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Kawasaki Disease at 50 Years

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IMPORTANCE Kawasaki disease (KD) is the most recognized vasculitis of childhood. The condition's characteristic high fever, rash, mucositis, conjunctivitis, lymphadenopathy, and extremity changes are superficially unexceptional, and resolve spontaneously within a mean of 12 days. It is the acuity and the potential for life-changing damage to the coronary arteries that distinguish KD from conditions that mimic it and exemplify the unique aspects and challenges of vascular inflammation in children.

OBSERVATIONS Although KD is an orphan disease, its role as a leading cause of acquired heart disease in children has led to significant efforts to determine its etiology, optimize diagnosis, and customize treatment according to individuals' needs. The result is that KD can now be controlled without sequelae in more than 95% of cases. Furthermore, advances in stratifying patients according to measurable risk factors allow therapy to be personalized in increasingly effective ways. High-risk patients, such as infants younger than 6 months, those with early evidence of coronary artery dilatation, and those with extreme abnormalities in laboratory test results, are often identified at presentation. This early identification allows them to be treated with corticosteroids in addition to intravenous immunoglobulin to improve their outcomes. Children with similar findings on laboratory tests and echocardiography may be treated based on algorithms for managing "incomplete KD" despite falling short of fulfilling classic diagnostic criteria. Children who do not respond to intravenous immunoglobulin are the focus of trials to minimize the duration of inflammation and thereby protect their coronary arteries in ways never before considered.

CONCLUSIONS AND RELEVANCE Kawasaki disease is a hybrid condition at the junction of infectious diseases, immunology, rheumatology, and cardiology. Rather than being left an orphan disease, KD is bringing disciplines together to identify its genetic, pathophysiological, and hemodynamic features. In turn, this work promises to shed light on many other inflammatory conditions as well.

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In the 50 years since Tomisaku Kawasaki first reported a new mucocutaneous lymph node syndrome in Japanese children,[1,2] much has been learned about diagnosing and treating the now eponymously named disease. Nevertheless, progress has been double-edged, for Kawasaki disease (KD) has become a leading cause of cardiac morbidity in developed countries, yet also the beneficiary of one of the most cost-effective therapies of any pediatric condition. This review provides an update on the current state of knowledge of KD as well as some of the more active areas of investigation.

Kawasaki disease is an acute, self-limited vasculitis that affects small- and medium-sized vessels; initially, it was regarded as just another self-limited pediatric exanthema. Recognition of the link between the clinical syndrome and potentially severe cardiac complications[3] greatly increased interest in KD. The disease subsequently has been reported in more than 60 countries,[4] and, for greater than 30 years, KD has been responsible for more cases of acquired heart disease among children in Europe, Japan, and the United States than any other condition.[5] Although Kawasaki's original diagnostic criteria remain intact, modifications, algorithms, and risk scores have changed the way that KD is evaluated, treated, observed, and investigated. In many ways, these dueling aspects of KD offer a lens for viewing the last half century's transition of modern medicine from clinical observation to molecular genetics and personalized treatment.

Observations

History

Early descriptions of conditions now recognized to be KD date back at least to the end of the 19th century.[6] An invariably fatal inflammatory vasculopathy primarily affecting young boys, known as *infantile polyarteritis nodosa*, likely represents extreme cases of the same disorder.[7] Various theories have attempted to explain the emergence of KD in the late 20th century, including the arrival of a new infectious agent, environmental changes, or simply increased awareness as the prevalence of scarlet fever decreased.[8] In any case, increasing awareness of KD and the ability to noninvasively monitor

coronary artery changes with echocardiography have given KD notoriety disproportionate to its relative rarity.

