

**PEDIATRIC RHEUMATOLOGY FOR THE GENERAL
PEDIATRICIAN**

**KAWASAKI DISEASE IN THE THIRD MILLINEUM: SYNDROME STILL AT
RISK TO BE UNRECOGNISED OR UNDERDIAGNOSED**

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ABSTRACT

Kawasaki Disease (KD) is a febrile systemic vasculitis complicated by coronary and peripheral arterial aneurysms in 20% to 35% of untreated patients. It is reported as the commonest cause of acquired heart disease in children in developed countries and may be a risk for adult ischemic heart disease. Prompt diagnosis is critical and the early administration of intravenous gammaglobulin (IVIG) dramatically reduces the rate of coronary abnormalities to less than 5% of patients. Despite the numerous efforts there is still no diagnostic test available for KD, and the diagnosis is based on clinical criteria after the exclusion of other diseases presenting with high unexplicable persistent fever. Since several conditions may mimic KD, the syndrome may be either unrecognised or under recognised, with high risk of coronary alterations. Although KD has been reported all over the world, it is overexpressed among Asian populations, especially Japanese. In the future, a role of the genetic predisposition to KD will be elucidated in order to recognise patients at risk to develop the disease and the coronary complications. A challenge for pediatricians facing children with high persistent fever is represented by atypical onset or incomplete cases of KD who are at high risk to develop coronary aneurysms (CAA) since they do not receive the appropriate treatment or they do not receive it timely. Most of CAA occurring during the acute phase of the disease regress within several years; however, recent studies show that abnormal vascular wall morphology and vascular dysfunction may persist at the site of regressed alterations despite normal angiographic findings. In adult life premature atherosclerosis may develop in these patients, with a risk for myocardial infarction. Smoking, dietary fat and additional risk factors for atherosclerosis should be avoided, and a long term follow-up into adult life by cardiologists is advisable.

No recent guidelines are available regarding sports in children who suffered from KD; stress testings may need to be performed even in absence of CAA, and strenuous athletics may need to be discouraged.

This review will focus on the approach to the diagnosis and treatment of KD; in particular, it should help pediatricians to recognise KD early in the disease course in order to prevent coronary alterations, even in atypical and incomplete cases, by early appropriate therapy.

INTRODUCTION

In 1967 Tomisuku Kawasaki described in Japan the first 50 patients affected with a disease characterised by high fever, cervical lymphadenopathy, conjunctival injection, red tongue, fissured lips, erythema and swelling of hands and feet followed by periungueal digital peeling. The association of these clinical manifestations, initially called mucocutaneous lymph node syndrome (1), is now recognised as Kawasaki disease (KD), the most common systemic vasculitis in childhood after Henoch-Schoenlein purpura (2).

After the first descriptions, it became evident that patients with KD are at risk to develop coronary involvement if they do not receive the appropriate treatment with intravenous high dose gammaglobulin (IVIG) and aspirin (3-5). In fact, KD is a systemic vasculitis complicated by coronary and peripheral arterial aneurysms in 20% to 35% of untreated patients, and by myocardial infarction (5). It is now reported as the most common cause of acquired heart disease in children living in developed countries (2) and may be a risk for adult ischemic heart disease (6, 7, 8). Prompt diagnosis is critical and the early administration of IVIG dramatically reduces the rate of coronary abnormalities to less than 5% of patients (4, 5). Despite the numerous efforts there is still no diagnostic test available for KD, and the diagnosis is based on clinical criteria after the exclusion of other diseases presenting with high persistent fever (9).

Since several conditions may mimic KD, particularly toxic shock syndrome, staphylococcal scalded skin syndrome, infection with parvovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus, and rickettsiae, the syndrome may be either unrecognised or under recognised. In these cases IVIG are not administered or they are given more than ten days after the onset of fever with high risk of coronary damage (5, 10).

Some cases of KD have been resistant to the first infusion of gammaglobulin and benefit from a second and third infusion (11, 12). In these patients other diseases such as polyarteritis nodosa, systemic onset juvenile idiopathic arthritis and malignancy have to be excluded. Moreover, several patients with severe KD do not respond to IVIG and require either corticosteroids (13, 14) or immunosuppressive drugs (14, 15). However, the role of steroids in KD is still controversial.

