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Review Article

Kawasaki Syndrome: A Special View To New Entities Like MIS-C, PIMS and Kawasaki-Like Features In Covid-19 Disease With Recommendation of Classification

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Introduction

Kawasaki syndrome or mucocutaneous lymph node syndrome (MCLS) is an acute, febrile, systemic illness characterized by inflammation (necrotizing vasculitis) of the small and medium-sized arteries. In addition, systemic inflammation is present in many organs. The cause is unknown; an infectious origin is suspected, favored by a hereditary basis.

A great number of genetic studies have been performed and multiple single nucleotide polymorphism (SNP) and gene loci have been found. Other studies suggest an association between viral super antigens as the origin of Kawasaki disease, where streptococcal pyrogenic exotoxin and toxic shock syndrome toxin 1 play a favorite role. Kawasaki syndrome primarily affects young children. The condition is named after the Japanese pediatrician Tomisaku Kawasaki. After him, the Kawasaki Research Center has been named. In Germany, about 9 out of 100,000 children under the age of five are affected each year, while the incidence of Kawasaki syndrome in Japan in the same age group is about 185 out of 100,000. Seventy-five percent of all patients are younger than five years, and children in their second year of life are very frequently affected. Boys are affected by the disease about one and a half times as often as girls. In the northern hemisphere, there is more disease in winter and spring than in summer and fall; in contrast, there is no seasonality in tropical regions. Since 1 year, due to Corona pandemic, new entities were described in Kawasaki syndrome like MIS-C or PIMS or Kawasaki-like entities triggered by an infection of COVID-19. A new classification was recommended.

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Classification

- K1: Complete Kawasaki Syndrome
- K2: Kawasaki-like-Syndrome (incomplete or associated Kawasaki Syndrome)
- K2a) Multisystem inflammatory syndrome in children (MIS-C), no COVID-19
- K2b) Multisystemic inflammatory syndrome associated with COVID-19, unspecified [19,20]
- K2c) Paediatric inflammatory multisystem syndrome (PIMS)
- K2d) Cytokine storm temporally associated with COVID-19 [21]

Since April 2020, a novel syndrome similar to Kawasaki syndrome has been observed in the United States and some European countries and has been named MIS-C (multisystem inflammatory syndrome in children). MIS-C may be related to infections caused by the SARS-CoV-2 agent. WHO called for surveillance and research of MIS-C in May 2020.As of mid-May 2020, 103 children in New York State alone had been treated with symptoms resembling Kawasaki syndrome. Of these children, 60% tested positive for COVID-19 disease caused by the pathogen, and antibodies to SARS-CoV-2 were detectable in the remaining 40%. The age group from 5 to 14 years is particularly affected.

Symptoms

1. Primary Symptoms

- **Fever at 100%:** Longer than 5 days, resistant to antibiotics, can be reduced by antipyretics, with recurrent peaks above 40 °C, persisting for about 10 days without therapy.
- Up to 90 % symptoms of the oral cavity, lips, dry, often swollen, highly red, cracked lips, strawberry tongue (varnish tongue), intense redness of oral mucosa and pharynx, as long as fever persists.
- **Up to 85 % Conjunctivitis:** Mostly bilateral conjunctival redness, not purulent, painless, begins shortly after fever, lasts about 7 days.
- **Up to 80 % Exanthem:** Multifaceted, usually non-pruritic, rash without vesicles, appears within 5 days after onset of fever ("variegated picture," often similar to measles or scarlet fever, but sometimes similar to purpura Schönlein-Henoch).
- **Up to 70 % hands and feet:** Acute redness and painful swelling in the area of the palms and soles. From the second to third week of illness, scaling of the skin that begins on the tips of the fingers and toes and may spread over the entire palms of the hands and feet.
- **Up to 70% enlargement of the cervical lymph nodes:** Acute, nonpurulent, little painful swelling of the cervical lymph nodes, often unilateral in the anterior triangle of the neck with a diameter of more than 1.5 cm.

2. Secondary Symptoms

- **Cardiovascular symptoms:** These occur mainly in the early phase and are largely responsible for long-term morbidity and mortality: myocarditis (50%), pericarditis, valvular problems, aneurysm formation of the coronary and

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other arteries, Raynaud's symptoms.

- **Neurological symptoms:** Often marked irritability, noninfectious meningitis, central hearing loss.
- **Respiratory:** Cough, rhinitis, hoarseness.
- **Abdominal symptoms (in 30% of all patients):** Abdominal pain, diarrhea, vomiting, paralytic ileus, gallbladder hydrops (sonographically detectable in 15% of all patients), enlargement of liver and spleen.
- **Urinary tract:** Urethritis with pain on urination and leukocytes in urine.
- **Joints:** Pain and, less commonly, inflammation in multiple joints during the first week of illness, with onset of these complaints after day 10 more likely in large weight-bearing joints.
- **Eyes:** Uveitis anterior, which improves rapidly and heals without consequences.

