter intervention techniques began with percutaneous transluminal coronary balloon angioplasty in the early 1990s. Subsequently, stent implantation and percutaneous transluminal coronary rotational ablation have been applied to lesions that were difficult to manage by PTCA. Intervention-based treatment has flourished in Japan, and guidelines for catheter intervention in Kawasaki disease have been published by the Research Committee of the Japanese Ministry of Health, Labor, and Welfare, although these guidelines were based on experience rather than on clinical trials. The guidelines are also cited in the American Heart Association statement for diagnosis, treatment, and long-term management of Kawasaki disease. According to the guidelines, catheter intervention should be considered in patients with ischemic symptoms, patients without ischemic symptoms but with ischemia on stress tests, and patients with ischemia but with >75% stenosis in the left anterior descending coronary artery that could potentially result in sudden cardiac death. The most important idea that should be kept in mind when selecting catheter intervention is that coronary artery lesions resulting from Kawasaki disease are different from those of adult atherosclerosis in that the arteries may become time-dependently stiffer, as best characterized by calcified lesions. Thus, detailed evaluation of lesion status before intervention is important for safe and effective treatment. PTCA is recommended for lesions in small children before the development of calcification (usually <6 years after onset). Older children without or with mild calcification are the best candidates for stent implantation. Percutaneous transluminal coronary rotational ablation is the treatment of choice for severely calcified lesions. In addition, a recent case report suggested the potential role of covered stents for the treatment of large aneurysms to prevent thrombotic occlusion or progression of stenosis by achieving a more laminar blood flow pattern. The outcome of these catheter interventions in Kawasaki disease have begun to be reported recently. Ishii et al reported the short-term to midterm consequences of catheter intervention performed for 23 stenotic lesions in 22 patients. With the procedures selected on the basis of the above-mentioned criteria, they reported an overall immediate success rate as high as 91%. Restenosis developed in 2 lesions within 6 months after PTCA, and 13% of all patients followed up developed restenosis between 5 and 8 years after intervention. Thus, based on the currently available data, catheter intervention for coronary lesions of Kawasaki disease potentially could be the sole therapy or could be used in conjunction with surgical revascularization: a bridge to surgery or repair for postoperative stenosis in the graft.

There are also lesions in which catheter or surgical intervention procedures are not feasible, such as completely occluded arteries with collateral circulation. A novel therapeutic approach to these lesions may be heparin/exercise-induced angiogenic therapy, as reported by Tateno et al. On the basis of clinical and laboratory findings that heparin promotes angiogenesis under myocardial ischemia, they examined the effects of twice-daily exercise along with intravenous injection of heparin on myocardial perfusion in 7 Kawasaki disease patients with totally occluded coronary arteries and stress-induced myocardial ischemia in the collateral-dependent areas. After 10 days of heparin and exercise treatment, they reported a dramatic improvement in myocardial perfusion. The results warrant both further clinical trials of this therapy and trials of other angiogenic therapies in Kawasaki disease. Because experience with the above intervention therapies is limited, and because follow-up data are relatively short-term, accumulation of evidence by prospective, multicenter clinical trials is essential to establish the benefits of each therapy and the indication for and selection of the best procedural technique.

Complications Other Than Coronary Artery Lesions

Valvular insufficiencies, particularly of mitral or tricuspid valves, are often observed in the acute phase of Kawasaki disease due to valvulitis or myocarditis-induced myocardial dysfunction, regardless of coronary involvement. These lesions mostly disappear with the resolution of acute illness, but a very small group of the lesions persist and progress. There is also late-onset aortic or mitral insufficiency caused by thickening or deformation of fibrosed valves, with the timing ranging from several months to years after the onset of Kawasaki disease. Some of these lesions require valve replacement. The incidence and outcome of valvular diseases in the high-dose γ-globulin era remain to be elucidated, and such information is important particularly for refining the follow-up protocol of Kawasaki disease (discussed later).

Another issue that raises concerns is vascular abnormalities other than those involving coronary arteries. Several reports indicated abnormal changes in systemic vascular physiology in Kawasaki disease patients with persistent or regressed
coronary lesions, including increased wall thickness and decreased distensibility of carotid arteries\textsuperscript{131,132} and increased stiffness of central and peripheral arteries with enhanced wave reflections.\textsuperscript{132–134} Patients with Kawasaki disease free of coronary involvement have been reported to have abnormal endothelium-dependent brachial artery reactivity\textsuperscript{135} and stiff conduit arteries, as demonstrated by high pulse-wave velocity\textsuperscript{133,134} although this finding remains controversial.\textsuperscript{137} In addition, children with Kawasaki disease, with or without coronary artery complications, may have a more adverse cardiovascular risk profile, such as high blood pressure, obesity, and abnormal serum lipid profile.\textsuperscript{132,133,138} Whether these abnormalities predict clinically relevant morbidities awaits future investigation.