EPIDEMIOLOGY

Although KD has been reported all over the world, the disease is overexpressed among Asian populations, especially Japanese. Nationwide epidemiological surveys indicate that the number of KD patients has gradually increased in Japan since the last 1960s, with three epidemics in 1979,

1982, and 1986. Hospital surveillance data suggest that the incidence of KD in Japan has risen by over 50% between 1987 and 1998. The annual attack rates are 120 to 150 cases per 100,000 children under 5 years, with 6000-8000 new cases annually (16). In US Caucasians the attack rate is 4 to 15 cases per 100,000 (17). In Europe the annual reported incidence ranges from 3 to 8 per 100,000 children under 5 years (18). A recent analysis of hospital admission data in England shows that the incidence of KD among English children has increased between 1991 and 2000 (19). It is possible that this reflects an increase in recognition rather than incidence. In Italy the epidemiology of KD is not fully known, since only few data from single Pediatric Units are available (20).

CLINICAL MANIFESTATIONS

The typical manifestations of KD are high fever lasting more than 5 days without reasonable explanation and unresponsive to antibiotics *plus* i) bilateral non exudative conjunctivitis; ii) polymorphous exanthemata; iii) bilateral non suppurative cervical lymphadenopathy (at least one lymph node larger than 1.5 cm); iv) mucous membrane changes (i.e. injected or fissured lips, redness of pharynx, strawberry-like tongue) ([Figure 1](#)) and v) extremity changes (e.g. erythema of palms and soles, edema of the hands and feet, periungueal digital peeling ([Figure 2](#))). Fever of five days duration plus four of the five remaining criteria or the presence of fever and coronary artery aneurysms (CAA) detected on 2D- echocardiogram with three additional criteria are needed for the diagnosis of complete KD (Table 1).

Patients with high fever and fewer of the required clinical findings are labelled “incomplete” cases. It has been reported that infants can present CAA without developing the classic diagnostic criteria, supporting the evidence that the disease is often under recognised or misdiagnosed (21). The management of less typical presentations of KD is controversial and guidelines are lacking.

Other patients can display an atypical onset of the disease, such as acute surgical symptoms, meningeal irritation, joint involvement, or lymphadenopathy not responding to the appropriate antibiotic therapy. These presentations often delay the diagnosis (22-25). These cases are defined “atypical”. Over time several “incomplete” or “atypical” KD patients develop the lacking prerequisite clinical criteria, therefore confirming the diagnosis. Cervical lymph nodes enlargement, a diagnostic criterion for KD, in a few patients may be the only clinical manifestation associated with a prolonged fever. Tashiro et al. performed an ultrasonographic evaluation of cervical lymph nodes in

KD patients and found different features in comparison to bacterial lymphadenitis; the authors concluded that echocardiography could identify KD at an early stage of the disease (26).

The eye findings in KD could play a role in the earlier diagnosis and treatment; the presence of iridocyclitis and conjunctivitis can provide additional support to the diagnosis in patients with incomplete KD. Ocular evaluation should be included as a part of the work-up of any suspected patient. Burns et. al reported asymptomatic anterior uveitis in approximately three quarters of children with KD (27). It is usually mild and bilateral, sometimes associated with keratic precipitates, and resolves within 2-8 weeks without any sequelae. Slit-lamp examination may be useful in helping to differentiate KD from diseases that closely mimic the condition, such as streptococcal and staphylococcal toxin-mediated diseases and drug reactions.

Atypical cases of KD are common (up to 10% of the total) and the diagnosis should be considered even without the full complement of diagnostic criteria. The risk of coronary damage is high if IVIG is not administered or is given after ten days from disease onset. In a large study from Hsieh et al., no differences were found in the age distribution, sex, and rate of coronary artery involvement between typical and atypical Kawasaki disease. At follow-up, patients with coronary arterial lesions had a prognosis as good as those with typical KD if they had received IVIG on time (28). According to these observations, atypical cases may be considered part of KD and likely occur *via* the same pathogenesis, but have incomplete clinical manifestations.

