Pediatr Pol 2024; 99 (1): 46-52
DOI: https://doi.org/10.5114/polp.2024.135987
Submitted: 17.04.2023, Accepted: 17.07.2023, Published: 06.03.2024

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

REVIEW PAPER

Kawasaki disease – characteristics, diagnosis, and management

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ABSTRACT

Kawasaki disease (KD) is an acute systemic vasculitis of medium – sized vessels that affects infants and children. The etiology of KD is unclear. Typical KD requires the presence of fever of at least 5 days duration and coexisting ≥ 4/5 principal clinical features: bilateral bulbar conjunctival injection, erythema and cracking og lips, skin rash, erythema and edema of the palms and feet, unilateral cervical nonpurulent lymphadenopathy. If patient presents less than 4 of the principal clinical features, the diagnosis of incomplete KD should be considered. The basis of initiate treatment of KD is a single dose of intravenous immunoglobulin (IVIG) with acetylsalicylic acid. But about 10–20% of patients do not respond to IVIG-therapy. Timely and adequate treatment of KD by IVIG and aspirin could help to prevent the development of coronary artery lesions, thats why diagnosis of KD is very important.

KEY WORDS:

coronary artery aneurysm, Kawasaki disease, infliximab.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis that affects small and medium-sized vessels throughout the body in infants and children. It is the leading cause of acquired cardiac condition in childhood in the developed world [1]. Although there are several theories, the etiology of KD remains unknown. The leading theory of its pathogenesis is that KD is triggered by some infectious agent in genetically predisposed children [2]. Typical KD can be diagnosed when fever lasts for 5 days or longer and at least 4 principal features are present. Patients who do not fulfil the criteria of the typical KD are considered to have the atypical KD after having other causes excluded. The most severe complication of KD is coronary artery abnormality development. Timely and adequate treatment of KD by intravenous immunoglobulin (IVIG) and aspirin usually guarantee good prognosis. Children with atypical KD and those who are resistant to the immunoglobulin therapy may have difficulties with treatment [2].

EPIDEMIOLOGY

Kawasaki disease was initially described by Japanese paediatrician Tomisaku Kawasaki in 1967. He reported

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50 cases of children who suffered from "acute febrile mucocutaneus syndrome with lymphoid involvement with specific desquamation of the fingers and toes" [3].

Although the highest incidence rates are among Japanese children, KD has been found worldwide. In Japan the annual incidence was 264.8 *per* 100,000 in 2012. There is considerable ethnic variation, which is shown by epidemiological data from Hawaii, where children of Japanese ancestry had the highest incidence (210.5 *per* 100,000 children under 5 years of age), while white children had the lowest incidence (13.7 *per* 100,000 children under 5 years of age). In the continental United States the incidence has been estimated at 25 *per* 100,000 children under 5 years of age.

Kawasaki disease is most common in children under 5 years old, with a slight male predominance – the ratio of males to females is approximately 1.5 : 1. There is a seasonable pattern in the number of new cases of Kawasaki disease. It is more frequent during winter and early spring months in moderate climatic zones [4].

The case fatality rate in KD in Japan is 0.015%. The peak mortality is observed 15–45 days after onset of fever. Moreover, KD can be followed by sudden death of myocardial infarction many years later in patients who have developed coronary artery aneurysms (CAAs) and stenosis [4].

ETIOLOGY AND PATHOGENESIS

Despite significant investigations, the etiology of KD is still unknown. The leading theory is that an unknown infectious agent causes activation of an inflammatory cascade in a genetically susceptible child.

According to that theory, activation of the immune system may be triggered by *Staphylococcus aureus*, *Streptococcus pyogenes*, Epstein-Barr virus, adenovirus, parvovirus B19, human herpes virus 6, measles, rotavirus, parainfluenza type 3, Dengue virus, varicella-zoster virus, 2009 H1N1 pandemic influenza, human coronavirus NL63, and bocavirus [5]. What is more, Burns *et al.* suggested that different antigens trigger innate and adaptive immune responses that lead to the expression of symptoms recognised as KD [6].

This theory is supported by the seasonality of KD and higher incidence of KD among children 9–11 months and 5 years old, which allows us to assume the existence of protective trans-placental antibodies, the level of which decrease after a few months of life [2]. The theory suggests that the infectious agent causes the activation of the innate and adaptive immune systems. Lymphocytes, cytokines, TNF-a, interleukin 1, 4, 6, matrix metalloproteinases, and oligoclonal IgA plasma cells play a prominent role in the inflammatory cascade leading to the development of vascular lesions [7].

