HEART INVOLVEMENT IN KAWASAKI DISEASE

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**Summary**
Kawasaki disease appears to be the most common cause of acquired heart disease and later on myocardial infarction in children. It draws special attention to itself because of its undisclosed etiopathogenesis of developing coronary arteries aneurysms and ischemic heart disease as well as lack of pathognomonic symptoms or definite diagnostic criteria. It is usually diagnosed when fever is present for five or more days together with various mucocutaneous manifestations. Although there are no specific laboratory findings, inflammatory markers are most often helpful to rule out Kawasaki disease or to predict the risk of its complications. Cardiac imaging is also essential because coronary abnormalities is one of the most severe complications of the disease. Though treatment schemes are established, new approaches appear due to intensive research programs and constantly updating news on etiology, pathogenesis and previous cases outcomes.

**Introduction**
Kawasaki disease (KD), first described by Tomisaku Kawasaki in Japan in 1967, is an acute systemic vasculitis of the small- and medium-sized arteries that most commonly affects children between 6 months and 5 years of age. However, older children and even adults with Kawasaki disease have been described [1, 2]. The clinical characteristics of KD are prolonged fever, conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, indurative edema of the hands and feet associated with subsequent peeling of the skin of the fingertips, and nonsuppurative cervical lymphadenopathy [3]. KD is the leading cause of acquired heart disease in children that results in coronary artery aneurysms in 20% to 25% if untreated [4, 5]. Advancement in treatment with intravenous immunoglobulin and aspirin has reduced the incidence of coronary artery lesions from about 25% to 5%. Studies reveal, that more than 20 percent of patients have various post Kawasaki disease cardiac sequelae, including coronary artery stenosis which occurs ≥15 years after the disease onset. As more patients with a history of Kawasaki disease and coronary aneurysms reach young adulthood, acute myocardial infarction is now being increasingly recognized in this population making the disease a matter of adults’ health as well [6, 7].

The aim of this review is to overview the latest information about kawasaki disease, news in ethiopathogenesis, diagnostics and treatment the main focus giving to the heart damage.

**Design and methods**
Epidemiology. Kawasaki disease (KD), first described by a Japanese pediatrician in 1967, is the second commonest vasculitis of childhood after Henoch Schönlein purpura and the most common cause of acquired heart disease in children of developed countries [8, 9]. The disease has a male predominance (the male to female ratio is 1.5:1) [1], seasonality and occasional epidemics [9]. KD is most often seen in children between 6 months and 5 years of age. The incidence of KD is highest in Japan and other Eastern Asia countries, as well as in Asians born and living in low incidence countries, suggesting a genetic predisposition to susceptibility [1, 10]. The disease has attracted special interest, because death is most frequently attributable to ischemic heart disease in children caused by thrombosed
coronary artery aneurysms, secondary to coronary arteritis [11]. Without treatment, 1 in 5 children develops coronary artery aneurysms and about 2.5% of KD cases are complicated with myocardial infarction [4, 12, 8].

**Etiology.** Despite four decades of research, the etiology of KD remains unproven; it seems most likely that KD is triggered by an infectious agent or agents in genetically susceptible children [4]. A number of bacterial and viral pathogens, including retroviruses, human adenoviruses, Epstein–Barr virus, coronavirus, propionibacterium acnes, staphylococcal and streptococcal superantigens, and unidentified virus particles were implicated as infectious triggers of KD. To date, no single pathogen has been confirmed in subsequent studies [1, 9, 13]. Many different studies suggest that the trigger of KD is most likely a currently unidentified virus, as viral-like cytoplasmic inclusion bodies have recently been detected in acute KD tissues [1, 14, 10]. Although an etiologic agent(s) has not been found, the role of genetic susceptibility to KD has long been evident through its striking predilection for children of Japanese ethnicity regardless of their country of residence [8]. Currently genetic studies have identified a number of immune and apoptosis-related genes which have been associated with susceptibility and/or disease outcome as well as genes, accountable for aneurysm formation and response to intravenous immunoglobulin (IVIG) [9, 13, 14, 15]. Susceptibility to KD is highly likely to be polygenic, and additional genes will undoubtedly be identified over time.