KD is rare in neonates (29), but if it occurs, it may follow a rapid and severe course (30). Infants may often present as atypical cases and commonly experience very severe inflammatory changes, especially vasculitic signs. In several cases, despite aggressive treatment with IVIG, aspirin, corticosteroids and antithrombotics, fatal outcome has been reported (30, 31).

In children older than 8 years of age, KD mainly affects male and Caucasian subjects; the diagnosis is frequently delayed in the acute phase, and the incidence of coronary artery abnormalities is higher than in younger children (32).

Digital peeling, a useful diagnostic hint, usually occurs 10-15 days from the onset of typical fever even in children who had received IVIG. A long- term follow-up of patients with KD has reported recurrent episodes of skin peeling for several years after the disease recovery. This event does not signal a recurrence of the disease and does not require expensive re-treatment with IVIG. It has been reported only in patients with complete KD and its significance and mechanisms are still unknown. It

may be also observed in a number of other conditions caused by infectious agents and their toxins (33).

Since the clinical criteria of KD present sequentially, and often the interval between the appearance of fever and the development of all clinical manifestations may be longer than 1 to 2 weeks, it often is a diagnostic dilemma for the clinician. Other causes of the non-specific symptoms can be difficult to exclude. In these patients KD should be suspected in the presence of high fever of unknown origin lasting more than 4 to 5 days, and IVIG should be administered even before diagnostic criteria are satisfied. A sign that could help physicians in the diagnosis, even though it is not included in the diagnostic criteria, is the irritability present in the majority of children with KD that can be related to aseptic meningitis (2). Recently, Brogan et al reported the appearance of erythema and induration at sites of BCG immunizations as a useful early diagnostic sign. (34).

Other minor criteria in KD include: arthritis that usually develops in the convalescent phase, urethritis, aseptic meningitis, pneumonitis, otitis media and gastroenteritis. Jaundice and hydrops of gallbladder are relatively uncommon, and abdominal ultrasound may be helpful in detecting this complication. Though unusual, this acute phase complication may support the diagnosis of atypical or incomplete KD (23). Neurological manifestations, such as febrile seizures or encephalopathy, may be the presenting features of the disease (24).

ETIOLOGY

Despite numerous studies, the cause of KD remains unclear. The role of an infectious trigger, inducing the disease in a genetically susceptible host, is still strongly suggested by the epidemiology of the disease in Japanese and North American epidemics that resembles the spread of viral or bacterial infections. The role of one or more superantigens, capable of stimulating large numbers of T-cells, produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the aetiology of KD with no general consensus. A recent report from Leung et al. that studied the prevalence of superantigen secreting bacteria in children with KD did not find a significant difference between patients and controls with other febrile illnesses (35). However, future studies should further examine the potential role of V β 2-stimulatory superantigens in KD. The role of climate, ethnicity and socio-economic status has been recently discussed (36), and a different disease outcome according to the patient ethnic group has been suggested (36,37).

Since KD is overrepresented in Japan and among Americans of Japanese descent, a genetic predisposition needs to be better investigated. Pro-inflammatory cytokines, including TNF- α , play a pivotal role in the pathogenesis of coronary alterations (38) and the cytokine response to an inflammatory stimulus is influenced by genetic polymorphisms (39). In the future, genotyping might identify children at higher risk to develop coronary alterations, who therefore require a closer monitoring and a more aggressive therapy in order to prevent cardiac injury (40).

LABORATORY FINDINGS

Laboratory findings are not specific of KD and are shared by other acute inflammatory febrile diseases. Early in the course of illness all parameters of inflammation are increased, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) and neutrophil counts. Platelet (PTL) count is normal in the acute phase and markedly increases at the end of the second week reaching as high as 1,000,000/mm³. Occasionally a low platelet count may be detected in the acute phase, as well as neutropenia. A moderate-high increase of serum concentration of liver enzymes may occur in the early stage, unrelated to aspirin administration. Urinalysis may show leukocytes and erythrocytes but no bacteria. CSF contains increased numbers of WBC, mainly lymphocytes, as expression of aseptic meningitis.