Epidemiologic Factors

Kawasaki disease most commonly affects children between ages 6 months and 5 years, and rarely occurs beyond childhood.[9] Boys are affected 50% more often than girls, and the overall number reported internationally is increasing, at least partially owing to the development of criteria for identifying children without clear signs of KD who nonetheless are at increased risk of developing cardiac sequelae ("incomplete KD"). Incidence varies by race/ethnicity; in the United States, children of Asian and Pacific Islander descent have the highest rates of hospitalizations associated with KD, followed by African American, Hispanic, and white children.[10] This finding is consistent with the higher incidence noted in the Eastern hemisphere. In Japan and Taiwan, active surveillance of KD records a per capita incidence 10- to 20-fold higher than in the United States.[11]

Histopathologic Findings

The histopathologic findings of KD most closely resemble those of polyarteritis nodosa, although there are significant differences in the cellular infiltrate, evolution, and healing of involved arteries. An early article described 20 autopsy cases with KD and the progression of lesions based on the duration of illness. Initially, affected children demonstrated perivasculitis and vasculitis involving vessels of all sizes.[12] Evolving arteritis led to destruction of the internal elastic lamina, with formation of aneurysms and associated thrombi. Healing followed, marked by regression of inflammation and evidence of granulation tissue in the major coronary arteries, culminating in scarring and stenosis of the arteries owing to myointimal proliferation. Cardiac tissue also showed evidence of myocardial fibrosis, coagulation necrosis, and endocardial fibroelastosis. Treatment with intravenous immunoglobulin (IVIG) likely alters the timing and details of this process, although the initial neutrophilic predominance of the vascular infiltrates, subsequently switching to a primarily lymphocytic inflammation with small numbers of plasma cells and eosinophils, does not vary. The appearance of macrophages in the vascular infiltrate is apparently unique to KD.[13] In addition to the coronary arteries, other sites of involvement include the renal, axillary, hepatic, iliac, mesenteric, and peripancreatic arteries.

Pathophysiological Findings

The 50 years since Kawasaki's seminal report have not yielded the cause of KD, but they have allowed researchers to explore a possible association between KD and most major medical advances of the last half century. The result is theories of pathophysiological causes that generally fall into 4 major categories: infectious agents, environmental triggers, immunologic aberrations, and genetic predisposition.

Based on the similarity of KD to other pediatric febrile exanthems, the most immediate and persistent impulse has been to seek an infectious cause. This approach is supported by the many features of KD that are typically associated with infections: KD tends to preferentially affect boys, to cluster in the winter and spring, to be most severe during the first year of life (as maternally acquired antibody levels reach a nadir), and to have epidemics originating at a geographical epicenter every few years.[14] The result has been hundreds of reports describing cohorts of children who showed serologic or culture evidence of infection by a variety of specific pathogens. Purported causes of KD have included various bacteria,[15,16] bacterial toxins,[17] and viruses.[18] In all cases, however, attempts by other groups to reproduce the findings have been unsuccessful. Similarly, screening patients with universal prokaryotic primers[19] and analyzing the antibody repertoire of immunoglobulin A–secreting plasma cells infiltrating the coronary arteries of children who died of KD have failed to identify a causative pathogenic organism.[20]

Environmental factors also have been proposed as the triggers of KD. First among these suggestions was mercury, based on the observation that acrodynia shares many features with KD.[21] The frequent association between KD and atopy, particularly atopic dermatitis, fed a search for a common immune susceptibility or trigger.[22] This initially led to suspicions that dust mites and rug shampoo might trigger KD, while a 10-year retrospective study in Kanagawa, Japan, spawned the proposal that cumulative pollen exposure might trigger KD.[23] More recently, analysis of seasonal variations and epidemics of KD concluded that cases are often linked with large-scale wind currents from central Asia, suggesting an airborne trigger carried in the troposphere.[24] Despite their plausibility, these and many other theories have not been independently confirmed.

The striking inflammation, leukocytosis, and lymphopenia of children with KD, accompanied by evidence of high levels of proinflammatory cytokines,[25] have led to a search for immunomodulatory or autoimmune causes. Despite exhaustive cataloging of phenomena reflecting the inflammation of KD, no coherent pathogenic model can account for the development and evolution of KD. Most recently, several groups have examined a potential role of regulatory T cells in the pathogenesis of KD. A Korean group reported that the number of CD4+CD25+ FoxP3+ T cells is decreased during the acute febrile phase of KD, rising after treatment with IVIG and thus offering a plausible mechanism of its effect in KD.[26] Guo et al[27] found increased levels of interleukin 17 (IL-17) and IL-6 in children with KD compared with febrile controls, as well as increased T regulatory cells after treatment with IVIG. At present, it is difficult to know whether these and associated findings are simply epiphenomena or true markers of pathogenic events in KD.

