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Case Report

# Recurrence of Kawasaki Disease in a Young Infant

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## Abstract

Kawasaki disease is an acute self- limited febrile illness of unknown cause that affects children less than 5 years old. It is prevalent amongst the Asian population, and ten times more common in Japanese children. There are three phases of the disease. Our patients, an 18 month-old female toddler had a recurrence of Kawasaki disease 7 months after the initial episode of incomplete Kawasaki disease at 4-months-old. She responded well to intravenous immunoglobulin and aspirin, and did not have cardiovascular complications.

## Introduction

Kawasaki disease is also known as mucocutaneous lymph node syndrome. It was first described by Tomisaku Kawasaki in 1967. The age group involved is usually 1 year to 5 years old [1]. Boys are more susceptible than girls with a ratio of 1.5;1. Siblings have a relative risk of tenfold in the Japanese population [2]. Twins have up to 100 fold risk of recurrence [3].

The acute phase in the first 2 weeks of illness, starts with high grade fever longer than 5 days, followed by at least 4 of the following 5 criteria: non-exudative conjunctivitis, polymorphous skin rash, lips and oral mucosa changes (redden, dry or cracked lips and strawberry tongue, diffuse oral and pharyngeal hyperemia, cervical lymphadentis, extremities and perineum changes (erythema of palms or soles, indurative oedema of

hands or feet and desquamation of perineal skin). Laboratory investigations reveal raised inflammatory markers, neutrophilic leucocytosis, normocytic normochromic anaemia, elevated serum transaminases and sterile pyuria [1].

The subacute phase lasts from 3rd to 4th week of illness. Majority of patients have skin desquamation starting in the subungual regions of the fingers and spreading to palms and soles in combination with rising platelet count. Arthralgias or arthritides may occur. Convalescence phase occurs 5th to 8th week after onset of illness. The prevalence of cardiac abnormalities is higher amongst infants, males and children older than 5 years old [1]. Children with incomplete Kawasaki disease do not fullfil the above criteria, and its incidence is higher in infants. They have a higher risk of developing coronary artery dilatation and aneurysm [1].

The standard treatment is intravenous immunoglobulin (IVIG) infused over 10-12 hours, aspirin 30 to 100mg/kg/day in 4 divided doses until normalisation of inflammatory markers and subsequent antiplatelet dose of aspirin 3-5mg/kg/day for 6 weeks starting in the subacute phase , and continued indefinitely if there are coronary artery abnormalities [1]. If fever is persistent or recrudescent, a repeat dose of IVIG is warranted or intravenous methylprednisolone 30mg/kg daily may be administered for 3 days. If large aneurysms develop, intravenous heparin or low molecular weight heparin is given. The alternative is warfarin with anti-platelet dose of aspirin [2].

## Case Report

We report an 18 month-old-girl who had Kawasaki disease at 4-months-old and a recurrence at 11-month-old. Our patient, a Chinese female infant, presented at the age of 4 months with fever for 4 days, diarrhoea, rash and conjunctival injection for 1 day. The rash started on the face and progressed to the back, with an indurated BCG scar. She was the second child in the family, with appropriate developmental milestones and immunized. Examination revealed a fretful infant who had bilateral conjunctival injection, reddened lips and a polymorphous rash. There was no lymphadenopathy or strawberry tongue. She had high grade temperature, more than 38.5°C during the admission and was treated for incomplete Kawasaki disease. Her haemoglobin was 11.8g/dL, total white cell count of 12.2 X 109/L and platelet count of 419 X 109/L. C-reactive protein (CRP) was 12.49mg/dL. IVIG 2g/kg was administered, and fever resolved. Anti-inflammatory dose of aspirin was started, and reduced to the anti-platelet dose. Transthoracic echocardiogram revealed normal intracardiac anatomy, normal coronary artery dimensions and good biventricular systolic function.

Her 3-year-old brother was admitted in another hospital at the same time for Kawasaki disease and was given IVIG. However, her brother had mild bilateral coronary artery dilatation. During her clinic visits, she remained well with normal coronary artery dimensions on transthoracic echocardiogram.