The suggestion that KD is related to genetic susceptibility is based on the observation of increased incidence of KD in Asian populations – even with transmigration, there is increased incidence among family members and siblings. Various studies have implicated several single-nucleotide polymorphisms in different genes and gene regions: caspase 3 (CASP3), CD 40, inositol 1,4,5-triphosphate kinase-c (ITPKC), FCGR2a, and B-cell lymphoid kinase (BLK).

There are studies that indicate an association between KD in European children and variants in the transforming growth factor (TGF) signalling pathway (*TGFβ2*, *TGFβR2*, and *SMAD3*) genes. In total, these studies demonstrate that the predisposition to KD, the response to IVIG, and the consequences of the disease are influenced by variants in several genes and signalling pathways [4].

Kawasaki disease is a systemic vasculitis that often causes coronary artery lesions (CALs). However, other medium-sized arteries in different organs and tissues are involved as well. It leads to clinical findings such as hepatitis, interstitial pneumonitis, abdominal pain, vomiting, diarrhoea, gallbladder hydrops, aseptic meningitis, myocarditis, pericarditis valvulitis, pyuria, pancreatitis, and lymphadenopathy (LKD) [4].

There are 3 pathological processes revealed in KD arteriopathy: necrotising arteritis, subacute/chronic vasculitis, and luminal myofibroblastic proliferation (LMP). The first process lasts for 2 weeks after fever onset. Due to the inflammation, the arterial wall is destroyed to the level of the adventitia, which leads to the development of aneurysms. The second one is a subacute/chronic vasculitis marked by an infiltration of lymphocytes, plasma cells, and eosinophils with fewer macrophages. This process begins in the first 2 weeks after fever onset but can prolong for months to years. Luminal myofibroblastic proliferation is the third process that takes place during KD vasculitis, which starts in the first 2 weeks, lasts for months to years, and can lead to arterial stenosis [4].

The pathological outcomes of coronary artery damage depend on the severity of the lesions.

Small or medium aneurysms typically regress during 1–2 years after disease onset. Nevertheless, these patients may still develop coronary stenosis. There are patients with aneurysms that do not decrease. Large aneurysms of more than 8 mm in diameter do not regress, they have hyalinised wall, and usually contain thrombi that can become occlusive, which results in the development of acute coronary syndrome. There is also another type of aneurysm which presents luminal thrombotic occlusion and partial recanalisations as a result of LMP. These aneurysms can become progressively stenotic. Certainly, there are patients without coronary artery aneurysm formation [4, 8].

DIAGNOSIS

The diagnosis of KD is clinical. There are no diagnostic tests for KD. The classic KD diagnosis requires

FIGURE 1. Periungual desquamation of skin of the fingers

the presence of fever of at least 5 days duration, which is minimally responsive to antipyretic therapy and rises higher than 38.5°C, and ≥ coexisting 4/5 principal clinical features:

- erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa,
- bilateral bulbar conjunctival injection without exudate,
- rash: maculopapular, diffuse erythroderma, or erythema multiforme-like,
- extremity skin changes: erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase (Figure 1),
- acute cervical nonpurulent LKD (≥ 1.5 cm diametr), usually unilateral [4].

FEVER

As a rule, fever is high-grade and remittent. After IVIG therapy the body temperature returns to normal within 36 hours; if not, the child may have IVIG resistance [4].

RASH

The rash usually appears within 5 days of the fever onset [4]. Often it is manifested as diffused maculopapular rash eruptions on the trunk and spreads to the extremities with disease progression. But KD can also be manifested by diffuse scarlatiniform erythroderma, erythema multiforme-like rashes [9].

EXTREMITY CHANGES

Extremity changes are presented by erythema on the palms and soles. The dorsum of the hands and feet may be edematous and sometimes painful [4]. During the subacute phase the desquamation begins. It usually starts in the periungual areas of the fingers and toes. In the resolution phase Beau's lines can appear, i.e. deep grooved lines across the nails of the fingers and toes [4, 9] (Figure 1).