As early as 1989, a Japanese group found a more than 10-fold increased risk of KD in family members, and a 50- to 100-fold increase in twins.[28] This finding suggested that genetic predisposition was a risk factor for KD; next-generation sequencing has allowed identification of multiple polymorphisms reported to confer an increased risk of developing KD in various populations. Highlighted genes include T and B cell survival factors, major histocompatibility complex class I chain-related gene B and some major histocompatibility complex haplotypes, leukocyte recruitment factors, and modulators of vascular function.[29] Despite painstaking efforts, no single genetic marker associated with KD can account for even 1% of disease susceptibility.

The number and divergent implications of these efforts to find the cause of KD have led many researchers to conclude that KD, like many inflammatory disorders, is likely the final common pathway of many infectious and/or environmental factors triggering exuberant inflammation in genetically susceptible individuals.[30] Indeed, even more than infectious diseases, KD clinically and epidemiologically resembles other pediatric vasculitides. Henoch-Schönlein purpura and polyarteritis nodosa, for example, have similar manifestations and demographics, differing

Table 1. Laboratory Test and Imaging Results Incorporated in the Algorithm for Diagnosis of Incomplete Kawasaki Disease

Laboratory Criteria	Echocardiogram Results Suggestive of Kawasaki Disease
C-reactive protein >3.0 mg/dL	Coronary z scores >2.5
Erythrocyte sedimentation rate >40 mm/h	Lack of tapering
Albumin <3.0 g/dL	Perivascular brightness
Anemia	Decreased left ventricular function
Elevation of alanine aminotransferase	Mitral regurgitation
Platelets >450 × 10^3/μL after 7 d of illness	Pericardial effusion
WBC >15 000/μL	
>10 WBCs/high-power field on urinalysis	

Abbreviation: WBC, white blood cell count.

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; albumin to grams per liter, multiply by 10; platelets to × 10^9/L, multiply by 1; WBC to × 10^9/L, multiply by 0.001.

from KD primarily in apparent triggers and target organs. This theory has the advantage of accommodating previous reports of causation rather than requiring the assumption that most other data on infectious, immunologic, and autoimmune etiologic factors have been erroneous.

Diagnosis

The diagnostic criteria for KD were established by Kawasaki in 1967 on the basis of personal evaluation of 50 patients in Tokyo.[1] These original criteria define classic KD to the present day. They require fever persisting for 5 or more days in addition to 4 of the following 5 signs of mucocutaneous inflammation: (1) bilateral conjunctival injection, most often without discharge; (2) mucosal changes, including cracked lips, strawberry tongue, or reddened oropharynx; (3) extremity changes, including redness of the palms and/or soles, swelling of the dorsal surfaces of the hands and feet, and periungual desquamation; (4) polymorphous eruption; and (5) cervical lymphadenopathy, with one node 1.5 cm or more in diameter.

Despite the sustained utility of these criteria for identifying cases of KD, over time it has become clear that they have significant limitations. Most important has been evidence from high-resolution echocardiography that at least 10% of children who ultimately develop coronary artery aneurysms do not meet the criteria for KD.[31] This finding has elevated the importance of imaging in the diagnosis and management of KD and necessitated a system for identifying and treating children at risk of developing coronary artery abnormalities despite not fulfilling the criteria for KD. Cases of incomplete KD are now identified according to an algorithm developed by a working group of the American Heart Association.[5] Children with at least 5 days of fever and the presence of 2 or more clinical manifestations of mucocutaneous inflammation plus coronary artery dilatation and/or characteristic laboratory test findings (**Table 1**) warrant further evaluation or empirical treatment with IVIG if the caregiver suspects a diagnosis

Table 2. Differential Diagnosis of Kawasaki Disease

Disease	Characteristics	Notes
Adenovirus	Fever, mucosal changes	Exudative conjunctivitis more common
Measles	Fever, mucosal changes	May have Koplick spots
Parvovirus	Fever, rash, arthritis	Typically lacks mucositis
Leptospirosis	Fever, conjunctivitis, prominent hepatitis	Mucositis, extremity changes usually lacking
Streptococcal scarlet fever	Fever, rash, oral mucosal changes, lymphadenopathy, palmar erythema	Ocular changes in <5% of patients
Staphylococcal toxic shock syndrome	Fever, rash, oral mucositis, lymphadenopathy	Ocular changes uncommon
Stevens-Johnson syndrome	Fever, rash, mucositis	Keratitis and oral ulcerations typical, unlike Kawasaki disease
Serum sickness	Fever, rash, lymphadenopathy, arthritis	Ocular and mucosal changes lacking; hepatosplenomegaly, diffuse lymphadenopathy common
Systemic juvenile rheumatoid arthritis	Fever, rash, lymphadenopathy	Ocular and oral changes lacking; commonly diffuse lymphadenopathy with hepatosplenomegaly
Polyarteritis nodosa	Fever, rash, arthritis	Persistent symptoms despite therapy for Kawasaki disease