**Pathogenesis.** Autopsy studies of fatal cases have clearly demonstrated that inflammation occurs in multiple organs and tissues in KD [14]. A large number of T cells, large mononuclear cells, macrophages and plasma cells, with a smaller number of neutrophils, are observed in various organ tissues in fatal cases of acute KD. Additionally, various inflammatory cytokines and chemokines (tumor necrosis factor alfa, nuclear factor-kappa B, interleukin (IL)-17, transforming growth factor beta, granulocyte colony stimulating factor, IL-1b, IL-6, follistatin-like protein 1, Toll-like receptors 2 and 4), matrix metalloproteinases, nitric oxide production, autoantibody production, and adhesive molecule expression are also overactivated in the acute stage of KD which are considered to facilitate vascular endothelial inflammation and then participate in the pathogenesis of KD and coronary arteries lesions (CALs) formation [1, 7, 16]. Inflammation of the coronary arteries is the most clinically significant aspect of the illness. Inflammatory cells invade the intima and destroy the internal elastic lamina continuing to infiltrate tunica media. With inflammatory cell invasion from the adventitia, panvasculitis develops. The internal and external elastic layers become fragmented, and when aortic blood pressure becomes unbearably high, aneurysm formation begins [10, 17]. Aneurysms develop on about the 12th day after disease onset, when the damage is severe. The blood eddies in the aneu-

| Table 1. Diagnostic criteria for Kawasaki disease delineated by the American Heart Association |
|---|---|
| **Fever persisting for at least 5 days** | **Fever is generally high and spiking (often to 40°C or higher) and persists in untreated patients for 1–2 weeks or longer.** |
| Presence of at least four of the following five principal features: | |
| 1) Changes in distal extremities | These changes are distinctive and acutely include erythema, edema and, sometimes, induration of the hands and feet and periungual desquamation of the fingers and toes. |
| 2) Polymorphic exanthema | Skin eruptions involve the trunk and extremities and may have several forms including urticarial exanthema, a morbilliformmaculopapular eruption (occasionally with target lesions) or a diffuse scarlatiniform rash. |
| 3) Nonexudative, painless, bilateral conjunctival injection (5% are exudative) | The bulbar conjunctivae, rather than the palpebral or tarsal conjunctivae, are involved. |
| 4) Changes in the lips and oral cavity | Strawberry tongue, redness and cracking of the lips, and erythema of the lips and oropharyngeal mucosa. Ulcerative lesions are not seen. |
| 5) Cervical lymphadenopathy (at least one lymph node with a diameter of 1.5 cm or more) | The lymphadenopathy is usually unilateral, with firm and slightly tender nodes. |
rysm, making it easy for thrombi to form, and thrombotic occlusion is found in the coronary artery aneurysm of many autopsies of acute-stage KD patients. However, two-thirds of patients have no symptomatic episodes. Moreover, 50% aneurysmal segments, regress to normal internal lumen diameter within 2 years after illness onset. The likelihood of regression is inversely proportional to aneurysm size, and regression rarely continues after 2 years [4, 11, 17].

**Clinical findings and diagnosis.** The clinical course for KD has been divided into 3 phases: acute (lasts from the onset of fever until its resolution, and without treatment lasts for an average of 11 days), subacute (begins once the fever resolves and lasts until all of the clinical features of KD have resolved, which typically takes about 2 weeks), and convalescent (starts after the subacute phase and is considered to be complete once the erythrocyte sedimentation rate (ESR) and platelet count have normalized, usually 4 to 8 weeks after fever onset) [1].