Lipid profile alterations occur in the early phase including decreased levels of high-density lipoprotein (HDL), and cholesterol, and increased levels of tryglicerides. Several authors report the persistence of low HDL levels over months to years, and after the acute phase, and hypothesise a correlation with CAA (2)

CARDIAC INVESTIGATIONS

All children with typical or suspected KD have to be closely monitored by electrocardiogram (EKG) and two-dimensional echocardiography (2D-echo). The EKG may reveal arrhythmia, myocardial dysfunction and ischemia. 2D-echo is useful in detecting coronary artery dilation and aneurysms. Ultrasound may reveal aneurysms and other changes in peripheral arteries.

Cardiac monitoring includes 2D-echo at onset and six to eight weeks after onset of the disease. However, in order to detect possible coronary alteration not observed at the first evaluation, a third 2D-echo study at 14 days has also been suggested. In patients with CAA, close followup by echocardiography is mandatory in order to evaluate the size of aneurysms and to detect the formation of thrombus.

EKG and 2D-echo studies need to be tailored to single patient depending on the size of CAA (9). Children with giant aneurysms (diameter greater than 8 mm) require stress testing to define myocardial function. Because of the risk of coronary stenosis in these patients, coronary angiography is also recommended (42). Cardiac monitoring reveals that about 50% of mild CAA normalise within two years, while 5-year follow-up shows a complete regression of all CAA. Unfortunately, giant aneurysms persist in most patients over time and may evolve in severe stenosis, myocardial infarction, and even death (43). The mortality rate has completely changed after the introduction of IVIG, and in Japan it is reported as low as 0.14 %.

THERAPY

The current treatment in any patient with definite or suspected KD includes aspirin and IVIG. The use of these drugs together for KD has unequivocally reduced the occurrence of CAA. The prevalence of coronary artery abnormalities is dependent on IVIG dose but independent from that of aspirin (44). The optimal dose of IVIG is 2 g/Kg given as a single infusion over 8-12 hours. In infants with cardiac compromise a single infusion in divided doses over several days may be more appropriate.

IVIG should be administered as soon as the disease is suspected and if all possible within the first 10 days from the onset of fever. However, in the presence of persistent signs of inflammation, IVIG may have to be given in patients who are diagnosed later than 10 days from onset. In most children the fever drops either during IVIG infusion or few hours after. In those children who do not respond to the initial infusion of gammaglobulin and present persistent fever or disease recrudescence, a second and third cycle may be required (11, 12, 14).

In the small group of non-responders to IVIG, corticosteroids may be considered, even though their use is still controversial (14, 45, and 46). Pulse methylprednisolone has been reported to be effective in KD refractory to initial gammaglobulin treatment (47).

Aspirin is administered at anti-inflammatory doses (50-80 mg/Kg) in the acute phase of the disease, and then reduced to 3-5 mg/Kg when fever disappears and platelets count rises. At this low dose, the role of aspirin is to inhibit platelets adhesion to endothelium thus reducing the release of thromboxane A₂ without involving the production of prostacyclin by endothelial cells. Low-dose aspirin is maintained until the ESR and platelet count are normal in absence of cardiac complications.

A long-term low dose aspirin treatment is required in children with coronary alterations. The therapy should be continued until normalisation of aneurysms is noted. Life-long low dose aspirin therapy may be advisable if these cardiac changes persist. In children with aspirin intolerance, another antiplatelet agent may be used to prevent the formation of thrombi such as dipyridamole (2-3 mg/Kg) (42).

In patients with giant aneurysms the addition of warfarin to aspirin has been suggested, but there is no general agreement on this subject. As the early phase of warfarin administration is sometimes associated with a paradoxical prothrombotic state, intravenous heparin is advisable for a short period (48).

Nonetheless, as reported by a recent multicenter collaborative study performed in Japan, even with the use of prompt IVIG treatment, coronary disease is common in a minority of KD patients (49-51). Oki et. al found a prevalence of cardiac sequelae due to KD of 10.2% one month after onset, and of 4.2% after one year (52).

FLORENCE DATA

Our experience on KD began in 1980 when the first two children in our region of Tuscany, Italy were recognised with the typical manifestations of the disease. Since 1980 another 157 patients have been observed. In our cohort the male to female ratio is 1.8 to 1 (101 M, 58 F), with a median age at diagnosis of 29 months. The majority of cases occurred in children younger than 5 years, with the youngest patient aged 51 days and the oldest 24 years. The seasonal distribution shows that 48 cases occurred in autumn, 46 in winter, 39 in spring and 26 in summer. Patients have been followed for a mean period of 3 years (range, 3 - 216 months).