At 11 months of age, she presented with fever for 4 days, indurated BCG scar, bilateral non-purulent conjunctivitis and papular rashes over both feet and hands. Her temperature was 38.2°C on admission. Examination revealed an appropriately grown infant with shotty cervical lymphadenopathy, indurated BCG scar, bilateral non-purulent conjunctival injection and a strawberry tongue. She had macular rashes over her hands and feet with edematous feet, and perioral skin peeling. Her haemoglobin was 11.3g/dL, total white cell count of 8.7 X 109/L and platelets of 430 X 109/L. C-reactive protein was 124mg/dL. She was treated

for recurrence of Kawasaki disease and IVIG 2g/kg was administered. Fever resolved with IVIG. Aspirin was administered. Transthoracic echocardiogram revealed normal intracardiac anatomy, coronary artery dimensions and good biventricular systolic function.

She has been well during her clinic visits with normal transthoracic echocardiograms findings.

## Discussion

Kawasaki disease is characterized by systemic inflammation in medium sized arteries and multiple organs and tissues during the acute phase. Clinical findings may include cardiovascular (myocarditis, pericarditis, valvular regurgitation, shock, peripheral gangrene), respiratory (interstitial pneumonitis), musculoskeletal (arthritis, arthralgia), gastrointestinal (diarrhoea, vomiting, abdominal pain, hepatitis, jaundice, gallbladder hydrops, pancreatitis), nervous system (irritability, aseptic meningitis, facial nerve palsy, sensorineural hearing loss) and genitourinary (urethritis, meatitis).

Children with incomplete Kawasaki disease may experience diagnostic delay. The following algorithm (fig. 1) is useful.

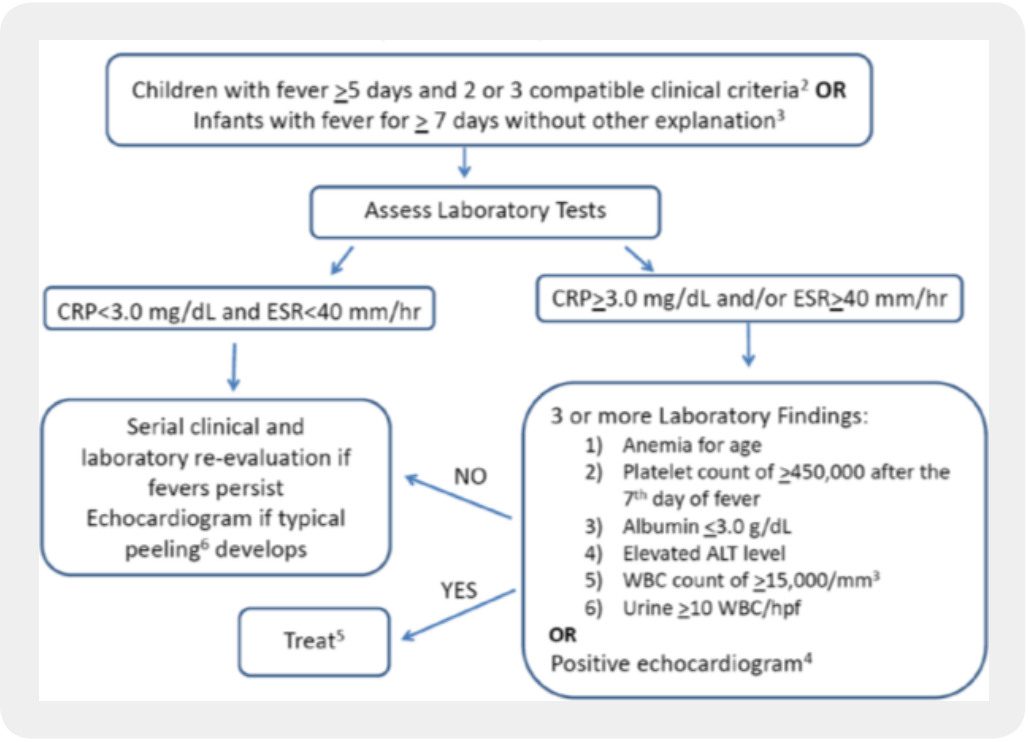


***Figure 1:*** *Evaluation of suspected incomplete Kawasaki disease*

Echocardiography remains the primary modality for cardiac imaging in Kawasaki disease. In uncomplicated patients, echocardiograms should be repeated at 2 weeks and 4 weeks after the treatment. In patients with evolving coronary artery abnormalities detected during the acute illness (z score >2.5), echocardiograms

should be performed twice weekly until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis [4].