EYE MANIFESTATIONS

Eye manifestations include bilateral nonexudative painless conjunctival injection and sometimes anterior uveitis. The other less common ocular manifestations are punctuated keratitis, retrodescemetic precipitates, vitritis, bilateral optic disc swelling with papillitis, bilateral iridocyclitis, and subconjunctival haemorrhage [9].

CERVICAL LYMPHADENOPATHY

Cervical LKD is the least common of the criteria. Usually, unilateral lymph node enlargement ≥ 1.5 cm in diametr is observed [4].

It is crucial to differentiate KD-related LKD from bacterial cervical lymphadenopathy (BCL). In that matter ultrasound or contrast-enhanced computer tomography can be helpful. Lymphadenopathy is noticed to be more frequent among older children, and it usually affects multiple lymph nodes. Nevertheless, abscesses or solitary lymph nodes with a hypoechoic core are more characteristic for BCL [9].

ORAL CHANGES

Oral changes in KD include erythema, dryness, fissuring, peeling, vertical cracking, and bleeding of the lips; a strawberry tongue with erythema and prominent fungiform papillae; and diffuse erythema of the oropharyngeal mucosa [9].

Incomplete KD should be considered in children with fever for 5 days or longer, who present 2 or 3 major criteria without an alternative explanation and there are also significative laboratory findings of the disease [10].

The American Heart Association (AHA) suggests an algorithm for the diagnosis of incomplete KD that enables the identification of patients who require additional diagnosis and specifical treatment. According to this algorithm, if C-reactive protein (CRP) is < 30 mg/l and there is an elevated erythrocyte sedimentation rate (ESR) < 40 mm/hr, the child should be monitored clinically. If CRP is < 30 mg/l and there is elevated ESR < 40 mm/hr and typical peeling of the skin occurs, then an echocardiogram should be performed. If the CRP is > 30 mg/l and there is elevated ESR > 40 mm/hr and there are 3 or more

of additional laboratory findings, then the child should get an echocardiogram. The additional laboratory findings include: anemia, thrombocytosis with platelet count of ≥ 450,000 after 17th day of fever, hypoalbuminaemia ≤ 3.0 g/dl, and elevated aminotransferase (ALT), leukocytosis ≥ 15,000/mm^3. If a patient has a positive echocardiogram, then the child should be treated whether there are additional laboratory findings or not [4].

PHASES OF KAWASAKI DISEASE

Typically, the clinical features are not all present at the same time. The course of the illness can be divided into 3 stages: acute, subacute, and convalescent. Some authors also add a chronic phase. The first stage (acute) begins with the fever onset and lasts for 7–14 days. If untreated, it resolves during 3–4 weeks, but after the appropriate IVIG-therapy the temperature reduces within 36 hours. The subacute phase begins with the fever reduction and continues for 4–6 weeks. During this phase patients experience skin desquamation of the palms and feet, thrombocytosis, and the development of CAAs. During this period the highest risk of sudden death is observed. The third convalescent stage is typically characterised by resolution of the symptoms. There is still a risk for the cardiac sequelae development. Approximately 60% of CAA cases resolve, but larger aneurysms may expand. The chronic phase can be distinguished in those patients who developed cardiac complications. There is a risk of adult rupture of the CAAs formed in childhood, or complications may relate to stenosis of coronary arteries [8, 10].

ANOTHER SYMPTOMS

Although cardiac complications are the most serious, the inflammatory process involves the middle-sized arteries in different organs and tissues, which causes the prevalence of the following symptoms:

- neurological findings: extreme irritability, aseptic meningitis, transient unilateral, rarely bilateral peripheral nerve palsy, profound sensorineural hearing loss,
- gastrointestinal findings: hepatitis, diarrhoea, vomiting, abdominal pain, gallbladder hydrops, pancreatitis, jaundice,
- musculoskeletal findings: arthralgia, arthritis,
- respiratory findings: peribronchial and interstitial infiltrates,
- genitourinary findings: urethritis and hydrocele and phimosis [4].

LABORATORY AND IMAGING FINDINGS

The diagnosis of KD is clinical, and there are no tests required to confirm the diagnosis. However, some tests may play a prominent role in the case of incomplete KD. The common findings are as follows:

- leukocytosis with neutrophilia,
- anaemia,
- thrombocytosis (peaks in the third week),
- hypoalbuminaemia,
- elevated ESR and CRP,
- elevated ferritin, ALT, γ-glutamyl transferase (GGT),
- mononuclear pleocytosis,
- sterile pyuria [2].