One hundred and twenty-one out of 159 patients (76.1%) fulfilled the criteria for diagnosis, while 38 (23.9%) had typical high fever and coronary aneurysm detected on 2D-echocardiogram plus two other clinical criteria.

Eight children (5.1%), 5 boys and 3 girls, had an atypical onset of KD: acute gastrointestinal symptoms resulting in surgical intervention in two, aseptic meningitis was seen in four, and isolated lymphadenopathy not responding to wide spectrum antibiotics in two. All these patients fulfilled the criteria for KD later during the disease course.

The majority of our cases, 139 out of 159 (87.3%), received aspirin (50-80 mg/Kg/day during the acute phase of the disease, and 3-5 mg/Kg/day thereafter). IVIGs was administered (400

mg/Kg/day for 5 days, 18 patients, and 2 g/Kg in a single infusion, 121 patients) from day one to day 51 from the onset of fever (mean day 8). All children who did not receive IVIG therapy were diagnosed before the introduction of gammaglobulin in the standard treatment of KD. Five patients received two cycles of IVIG for the persistence of high fever and severe coronary damage, and all had a prompt amelioration of both systemic features and coronary dilatation. None of our patients required steroids for the control of the disease.

Echocardiographic evaluation of the coronary arteries has been performed in all patients at presentation, and at 2, 4 and 8 weeks after the onset of clinical symptoms, and follow-up at 6 to 12 months. Patients with coronary abnormalities were followed up to the echocardiogram normalisation; patients with normal echocardiograms at 2-month follow-up did not present alterations at subsequent evaluations.

Coronary artery abnormalities, including ectasia (lumen diameter > 2.5 mm in a child < 5 years), and aneurysms (lumen diameter at least 3.5 mm in a child < 5 years and 4 mm in a child \geq 5 years) were observed in 30 (18.8%) out of 159 children; 21 were males and 9 females, with 2 children, one infant of 4 month and 1 boy aged 5 years, developing giant aneurysms (lumen diameter > 8 mm).

Mean fever duration, ESR and CRP values in patients with CAA were not different from the whole group, whilst baseline hemoglobin levels were lower with CAA than in patients not developing coronary alterations. IVIG had been administered in 28 out of 30 patients with coronary abnormalities. The day of administration of IVIG was not different in the children with coronary abnormalities than in the whole group. Other cardiac complications were pericardial effusion detected in 21 patients, and ECG conduction alterations in 10 patients.

The disease course was typical in the majority of our children and the outcome was favorable. Only a four month old infant had a fatal outcome as he developed cardiac arrest and myocardial infarction seven weeks after the onset of fever. 2D-echocardiogram revealed giant aneurysms in both coronary arteries. In this baby KD was not initially suspected and IVIG was only administered at admission in the Intensive Care Unit, 40 days from fever onset. In most of the patients coronary abnormalities normalised in a period ranging from 6 months to 1 year; only in 8 patients did they last more than one year, and in 4 the lesions were permanent, even though the lumen diameter of the aneurysm decreased.

CONTROVERSY AND CHALLENGES

Despite the numerous efforts to improve the early diagnosis, KD remains a disease at risk to be under recognised or misdiagnosed with other febrile illnesses in young children. Since no diagnostic tests are available, the diagnosis of KD is still based on clinical criteria. The atypical onset and the incomplete cases represent a major challenge for pediatricians.

Even though the early administration of IVIG has dramatically reduced the rate of coronary abnormalities to less than 5 %, KD is still the most common cause of acquired heart disease in children living in UK and the USA, and represents a risk for adult ischemic heart disease. Moreover, a considerable proportion of children with acute KD do not respond to standard therapy with IVIG, and 10% - 30 % of children have fever for 72 hours or more after the initial therapy with IVIG. At onset it is impossible to distinguish IVIG responders from non-responders, as both may have similar demographic and clinical characteristics, initial cardiac involvement, and overall outcomes (49-53).