**Diagnostic criteria.** If possible, it is best to make a diagnosis of Kawasaki disease within 10 days of the onset of illness. To date, there is no specific diagnostic test or pathognomonic finding for KD. Diagnosis is based on the presence of fever lasting 5 days or longer with at least 4 of 5 specific clinical criteria delineated by the American Heart Association (AHA) (Table 1) [4, 1, 15, 18]. Approximately 90% of patients have mucocutaneous manifestations. Polymorphous eruptions, that in almost all cases occurs on the trunk and extremities, often with perineal accentuation, a scarlatiniform groin area dermatitis, erythema and edema of the hands and feet, oral mucosa changes, conjunctival injection, and cervical lymphadenopathy are key mucocutaneous signs of Kawasaki disease [1].

The classic criteria for KD are not fulfilled in almost one-third of children with coronary aneurysms. Therefore patients with fever for at least 5 days and less than four principal features can be diagnosed as having Kawasaki disease when coronary artery disease (coronary aneurysm or dilatation) is detected by two-dimensional echocardiography or coronary angiography [4, 15, 18].

A variety of nonmucocutaneous features that are not part of the diagnostic criteria may be seen in association with KD. It includes arthritis that may be polyarticular or oligoarticular, mainly involving the large and it is often quite painful. Gastrointestinal complaints, mainly abdominal pain, diarrhea, and vomiting, are another common feature that may be seen in up to one-third of patients. Bile duct inflammation, hepatitis, gall bladder hydrops, jaundice, pancreatitis, aseptic meningitis, respiratory symptoms, otitis media or tympanitis, facial nerve palsies have been reported to be associated with KD [1].

**Laboratory findings.** No laboratory result is specific for Kawasaki disease, but laboratory studies help to rule out Kawasaki disease and predict the risk of complications. KD is invariably associated with an inflammatory process, with elevation of ESR, C-reactive protein (CRP) and white cell count (elevated neutrophil count and decreased lymphocyte count). In the absence of significant inflammation, the diagnosis of KD is unlikely [1, 9].

Abnormal laboratory values such as high ESR, high platelet count (>450,000/mm3), low hematocrit, low albumin levels, and refractory Kawasaki disease have been found to correlate with the development of coronary artery lesions after KD [1, 19]. Moreover, patients with WBCs, neutrophils, and CRP levels that continue to increase after IVIG therapy also portend a higher risk for coronary artery complications [1].

**Cardiac imaging.** Cardiac imaging is essential early in the disease course to seek coronary abnormalities [5]. Echocardiography, as the American Heart Association (AHA) 2004 guidelines recommend, is the first choice for routine coronary artery surveillance and is used to screen patients with KD for the presence of coronary artery pathology [20]. Conventional coronary angiography is the gold standard for coronary artery lumen evaluation and is able to detect CAAs, coronary artery stenosis and coronary occlusion. Angiography finding shows that CAAs of Kawasaki disease usually involve the proximal segments of the major branches, left anterior descending and right coronary arteries, and tend to be localized [2]. However, these imaging modalities have some significant limitations. With echocardiography it is only usually the proximal part of the coronary arteries that can be visualized adequately. Furthermore, there are risks associated with conventional coronary angiography because of its invasive nature and with the exposure to contrast agents and radiation. Cardiovascular magnetic resonance (CMR) has the ability to perform non-invasive and radiation-free evaluation of the proximal and mid-portion of the coronary artery lumen and vessel wall. It can also image myocardial inflammation, ischemia that can be accessed by using pharmacological stress testing, and fibrosis [5, 20].