of KD. An evaluation of these guidelines found that they identified 97% of children at risk of developing coronary artery abnormalities, whether or not they met the criteria for KD.[32] As viral syndromes can cause transient coronary artery dilatation, however, the actual degree to which morbidity associated with KD is being prevented with this approach is not known.

This development has fostered a concerted effort to identify tools to improve the accuracy of diagnosing children suspected of having KD. Clinical and laboratory test findings can help rule out some of the most common conditions that mimic KD (**Table 2**), but clinical diagnoses are inherently prone to error. Accordingly, researchers have sought biomarkers that can increase the speed, sensitivity, and accuracy of diagnosis. Groups have proposed N-terminal pro–brain natriuretic peptide and a biologically active fragment—brain natriuretic peptide—that is released by the cleavage of pro–brain natriuretic peptide in response to cardiac myocyte stretch as useful markers of KD.[33] Low levels of plasma clusterin may be associated with progression of coronary artery lesions, and serum troponin, creatinine kinase, and inducible nitric oxide synthase in neutrophils, among others, also have received interest as potential markers of KD.[34] High-accuracy mass spectrometric analysis of urinary proteomes of children with KD are reportedly enriched for markers of cellular injury, such as filamin and talin; immune regulators, such as complement regulator CUB and Sushi multiple domains 3 (CSMD3); immune pattern recognition receptor muclin; and immune cytokine protease meprin A.[35] However, none of these approaches is ready for widespread clinical use. For now, no known laboratory markers can replace experienced clinicians using history, physical examination, routine laboratory studies, and echocardiographic imaging of the coronary arteries as the criterion standard for diagnosing KD.

Table 3. Current Practice: Treatment of Acute Kawasaki Disease

Population	Therapy	Comments
Routine risk	IVIG 2 g/kg plus aspirin 30-50 mg/kg/d	American Heart Association and American Academy of Pediatrics recommendations[5]
High-risk: patients in Japan	IVIG 2 g/kg plus aspirin 30-50 mg/kg/d plus prednisone 2 mg/kg/d tapered for 10-15 d	High risk defined as Kobayashi score ≥5; treatment according to RAISE protocol[51,52]
High-risk: non-Japanese patients	IVIG 2 g/kg plus aspirin 30-50 mg/kg/d plus prednisone 2 mg/kg/d tapered for 10-15 d	Age under 6 mo or z score >3 on initial echocardiography; treatment according to RAISE protocol[53]
Persistent or recrudescent fever after treatment with IVIG	Second dose of IVIG 2 g/kg	General practice based on dose-response to IVIG[54]
Persistent or recrudescent fever after 2 doses of IVIG	Salvage therapy: no agent demonstrated to be effective for this indication	Consider corticosteroids,[55] cyclosporine,[56] infliximab,[57] anakinra,[50] cyclophosphamide[49]

Abbreviations: IVIG, intravenous immunoglobulin; RAISE, Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease.

Treatment

Perhaps the most remarkable aspect of the history of KD has been the discovery of therapy that converted the disease from one that caused persistent coronary artery aneurysms in 20% to 25% of patients and mortality in up to 2% of patients to a routine pediatric diagnosis that is fully curable in as many as 98% of children. This breakthrough was largely fortuitous, as the seminal report by Furusho et al[36] was based on the recently published, but ultimately unrelated, discovery of intravenous immunoglobulin as treatment for idiopathic thrombocytopenic purpura. After their initial finding that IVIG appeared to decrease the incidence of coronary artery aneurysms in patients with KD, the next year, Furusho et al[37] published a controlled study comparing 40 children treated with IVIG plus aspirin with 45 children treated with aspirin alone for KD. The definitive United States–based multicenter trial by Newburger et al[38] showed that children who received 4 daily doses of IVIG plus aspirin had approximately one-third the risk of developing aneurysms after 2 weeks, and one-fifth the risk after 7 weeks, compared with children who received aspirin alone. Five years later, the same Boston-based group established what remains the preferred initial therapy for KD when they showed that a single 2-g/kg dosage of IVIG is more effective at reducing the risk of developing aneurysms than the same total dose administered once per day for 4 days.[39] In fact, treatment of KD with IVIG has proven to be one of the most cost-effective therapeutic interventions in pediatrics.[40]