**Follow-Up and Future Recommendations**

The American Heart Association and American Academy of Pediatrics provided recommendations and guidelines for follow-up of patients with Kawasaki disease by stratifying the future risk of cardiovascular events on the basis of the status of coronary artery lesions.\textsuperscript{73} The Japanese Circulation Society\textsuperscript{139} and London Kawasaki Disease Research Group\textsuperscript{140} also presented their own guidelines. These guidelines are in agreement with the follow-up of patients with large aneurysms (usually defined as ≥6 mm) who are at high risk for developing stenosis and myocardial ischemia/infarction. These patients require aggressive anticoagulation with lifelong follow-up, including stress tests and coronary angiography. Magnetic resonance imaging angiography or multislice spiral computer tomography may be better alternatives to catheter-based angiography to less invasively check the morphological status of coronary arteries.\textsuperscript{139,141}

Patients with the second-highest risk for cardiovascular events are those who have persistent but smaller aneurysms or regressed large aneurysms. Morphological (IVUS), functional, and histopathological data appear consistent in that these vessels are not entirely normal, even if they look normal on angiography or echocardiography. Although clinical evidence is scant, all the guidelines mentioned above recommend long-term follow-up of this group. Recent case reports of 2 young adult patients with regressed aneurysms who developed acute coronary syndrome >20 years after the onset of disease add support to this notion.\textsuperscript{142}

There is ongoing controversy about the appropriate follow-up protocol for those patients without evidence of coronary artery lesions. Patients with transient coronary artery ectasia may also be included in this group. Establishment of a follow-up protocol (including discontinuation of follow-up) for these patients is in a sense as important as that for patients with cardiac complications, because these patients constitute the majority of patients with a history of this disease (>80%).\textsuperscript{4,5,74} The coronary arteries of this group of patients are not necessarily normal, but this remains controversial. In addition, there is concern about late-onset valvular heart disease and about an abnormal systemic arterial bed that may carry a risk for future cardiovascular-cerebral events; however, there is no clinical evidence that indicates that these patients encounter cardiovascular-cerebral events earlier or more frequently than expected relative to the general population. Analysis of 6576 Japanese patients with Kawasaki disease enrolled in a nationwide survey from 1982 to 1992 revealed no difference in mortality rates between the general population and these patients, especially those free of cardiac complications.\textsuperscript{141} In addition, such patients rarely showed abnormal findings on routine, outpatient-based examination, such as electrocardiography or echocardiography, during follow-up after acute illness.\textsuperscript{5,74,144,145} A reasonable compromise that balances a bottom-line consensus (the fate of these patients must be monitored) with medical economics (cost-effectiveness) and burden on the patients and their families may be to have patients keep an information card that describes their past history of Kawasaki disease and contains data related to acute illness, as proposed by the Japanese Association of Kawasaki Disease.\textsuperscript{143} The establishment of a registry for Kawasaki disease in each country is also desirable to help collect meaningful data.

Pregnancy is a general issue of concern whenever female patients with diseases predominantly affecting childhood grow into adulthood. This issue is of particular importance in Kawasaki disease, because pregnancy and parturition potentially increase the risk of myocardial ischemia or infarction due to significant changes in coagulability and hemodynamics and/or labor-related cardiac load. After the appearance of several case reports,\textsuperscript{146–149} the results of a Japanese nationwide survey on the current status of pregnancy and delivery in patients with coronary aneurysm or stenosis have been reported recently.\textsuperscript{150} Among 46 deliveries of 30 patients identified, there were no cardiac events irrespective of the mode of delivery (vaginal or cesarean) or the use of anticoagulation therapy (aspirin or heparin). However, these data do not provide any definitive information on this issue, and future prospective trials need to address the appropriate management of this population.

Changes in female hormones associated with menopause are another issue of concern specific to female patients with Kawasaki disease. The adverse effects of menopause on cardiovascular morbidity and mortality have well been established.\textsuperscript{151} How menopause affects the outcome of female patients with Kawasaki disease is an issue that should not be overlooked in future follow-up.

**Summary**

Almost 40 years have passed since the first description of Kawasaki disease, but the full picture of the outcome remains hazy, including the fate of echocardiographically normal coronary arteries, valvular diseases, and systemic arteries, as well as coronary aneurysms. Furthermore, the long-term prognosis of patients who receive intravenous γ-globulin and other therapies must be determined. In the meantime, continuing collaborative efforts among various centers around the world will help define the optimal management of patients. Such efforts should also help uncover the causative mechanism(s), which should contribute to the improvement of treatment strategies and even the prevention of this disease.

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References


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