There is still debate about the appropriate treatment of children who are unresponsive to the first treatment with IVIG. While there is general agreement that gammaglobulin significantly reduces the risk of cardiac complications compared with aspirin only as initial treatment, additional administration of IVIG do not appear to be highly effective against persistent or recurrent fever, even though they have been shown to be safe. In contrast, corticosteroids seem to be more effective in the control of fever when compared to IVIG. Previous studies suggested that children who received corticosteroids and aspirin as initial treatment may have an increased risk of developing CAA. Recently the use of corticosteroids is being reevaluated as an optional therapy in non-responders to IVIG. A very intriguing topic is the role of different parameters on the risk of developing coronary disease. Although no definitive data have been obtained; determinants of the risk of coronary aneurysms have been considered longer duration of fever, lower IgG levels, higher IgA levels, and a lower hemoglobin value after IVIG infusion (52, 53).

Even after IVIG introduction, KD remains a disease with high morbidity. In a recent study from Nakamura et al., the mortality among persons with a history of Kawasaki disease and cardiac sequelae in Japan was higher than in normal population (6). An improved understanding of the etiology of this disease and a clearer definition of the possible predictors of coronary involvement are needed to better control coronary damage (51).

Therefore, pediatricians have to be extremely cautious when facing young children with persistent high fever, red lips and irritability. If KD is not recognised early, the child may not receive the effective early therapy and may develop coronary alterations that in some cases may be severe and irreversible, leading to myocardial infarction or giant aneurysms. Conversely, if KD is diagnosed in a child with another disease, the appropriate treatment for the unrecognised disease is delayed and costly diagnostic and therapeutic interventions may be performed. The high-risk groups for coronary artery disease are infants younger than 6 months of age, and older children with very high platelet count, high ESR and fever lasting for more than 2 weeks.

CONCLUSION

Pediatricians have to be very aware of KS when facing a child with persistent high fever of unknown origin, red lips and irritability. In many cases the diagnosis represents a diagnostic dilemma, in particular in neonates and older children. However, the high risk of coronary alterations obligates early and aggressive introduction of the appropriate treatment even in those patients who do not fulfill the diagnostic criteria. The atypical onset or incomplete cases of KD present a special and difficult challenge for pediatricians caring for children with high persistent fever. One clinical tip that could help in the diagnosis is the irritability present in the majority of children with KD.

It has been reported that most of coronary aneurysms occurring during the acute phase of the disease regress within several years. Yet recent studies show that abnormal vascular wall morphology and vascular dysfunction may persist at the site of regressed alterations despite normal angiographic findings (54, 55). The long-term prognosis and natural history of KD remain uncertain. In adult life premature atherosclerosis may develop in these patients, with a risk for myocardial infarction. Smoking, dietary fat and additional risk factors for atherosclerosis should be avoided. Cardiologists should follow KD children with CAA well into adult life.

No recent guidelines are available to use to counsel parents and children about sports in children who suffered from KD. Lacking guidelines, it may be prudent to perform stress testing even in absence of CAA and consider avoidance of strenuous athletics. Despite the fact that more than 30 years have elapsed since KD was recognised in Japan, many questions still remain unanswered. A

better understanding of etiologic agents and genetic predisposition is required in order to improve the quality of life of children with KD in the third millennium.

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Legends.

Figure 1. The picture shows typical bilateral conjunctivitis and red lips in a four-year old boy with Kawasaki Disease.



Figure 2. Digital peeling in a 18-month old boy with typical Kawasaki Disease.



TABLE 1

KAWASAKI DISEASE: DIAGNOSTIC CRITERIA	
Fever	Duration of 5 days or more plus 4 of the following
1. Conjunctivitis	Bulbar, non-suppurative, bilateral
2. Lymphadenopathy	Cervical > 1.5 cm
3. Rash	Polymorphous, non vesicles or crusts
4. Changes of lips or oral mucosa	Red cracked lips; "strawberry tongue; diffuse erythema of oropharynx
5. Changes of extremities	Initial stage: erythema and oedema of palms and soles Convalescent stage: peeling of skin from fingertips

Kawasaki disease may be diagnosed with fewer than 4 of these features if coronary artery aneurysms are detected