The mechanism by which IVIG controls the vascular inflammation of KD is unknown. High-dose immunoglobulin has many immunomodulatory effects, of which down-regulation and adsorption of proinflammatory cytokines, augmentation of suppressor T-cell activity, down-regulation of antibody synthesis, saturation of Fc receptors, and anti-idiotype binding have been proposed to be important in KD.[5] Although all treatment trials of IVIG have included aspirin for its antiplatelet effect, prospective studies[41] and meta-analyses[42] suggest that aspirin has no appreciable effect on the formation of coronary artery aneurysms.

Even though IVIG is a safe and reliable treatment for KD, it is expensive at several thousand dollars per dose and may cause fever and severe hemolytic anemia.[43] It is also incompletely effective: at least 10% of children respond only partially, although up to half of those who fail to respond to a single dose improve after a second 2-g/kg dosage.[44] Ultimately, only 2% to 4% of children who receive optimal treatment with IVIG develop coronary artery aneurysms. Attempts to improve outcomes in KD usually involve augmenting initial IVIG treatment with a second agent, or adding another immunosuppressive medication in an attempt to salvage children who remain ill after IVIG treatment.

One of the first studies of augmented treatment for KD was a prospective, randomized trial of IVIG plus a single dose of pulsed-dose methylprednisolone vs IVIG alone as initial therapy.[45] With only 4 of 199 children enrolled in the study demonstrating coronary artery aneurysms, it is not surprising that the trial failed to demonstrate benefit from the addition of corticosteroids. Post hoc analysis, however, suggested that children who ultimately failed to respond completely to IVIG were protected from developing coronary artery abnormalities if they had received methylprednisolone.[45] Accordingly, in 2012, Kobayashi et al[46] published a randomized trial of IVIG plus prednisolone vs IVIG alone for patients with severe KD who were predicted to be at increased risk of failing to respond to IVIG. High-risk patients were identified using the Kobayashi score based on a logistic regression model incorporating day of illness at initial treatment, age in months, neutrophil percentage of white blood cells, platelet count, serum aspartate aminotransferase and sodium levels, and C-reactive protein.[47] In this high-risk group, addition of 2 weeks of 1 to 2 mg/kg/d of prednisolone resulted in a significant decrease in the rate of coronary artery lesions.[46] This approach has become the standard of care in Japan, but the Kobayashi score has a low sensitivity and predictive value in non-Japanese populations.[48] Accordingly, the ability of other markers to prospectively identify children at increased risk of failing treatment with IVIG, such as age below 6 months and increased coronary artery diameter at presentation, are being evaluated in the United States and Europe.

Several agents apart from corticosteroids have been administered to children refractory to initial therapy with IVIG, including cyclophosphamide,[49] anakinra,[50] rituximab, and plasmapheresis (**Table 3**).[5,49-57] Initial reports have suggested that rescue treatment with corticosteroids,[55] tumor necrosis factor inhibitors,[57] and cyclosporine[56] might reduce the incidence of coronary artery lesions. Most of these reports, however, have been uncontrolled and confounded by the use of several immunosuppressive agents sequentially in attempts to salvage children whose condition was deteriorating. Several of these agents currently are being examined in larger, prospective studies, but to date and to our knowledge, no salvage treatment can be recommended as having documented cardioprotective effects in children with KD that is refractory to IVIG.