The treatment of classic and incomplete Kawasaki disease is similar. Measles, mumps, rubella vaccination should be delayed 11 months after receiving IVIG [4]. Avoidance of contact sport is indicated during aspirin therapy [2]. Administration of IVIG is also recommended for children presenting after 10 days of illness if they have persistent fever or coronary artery abnormalities as well as elevation of erythrocyte sedimentation rate (ESR) and CRP >3.0mg/dL. Treatment options for IVIG resistant Kawasaki disease, defined as persistent or recrudescent fever for at least 36 hours and less than 7 days after completion of IVIG treatment are a second dose of IVIG or steroids (usually methylprednisolone 20-30mg/kg intravenously for 3 days, with or without a subsequent course and taper of oral prednisolone) or infliximab (5mg/kg). Cyclosporine may be considered in patients with refractory Kawasaki disease in whom a second IVIG infusion, infliximab, or a course of steroids has failed. Administration of immunomodulatory monoclonal antibody therapy (except TNF-α blockers) or rarely plasma exchange may be considered in highly refractory patients who have failed to respond to a second infusion of IVIG, an extended course of steroids, or infliximab [4].

Thrombolytic therapy such as streptokinase, urokinase or tissue plasminogen activator is indicated in myocardial infection due to acute coronary artery thrombosis. [2].

Recurrence of Kawasaki disease is rare [5]. The recurrence rates in Japan, China, Taiwan, Korea and the United States of America are 3%, 3.5%, 1.82%, 1.5% and 0.8% respectively [6]. It has a similar presentation to the initial episode but the duration of fever has been reported to be shorter [6]. Recurrence usually occurs within 2 years of the initial attack but may occur decades later [5]. The risk factors for recurrence are incomplete Kawasaki disease, atypical Kawasaki disease and resistance to IVIG [7].

A Chinese study showed that children with recurrent Kawasaki disease are more likely to present with incomplete signs, where as a Japanese study revealed that Kawasaki disease recurs less than 3 years after the initial episode and may present with a more serious illness compared to the initial presentation [8]. The highest recurrence rates are between the ages of 1 and 2 years old [6].

Two cohort studies in the United States of America and Japan respectively have shown that recurrence is more likely amongst Asian children and children treated with IVIG. A study by Nakamura *et al* showed that cardiac sequel are more often after a recurrence than the initial episode [9]. The risk factors of developing sequel at the second episode are male sex and cardiac sequel at the onset of illness [10]. Patients with recurrence of Kawasaki disease are at increased risk of developing cardiac complications [5].

Cardiovascular involvement is the most serious complication of Kawasaki disease. There are four stages of cardiovascular pathology. Stage 1 (less than 10 days) includes microvascular angiitis, acute endoarteritis and perivasculitis of major coronary arteries, pericarditis, valvulitis, myocarditis and endocarditis. Stage 2 (12-25 days) includes panvasculitis of major coronary arteries with aneurysms and thrombus formation, myocarditis, endocarditis, and pericarditis. In stage 3 (28-31 days), granulation of coronary arteries and marked intimal thickening occurs. In stage 4 (40 days-4 years), scarring, stenosis, calcification, recanalization of major coronary arteries and fibrosis of myocardium and endocardium may develop [2].

Coronary aneurysm develops in 15% to 25% of untreated patients and is responsible for myocardial infarction (<5%) and mortality (1% to 5%) [11]. Coronary aneurysms tend to develop in the left main coronary artery and proximal segments of left anterior descending and right coronary arteries (10). Significantly higher temperature on days 9 to 12 and longer duration of fever (more than 14 days) appear to be risk factors for coronary aneurysm. Despite prompt treatment with IVIG, transient coronary artery abnormalities develop in 5% of the patients and giant aneurysm in 1%. Angiographic resolution of aneurysm 1 to 2 years after the illness occurs in 50% to 67% of the patients, but these arteries do not dilate in response to exercise or coronary vasodilators. In some patients, stenosis, tortuosity, and thrombosis of the coronary arteries result. The resolution appears to be more likely to occur with a smaller aneurysm, age at onset younger than 1 year, fusiform rather than saccular aneurysm, and aneurysm located at a distal coronary segment [11].

Rarely, balloon angioplasty, rotational atherectomy or stenting may be indicated patients with evidence of reversible ischemia from coronary artery stenosis. However, in a long-term follow-up, neoaneurysm formation or restenosis may occur. On rare occasions, coronary artery bypass surgery may be indicated [11].

## Conclusion

Incomplete Kawasaki disease should be considered in children who present with fever for more than 5 days and 2 or 3 compatible clinical criteria or unexplained fever longer than 7 days for infants. Recurrence of Kawasaki disease usually occurs in the 2 years of life. The treatment and complications are similar to classical Kawasaki disease.

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