**Cardiac complications.** Cardiac complications including myocarditis, pericarditis, valvular dysfunction, arrhythmias, coronary artery aneurysms, thrombosis, congestive heart failure or myocardial insufficiency are the leading causes of morbidity and mortality in patients with Kawasaki disease, affecting an estimated 20 – 30% of patients. Despite the fact that coronary disease requiring revascularization is rare, coronary artery lesions such as coronary artery fistula formation, coronary artery dilatation, and cor-
Coronary artery aneurysms resulting in myocardial infarction are the most common complications of Kawasaki disease. [4, 5, 15, 12]. The most widely used definition of CAL is based on the Japanese Ministry of Health criteria: maximum absolute internal diameter >3 mm in children younger than 5 years of age or >4 mm in children 5 years and older, or a segmental diameter 1.5 times greater than that of an adjacent segment, or the presence of luminal irregularity. Coronary artery aneurysms are considered small when the diameter is <5 mm, medium when the aneurysm is 5 to 8 mm in diameter, and giant when the diameter is >8 mm; the larger the aneurysm, the poorer the prognosis, especially in these who occasionally have aneurysms not only in coronary arteries but also in systemic vessels. [4, 5, 15]. Risk factors for coronary aneurysms include male gender, age younger than 1 year (especially <6 months) or older than 5 years (especially >9 years), persistent fever despite adequate treatment using IVIG therapy, anemia, hypoalbuminemia, high CRP levels at presentation and other laboratory markers indicating more severe vasculitis [4, 5, 20].

Aneurysms which form during the acute phase of Kawasaki disease can remodel, remain unchanged, progress to stenotic lesions, or thrombose. Low blood flow within the aneurysm predisposes to thrombus formation leading to ischemia and/or infarction [2, 6, 20]. The most prominent late histological feature of CAL in Kawasaki disease is intimal thickening. Excessive intimal thickening can develop into localized stenosis. Regional stenosis is caused mainly by inward luminal intimal thickening and usually develops in both the inflow and outflow shoulders of the aneurysm [17, 7].

Myocardial infarction due to thrombosis in inflamed coronary arteries may present with symptoms of unrest, vomiting, and abdominal pain. However, two-thirds of patients with occlusion have no symptomatic episodes. This is a characteristic finding of KD which is consistent with histological findings, such as recanalization and well-developed collateral arteries. “Arteries in artery” is the typical histological form of Kawasaki disease, which is the result of recanalized vessels after aneurysm occlusion [5, 17, 7].

Advancement in treatment with intravenous immunoglobulin and aspirin during the acute phase has dramatically reduced the incidence of CALs from about 25% to 5%. However, up to 5% of those affected develop coronary aneurysms, predisposing them to thrombotic complications [12, 7].

Most aneurysms tend to decrease in size. Small-to medium-sized aneurysms are likely to regress within 1 to 2 years after disease onset, after that, regression is less likely to occur. The frequency of regression is 32% to 50%. However, patients with giant coronary aneurysms are less likely to experience aneurysm regression. In addition, morphological changes such as intimal thickening, reduced ability to dilate and abnormal endothelial cell function have been reported in affected segments [17, 12, 20].

Carotid intima-media thickness, a surrogate marker of atherosclerosis, is associated with systemic arterial stiffness in children several years after diagnosis of Kawasaki disease. This finding is more frequent in those who had coronary lesions, but can also occur in the group with normal coronary arteries. Atherosclerosis in KD patients greatly differs histologically from common atherosclerotic findings. Autopsies of patients who died late after KD revealed calcified aneurysms (a pathognomonic sign of KD in later life), myointimal proliferation and organised thrombi with recanalisation, whereas lipid-laden macrophages and cholesterol crystals, the hallmark of common atherosclerosis were not observed [21, 22, 2].

**Atypical KD.** Incomplete and atypical forms of KD have been described for patients who do not meet clinical criteria but have no other diagnosis that fits their symptoms. According to the 2004 AHA guidelines, a patient with at least 5 days of fever, 2 or 3 additional clinical diagnostic criteria, and abnormal laboratory values typical for KD should be diagnosed with incomplete KD. These patients may be outside the age range for KD: incomplete KD is more common in young infants than in older children [1, 15]. In atypical KD, the clinical picture is dominated by an unusual symptom as seizure, bloody diarrhea, compressive cervical adenopathy, nephrotic syndrome or hypotenatremia [21].