Thrombocytopaenia may be present in the acute phase and is correlated with a greater risk for development of coronary aneurysms, and it can be a sign of disseminated intravascular coagulation [9].

Several cardiovascular biomarkers are significantly raised in KD patients: N-terminal prohormone brain natriuretic peptide (NT-proBNP), cardiac troponin I, plasma soluble suppression of tumourigenesis-2, GGT, and ALT, but none of them are specific. The most studied is the NT-proBNP, which correlates with the manifestation of CAAs and can predict the presence of IVIG resistance in KD patients when its level is raised [9].

During the acute phase of KD, electrocardiography may show arrhythmia, including sinus node and atrioventricular node functional abnormalities or low voltage if there is myocardial or pericardial involvement [4].

Echocardiography is the standard imaging modality in the KD, thanks to which, CALs and other cardiac abnormalities can be identified. Echocardiography is performed at diagnosis, 1–2 weeks after diagnosis, and 6–8 weeks later. During echocardiography coronary arteries can be evaluated for dilation (by using Z-scores) and thrombosis, but also other signs of cardiac involvement can be revealed: aortic root dilation, depressed contractility, ventricular and valvular dysfunction, and pericardial effusion [10].

According to AHA gidelines, the use of coronary Z-scores allows to evaluate the severity of coronary artery dilation. Z-score classification: no involvement: always < 2, dilation only: 2 to < 2.5; or if initially < 2, a decrease in Z-score during follow-up ≥ 1, small aneurysm: ≥ 2.5 to < 5, medium aneurysm: ≥ 5 to < 10, and absolute dimension < 8 mm, large or giant aneurysm: ≥ 10, or absolute dimension ≥ 8 mm [4].

Coronary artery abnormalities during the acute illness range from dilation only to aneurysms, with the involvement occurring first in proximal segments and then extending distally. Dilation resolves within 4–8 weeks in most cases. Some patients will have coronary artery dimensions always within the normal range, but serial measurements show gradual dilation of the coronary arteries compared to the first study in the same patient [4].

Although echocardiographic detection of thrombi and coronary artery stenosis has been reported, the sensitivity and specificity of echocardiography for identifying these abnormalities is unclear. Computed tomography coronary angiography, cardiac magnetic resonance imaging, or invasive angiography offer better characterisation

of dilatations and aneurysms especially in distal segments of coronary arteries [4].

DIFFERENTIAL DIAGNOSIS

Other diseases with similar symptoms should be considered before the diagnosis of KD is made [4]. But at the same time, the presence of respiratory symptoms or positive tests for respiratory viruses cannot exclude the diagnosis of KD. There are some common and important differential diagnoses: group A β-haemolytic streptococcal infection, adenovirus, enterovirus, mononucleosis, parvovirus B19 infection, scarlet fever, staphylococcal or streptococcal toxic shock syndrome, and meningitis. Also there are systemic inflammatory conditions (juvenile idiopathic arthritis, systemic lupus erythematosus, infantile polyarteritis nodosa, multisystem inflammatory syndrome in children [MIS-C]) and drug sensitivity reactions that should be considered [10]. Kawasaki disease and MIS-C are very similar in clinical presentation and symptomatology. It is crucial to understand the differences in the epidemiology, diagnostic criteria, organ involvement, and laboratory markers to differentiate between these 2 diseases. Kawasaki disease is more typically seen in younger children, while MIS-C is more frequent among adolescents and teens. Recent COVID-19 infection, exposure to a confirmed COVID-19 case, or positive polymerase chain reaction, serology, or antigen testing is needed to make the diagnosis of MIS-C. Coronary artery dilation or aneurysms can be found in both diseases, but it is more common in Kawasaki disease. Elevated white blood cell count with eosinophilia and elevated platelets are more common in Kawasaki disease. Laboratory findings, such as thrombocytopaenia, and elevated D-dimer and ferritin, can support the diagnosis of MIS-C [11].

PRIMARY TREATMENT

INTRAVENOUS IMMUNOGLOBULIN

The basis of initial treatment of KD is a single high dose of IVIG together with acetylsalicylic acid (ASA). Intravenous immunoglobulin should be administered during the first 10 days of the illness [4]. Patients with a delayed diagnosis of KD, who present elevated ESR or CRP with either persistent fever that cannot be explained by other causes or with revealed CAAs, also need IVIG treatment. Patients with repeat episode KD after complete resolution of the previous episode require the standard treatment [4].