Diagnostic Tests

The diagnosis of complete Kawasaki syndrome is made clinically and requires the presence of fever and four out of five of the other criteria mentioned, as well as the exclusion of other diseases with similar symptoms. In that case, the diagnosis may be made after only five days of fever. Children who do not meet these criteria are diagnosed as having so-called incomplete Kawasaki syndrome if secondary symptoms and/or laboratory findings listed below are partially or predominantly true. This is more common in children less than one year of age and is particularly problematic here because of the increased risk of coronary artery aneurysms. Laboratory findings cannot prove or disprove the disease; they may make the tentative diagnosis more likely or less likely in the presence of inconclusive clinical signs:

Serology

AECA (anti-endothelial cell antibodies)

Leukocytes

Leukocytosis with left shift (50% of patients have > 15 leukocytes/nl).

Blood cell sedimentation rate, CRP

Frequently elevated, sometimes severely elevated.

Hemoglobin

Increasing anemia with longer duration of disease.

Platelets: Severely increased number, often from the second to third week of illness, then also > 1 000 platelets/nl.

Transaminases: Frequently slightly elevated serum levels.

Albumin: Decreased, more pronounced with prolonged and severe disease.

Sodium: Decreased, possibly also reflecting increased ADH secretion.

Urine: Sterile leukocyturia.

CSF: Increased monocytes in 30 to 50%, often without protein elevation.

Articular fluid: Sterile, > 100 000 leukocytes/ml.

New Biomarker in Kawasaki Syndrome

New marker in urine. In 2012, American researchers succeeded in finding markers in the urine of affected children that make the disease more quickly diagnosable with certainty. These biomarkers are filamin C (excreted in the urine from necrotic heart and skeletal muscle cells) and meprin A (enzyme of the inflammatory response). Diagnosis using these markers was made

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with 98% accuracy in a study of 107 patients.

Therapy

The long-term course of the disease depends on whether changes occur in the coronary arteries and which kind of Kawasaki entity it is. In about 25% of untreated children, one or more aneurysms develop. In this case, daily use of a mild blood thinner, such as acetylsalicylic acid (100 mg) is recommended in children. About half of these aneurysms regress within a year. In about 20% of patients, stenoses develop over the course of years, which in turn lead to myocardial infarction in almost half of cases if left untreated. The disease is commonly treated as an inpatient. Therapy aims to reduce inflammation and prevent aneurysms of the coronary arteries, which usually develop in the second to third week. It has been shown that therapy can reduce the incidence of coronary artery aneurysms from 25% to 2% to 4%. Therefore, initiation of therapy before day ten is critical for a favorable outcome. In Kawasaki-like features like MIS-C, PIMS etc. different treatment options were initiated and clear guidelines in treatment are not clearly ruled out and part of further clinical study and research.

Initial Therapy

Immunoglobulins: 2 g/kg body weight in twelve hours as an infusion, possibly another time after very early administration and unsatisfactory response. Acetylsalicylic acid (ASA) in high doses (30 to 100 mg/kg/day) for 14 days until the acute inflammation subsides. The dose is controversial. Whether cortisone-like drugs are helpful in "treatment failures" is still a subject of research; they probably show at least an additive effect. Cortisone pulse treatment was no better than placebo. Longer-term follow-up therapy is recommended with acetylsalicylic acid 3 to 5 mg/(kg*day) for about six to eight weeks. Further measures depend on the occurrence of coronary aneurysms: As long as an aneurysm exists, ASA should not be discontinued in the low dosage under any circumstances. If a large aneurysm with narrowing has formed, blood clotting should be inhibited, if necessary, using other drugs such as phenprocoumon. Furthermore, bypasses etc. may be considered.

Long-term Expectations

The acute disease usually heals without complications (1-11). If complications occur in the coronary arteries, the current assessment is that the risk of atherosclerosis is increased due to the altered vessel wall (2-13). For this reason, Kawasaki patients should undergo long-term cardiac follow-up (1-21). Research is focusing on analyzing viral super antigens and the concrete gene loci in the different types of Kawasaki disease to get prognostic information's about the course of the disease. Kawasaki disease is, despite extensive research, still not completely understood. Further intensive research; especially in the new entities since begin of corona pandemic, necessary and important to completely understand the disease and their similar features in children like MIS-C or PIMS.

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