When coronary aneurysms are already established, antiplatelet agents and anticoagulation are important adjuvants to anti-inflammatory agents. The intensity of antithrombotic therapy increases with the severity of coronary artery dilatation based on z scores (SD units separating the child's coronary artery diameter

from the population mean). American Heart Association statements recommend that all children with persistent coronary dilatation continue to receive low-dose aspirin therapy,[5] based on consensus guidelines for anticoagulation in pediatric congenital heart disease. Platelet aggregation inhibitors, such as warfarin (with a goal international normalized ratio of 2.5-3.5) or clopidogrel, are added to aspirin based on coronary artery diameter.[58] For acute coronary thrombosis, systemic thrombolysis with alteplase and anticoagulation with heparin and low-dose aspirin are often recommended, although specific evidence of their efficacy in KD is lacking.[59] Both coronary artery bypass graft surgery and percutaneous coronary intervention have been used in severe cases of KD with thrombosis. Although data comparing them directly are scant, longitudinal follow-up suggests good outcomes for coronary artery bypass graft surgery using mammary arteries, with 20-year graft patency rates around 87%.[60] In the worst cases, cardiac transplant also has been performed successfully in children with severe arrhythmias and myocardial dysfunction.[61]

As a systemic vasculitis, KD may cause serious complications beyond the heart as well.[62] The gastrointestinal system is frequently involved in KD, and abdominal pain is a common symptom of children with KD, presumably owing to intestinal vasculitis. Hepatomegaly, hydrops of the gall bladder, liver enzyme elevation, and cholestasis are relatively frequent findings, while surgical abdominal emergencies, including gastrointestinal hemorrhage, rarely may result from KD.[63] Central nervous system manifestations are relatively uncommon, although children with KD are typically quite irritable, likely a result of aseptic meningitis and improving only slowly after treatment. Uveitis is apparent in up to 70% of cases of KD,[64] and retinal vasculitis and persistent sensorineural hearing loss[65] also have been reported. The kidneys are uncommonly involved in KD despite rare case reports of tubulointerstitial nephropathy, hemolytic uremic syndrome, and interstitial nephritis.[66] Vascular inflammation also can cause aneurysms of the aorta, axillary artery, and distal extremities, particularly in children with very severe refractory disease.[63,64] Potentially fatal complications of KD include macrophage activation syndrome, marked by persistent fever, cytopenias, and risk of intravascular thrombosis,[53] and "Kawasaki shock syndrome," characterized by hypotension owing to decreased systolic function and peripheral vasodilation.[54] Both of these conditions are associated with an increased risk of coronary artery abnormalities, failure to respond to IVIG, and mortality, largely owing to delayed diagnosis of KD.

Prognosis

Mortality in KD is generally low, and short- and long-term prognosis is dependent on the extent of coronary artery involvement. In a large Japanese cohort study of KD, death during the acute phase accounted for nearly half of all mortality.[67] The most recent longitudinal Japanese study of prognosis in KD reported that males with cardiac sequelae from KD (defined as any dilation, stenosis, aneurysms, occlusion, or infarction within 1 month of onset) had a 1.86-fold increase in the standardized mortality rate.[68] Those without cardiac sequelae had normal 25-year life expectancies, and the mortality rate for females was difficult to assess given only a single such death. A recent large, matched, retrospective US cohort study in patients with KD found a low rate of cardiovascular events during a mean follow-up of 14.9 years.[69] Five percent of patients with KD had persistent coronary abnormalities, resulting in complications in 25%, but there were no deaths in the KD group. Despite these reassuring data, long after recovery, parents of children with KD express perceptions of increased vulnerability when compared with parents of children who did not have KD, regardless of whether they have confirmed disease sequelae.[70]

Conclusions

Much has been learned about KD since its original description in 1967. Understanding of its pathophysiologic findings, diagnosis, and treatment has become significantly more detailed and sophisticated, but important challenges remain. Most notable is the persistent inability to identify the cause of KD, likely because the disease is actually a final common manifestation of vascular inflammation triggered by many infectious and environmental exposures in genetically susceptible individuals. Development of algorithms to diagnose incomplete KD has limited the number of cases that go unrecognized, although at the cost of treating more children who might not have KD. Many of the remaining issues will be resolved by the discovery of specific biomarkers for KD, which in addition will likely improve the ability to identify patients who can benefit from more aggressive therapy than IVIG alone. In any event, the nature of this challenging condition has long attracted an outsized number of investigators. Thus, the safest prediction of all is that the list of mysteries regarding KD likely will be much shorter in another 50 years.

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