The AHA 2004 supplemental laboratory criteria are helpful for diagnosing incomplete KD (Table 2). Patients with unexplained fever lasting more than five days (with 2 or 3 principal clinical features of KD) should undergo laboratory testing, and if there is evidence of systemic inflammation, an echocardiogram should be obtained even if the patient does not fully meet the clinical criteria of KD. [15]

**Post-Kawasaki and follow-up.** The follow-up is orga-

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<th>Table 2. The 2004 AHA supplemental laboratory criteria</th>
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<td>Fever of &gt;5 d associated with 2 or 3 clinical criteria and:</td>
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<tr>
<td>• C-reactive protein ≥3.0 mg/dL and/or:</td>
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<td>• erythrocyte sedimentation rate ≥40 mm/h with the following criteria:</td>
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<td>1) albumin ≤3.0 g/dL;</td>
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<td>2) anemia for age;</td>
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<td>3) elevation of alanine aminotransferase;</td>
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<td>4) platelets after 7 d ≥450,000/mm³</td>
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<td>5) white blood cell count ≥15,000/mm³</td>
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<td>6) urine ≥10 white blood cells/high-power field</td>
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nized according to the existence or non-existence of coronary artery lesions. For children, who had no or regressive CALs, it is essential to recommend a cardiovascular risk factors prevention strategy further in life. All patients with KD should undergo echocardiography at diagnosis and 6–8 weeks after the onset of the disease. Echocardiography should be performed at least weekly in those with aneurysms detected on initial echocardiography and those with ongoing active inflammation to monitor aneurysm size progression or thrombi formation. Depending on the size of the aneurysms, electrocardiography and echocardiography performed 6–12 monthly is recommended [21, 9].

Treatment

The standard of care for KD is the intravenous administration of immunoglobulin (a single 2 g/kg dose) plus high dose aspirin (usually 80-100 mg/kg per day) as early as possible within 10 days of symptom onset [5, 15, 18, 21, 23]. Practices regarding the duration of high-dose aspirin administration vary across institutions, and many centers reduce the aspirin dose after the child has been afebrile for 48 to 72 hours. Other clinicians continue high dose aspirin until day 14 of illness and 48 to 72 hours after fever cessation. This treatment is effective in reducing systemic inflammation and the occurrence of CALs. When high-dose aspirin is discontinued, low-dose (3-5 mg/kg/day) is given until there is no evidence of CAL and inflammatory markers as well as until normal echocardiogram is observed in children, who develop CALs [15, 22]. If giant aneurysms predilected to thrombosis develop, a combination of anti-platelet agents and anticoagulants is used [4]. Unfortunately, IVIG resistance occurs in up to 20% of cases [9, 21]. It is alternatively cured with a second IVIG pulse or additional 3 day methylprednisolone pulse therapy or alternative medications such as tumour necrosis factor-alpha (TNF-a) blockers or inhibitors, cytotoxic agents and plasmapheresis [5, 15]. It is important to note, that corticosteroids may be a beneficial adjunctive treatment but should not be administered as monotherapy [5].

In addition to this, therapy with statins is being investigated as they seem to significantly improve chronic vascular inflammation and endothelial dysfunction in children with coronary arterial abnormality in the chronic stage of KD [24].

Myocardial infarction in KD patients has a standart treatment: series of percutaneous coronary interventions (PCI) and coronary artery bypass graft (CABG) operations have been performed as well as thrombolytic therapy with urokinase, streptokinase or tPA [12].

Conclusions

Kawasaki disease is a serious matter of children’s rheumatology and cardiology today. Though its etiopathogenesis is still in research stage, it is essential to continue studies and clarification of the disease itself and of its treatment. Laboratory tests and cardiac imaging are useful in predicting severe complications such as CA aneurysmatic lesions and myocardial infarction. Early and precise diagnosis together with adequate multidisciplinary treatment plays a key role in preventing poor outcomes of Kawasaki disease.

References


**KA VS AKI LIGOS SUKELTAS ŠIRDIES PAŽEIDIMAS**

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**Raktažodžiai:** Kawasaki ligai, vainikinių arterijų pažeidimai, aneurizminis išsiplėtimas, immunoglobulinas.

**Santrauka**


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