According to studies, the start of treatment before the fifth day of fever onset does not appear to be more effective in the presentation of CAA development than the treatment at 5–9 days [12].

Intravenous immunoglobulin given together with aspirin within 10 days of fever onset accelerates elimination of symptoms in 80–90% of children. What is more, it reduces the risk of coronary disease from 20–25% to about 2–4% [13].

The role of prevention of CAAs in children with KD has been proven by many studies, but the mechanism remains unclear. Various mechanisms are suggested: modulation of cytokine production, neutralisation of toxins or other pathogenic agents, augmentation of regulatory T-cell activity, suppression of antibody synthesis, and provision of anti-idiotypic antibodies [4].

Children with KD should receive 2 g/kg of IVIG during 10–12 hours [4]. A randomised controlled trial has shown that the efficacy and the safety of IVIG administered over 12 h were similar to those administered over 24 hours [14].

Intravenous immunoglobulin is made from donor plasma, and there are some differences in manufacturing that can affect the properties of the drug, which in turn can change the effectiveness of the treatment. There is research on the association between the preservation conditions and the efficacy of the treatment. For instance, there are studies reporting that the acidification of the IVIG preparation leads to elevated risk of treatment failure [12].

The American Heart Association recommends to delay measles, mumps, and varicella immunisations for 11 months after high-dose of IVIG treatment, but in children with high risk of exposure to measles an earlier vaccination could be recommended, and they should then be re-immunised at least 11 months after IVIG administration if they have an inadequate serological response [4].

ASPIRIN

Aspirin has been used for therapy of KD for a long time, but reduction of CAA development has not been shown. During the acute phase of KD, ASA is typically scheduled every 6 hours with a total daily dose of 80–100 mg/kg/day in the United States and 30–50 in Japan and Western Europe. No evidence was found that high-dose or low-dose ASA is more effective. Some clinicians continue administering the high-dose ASA until the 14th day of illness, while others decrease the dose after the child is afebrile for 48–72 hours. After the acute phase a low-dose ASA is administered (3–5 mg/kg) for anti-platelet effect, and it is continued for 6–8 weeks after the exclusion of any coronary changes. For children who develop aneurysms, ASA is continued until the aneurysms resolve or longer [4].

Patients receiving ASA should be warned about the antagonism in anti-platelet inhibition between aspirin and ibuprofen and the necessity to avoid ibuprofen [10].

ADJUNCTIVE THERAPY

CORTICOSTEROIDS

Corticosteroids were the mainstay of treatment of KD in Japan in the 1960s and 1970s, before the effectiveness of IVIG had been proven. Although corticosteroids may

be harmful due to their prothrombotic effects, studies suggest that they may be used as adjunctive therapy [13].

The use of corticosteroids in KD is a controversial issue. There are studies that compare different treatment options with or without corticosteroids. Some studies have shown that the steroid therapy is associated with shorter fever duration, lower risk of treatment failure, and more rapid decline in CRP levels in steroid groups [4].

Also, there are studies that noted a decrease in the incidence of CAAs among patients with a high for on-response to IVIG, who received steroids combined with ASA and IVIG [4].

BIOLOGICAL THERAPY

Infliximab (IFX) is a chimeric monoclonal antibody against TNF-α. Early studies in Japan reported a correlation between elevated level of TNF-α in plasma and development of CAAs. The potential beneficial effects of a single dose of IFX in highly resistant KD have been noted in case reports and small clinical trials. The authors identified a reduction in the inflammatory parameters and the decrease of fever days number, but there was no significant difference in the rate of CAAs between the groups [4].

Burns *et al.* in a randomised doble-blinded, placebo controlled clinical trial reported that children receiving IFX plus IVIG had a more rapid reduction in inflammatory parameters, more rapid resolution of fever, and greater decrease in left anterior descending (LAD) coronary artery Z-score, compared to subjects who were treated with IVIG without IFX. If we take the LAD Z-score as an indicator for inflammation in the arterial wall, then these data point us to the benefit of IFX [15].

Han *et al.* showed that IVIG and IFX in the treatment of patients with KD has advantages over the traditional IVIG treatment [16].

Mori *et al.* compared the efficacy of the IFX with therapy by polyethylene glycol-treated human immunoglobulin (VGIH) in children who did not respond to initial IVIG-therapy. The infliximab group achieved faster resolution of fever. Coronary artery aneurysms occurred in one patient receiving IFX (6.3%) and in 3 patients receiving VGIH (20%) up to day 21. Also, IFX showed good tolerability [17].

The KIDCARE trial showed that patients with IVIG resistance treated by IFX had fewer days of fever, less need for additional therapy, less severe anaemia, and shorter hospitalisation, compared with patients treated by a second infusion of IVIG. But the difference in resolution of laboratory markers of inflammation or coronary artery outcomes between the groups was not established [18].

ETANERCEPT

There is insufficient convincing information about the effectiveness of etanercept, which requires further research [4]. In the Portman *et al.* study, etanercept did not show a significant reduction in immunoglobulin resistance. Intravenous immunoglobulin resistance occurred in 22% (placebo) and 13% (etanercept) of patients. Nevertheless, the researchers found that etanercept reduced the coronary Z-score, especially in children with baseline dilation in coronary arteries [19].

INTRAVENOUS IMMUNOGLOBULIN RESISTANCE

Intravenous immunoglobulin resistance can be defined as persistent or recurrent fever that begins at least 36 hours and up to 7 days after the completion of the first IVIG- infusion. The frequency of immunoglobulin resistance among patients with KD is 10–20%. The cause of IVIG-resistance is unknown, as the mechanism of action of IVIG remains unclear. Hypothetically, it can be related to genetic factors, such as polymorphism in Fc γ receptors [4].

Guidelines from the AHA recommend IVIG-retreatment for resistant patients. High-dose pulse steroids can be used as an alternative treatment option for the second dose of IVIG or after ineffective treatment by the second dose of IVIG. Infliximab can be prescribed instead of steroids.

If all the previously mentioned treatment options fail, administration of cyclosporine, immunomodulatory monoclonal antibody therapy, cytotoxic agents, or plasma exchange may be considered [4].

PROGNOSIS

With timely treatment of Kawasaki disease, CAAs develop in approximately 5% of patients [1]. At the same time, in untreated patients, they develop in 15–25% of them [7].

Data on long-term complications of KD remain limited. Patients with KD history may be at risk of development premature atherosclerosis. But the relationship between KD and atherosclerosis is a subject of controversy. It remains unknown if atherosclerotic risk factors affect the long-term progression of KD. Carotid intima-media thickness (cIMT), abnormal lipid profile, including total cholesterol, triglycerides, low-density lipoprotein, cholesterol, arterial stiffness, flow-mediated dilatation, and inflammatory biomarkers (CRP, myeloperoxidase) can be used to assess the risk of atherosclerosis development. Most studies found no significant differences in the lipid profile between KD patients and controls. The carotid intima-media thickness is a noninvasive marker of atherosclerosis, and some studies showed that the mean cIMT was significantly higher in KD patients than controls [20].

Long-term management begins after the end of the acute phase and after Z-score stabilisation. It is necessary to assess the cardiovascular risk of patients and manage them according to the results. The goals of long-

term management are the prevention of thrombosis and myocardial ischaemia [4]. The prognosis depends on the severity of cardiovascular complications. Kawasaki disease can lead to aneurysm formation, heart failure, MI, myocarditis, valvulitis, pericarditis with pericardial effusion, and rupture of the coronary arteries leading to hemopericardium and sudden death [7]. Children with serious complications may require catheterisation, coronary artery bypass surgery, or even cardiac transplantation [10].

Even children without any symptoms need to be observed, because even giant aneurysms of the coronary arteries can be almost asymptomatic [21].

CONCLUSIONS

Kawasaki disease is a systemic vasculitis of medium-sized arteries. The etiology and pathogenesis remain unclear, further research is needed. Kawasaki disease should always be considered in children with a fever that lasts ≥ 5 days and does not respond to antipyretic treatment. There are no specific diagnostic tests, so the diagnosis of KD is clinical. If the child does not present all the principal features of KD, then incomplete KD can be diagnosed. A delayed decision of IVIG and aspirin treatment can lead to the development of severe complications, especially CAAs. Therefore, the main goal of therapy is the prevention of their development and further complications based on them.

DISCLOSURE

The authors declare no conflict of interest.

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