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CLINICAL CHARACTERISTICS, DIAGNOSIS AND THERAPY OF KAWASAKI DISEASE IN CHILDREN

Pediatrics

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ABSTRACT

Kawasaki disease is an acute systemic vasculitis that was initially reported in 1961. Since more than last 50 years numerous research articles have been published which are useful in comprehending this disease. The diagnosis of Kawasaki disease completely depends on the clinical findings. Classical Kawasaki patients fulfill all the AHA criteria whereas Patients with atypical Kawasaki diseases are those who present with only few criteria. The chief impediment of Kawasaki disease is coronary aneurysm, and the treatment is intravenous immunoglobulin, aspirin, corticosteroid, anti-platelets agents and oral anticoagulant. A 2nd dose of immunoglobulin is administered if the patient does not improve, and various other drugs have been recently suggested over the last 5-10 years as subsequent and alternatives treatment for Kawasaki disease.

KEYWORDS

Kawasaki Disease, Coronary Aneurysm, Aspirin, Vasculitis, Inflammatory Disorders, Intravenous Immunoglobulin

INTRODUCTION:

Kawasaki disease (KD) is a systemic vasculitis generally affecting medium-sized arteries. Foremost symptoms comprises of fever, conjunctivitis, skin and mucous membrane involvement as well as cervical lymphadenopahty (1). The name Kawasaki disease had been assigned to this disease after Japanese pediatrician Tomakisu Kawasaki who gave detailed explanation of occurrence of this type of vasculitis in 50 children in 1967 (2). Though, inflammatory alterations can affect any arterial vessels of the body, coronary arteries are the most commonly affected ones(3). In cases of late diagnosis and delayed commencement of treatment, inflamed coronary arteries can progress to aneurysmal changes leading ultimately to fatal myocardial infarctions. Worldwide, Kawasaki disease is the most common and important cause of childhood vasculitis (4).

History of Kawasaki disease:

The disease was first described by the Japanese pediatrician Tomisaku Kawasaki in January 1961 who died recently in 2020 (5).

It is also called "muco cutaneous lymph node syndrome ". Kawasaki came across a 2-year-old male patient in 1962 who presented with high fever for two weeks, bilateral conjunctival hyperemia, fissured, dried, reddish and bleeding lips, strawberry tongue and diffuse erythema of the oral cavity and mucous membrane (6). The patient also had left cervical lymphadenopathy which was followed by right cervical lymphadenopathy. He had Red palms and soles and polymorphous erythema were present throughout his body (7). After almost five years of this primary case, Dr. Kawasaki reported fifty cases with comparable presentations, following which he published a article titled "Acute febrile musculocutaneous lymph node syndrome: clinical examinations of fifty cases" in the Japanese Journal of Allergy in 1967. During 1970, Kawasaki was allotted appropriate financial support to study the disease and he succeeded in establishing the early diagnostic strategy (5).

Epidemiology:

Kawasaki disease has a worldwide prevalence and has been established in children of different ethnicities globally. The frequency of KD is more in Asian nations like Japan, where the yearly prevalence rate is 264/ lac children which was 239/ one lac children in 2010 (8). It has been accounted that the highest occurrence of Kawasaki disease is in months of January and July and lowest in month of October. The prevalence of the KD was also highest in the united state through winter and early spring. Korea (134/lac children) and Taiwanese (66/lac children) are at second and third places respectively as far as prevalence of the disease is concerned (9). The prevalence is significantly less in non-Asian countries, 8/ one lac children in England and 9/ one lac children in Australia (10).

Etiology-pathophysiology and clinical presentation:

Numerous hypotheses have been proposed for the etiology of KD. A modern fact sturdily recommends that genetic aspects have a more significant role in the incident of KD. Polymorphisms of the IgG receptor can amplify the vulnerability of children to disease and raise the jeopardy of rising coronary artery aneurysm. In 2013 Jaggi et al. advised that there might be an association between an infection with adenovirus and the inception of disease (11). Another study has reported that a virus might have been inhaled and afterward engulfed by tissue macrophages leading to activation of the innate immune system (12). Furthermore, activation of the adaptive immune responses can lead to antigen specific T lymphocytes and plasma cell activation. The presence of the infection in coronary tissue leads to secretion of multiple growth factors like vascular endothelial growth factors (VEGF), tumor necrosis factor-Alfa (TNF-α), and metalloproteinase , leading to devastation of the intima, and fragmentation of the internal and external elastic lamina of the coronary artery resulting in the development of coronary artery aneurysm (13). Furthermore, there is swelling of the Lymph node and the skin and the mucous membrane inside the mouth, throat and nose has been affected. The disease causes inflammation of the wall of medium sized arteries throughout the body and it has a tendency to affect the coronary arteries (9). It primarily affects children under the age of 5 years but during this covid pandemic it has been largely diagnosed in adolescent age group patients (14). The disease is treatable and most children recover without any complication but presentation of Kawasaki as high fever and skin peeling can be frightening to the parent and the patients. During this covid era children may present with symptoms of Kawasaki which is due to systemic inflammatory syndrome (SIS-C)(15). Symptoms usually appear in three phases. Phase 1: Temperature is greater than 102° F lasting for more than 3 days, extremely red eye without thick discharge, rash over body and genital area, erythematous palms and soles, enlarged inflamed lymph nodes in cervical region and irritability.Phase2: Peeling of skin on the hands and feet specially the tips of the fingers and pain in joints of toes, diarrhea, vomiting and abdominal pain Phase 3: If complication does not develop patient starts showing signs of recovery which may take as long as 8 weeks (16).

Complications of Kawasaki disease:

It is the most leading cause of acquired heart disease in children. It can lead to many cardiac complications which includes Inflammation of coronary arteries, dilatation of coronary arteries, inflammation of cardiac muscles, pericarditis, pericardial effusion, left ventricular dysfunction, arrhythmias, cardiac valve disease. In addition, inflammation of the coronary arteries can lead to weakening and bulging of its wall leading to aneurysm which can lead to formation of blood clots in it leading to heart attack or life threatening internal bleeding (17).

DIAGNOSIS:

The diagnosis of Kawasaki disease depends generally on the various clinical signs and symptoms in patients. The diagnostic criteria of KD necessitate the existence of fever of at least five days along with four out of five other clinical features which is suggested by the American Heart Association (AHA) in 2004 1.Conjunctival injection : Bulbar , Bilateral, Painless, Nonexudative 2. Lymphadenopathy: Cervical, usually unilateral and of more than 1.5 cm diameter, 3. Skin rash: Commonly maculopapular 4. Extremity changes: During acute phase erythema and indurations of hands and/or feet, subsequently periungual desquamation may follow 5. Mucosal changes: Red, cracked lips, Glossitis with hyperplasic fungi form papillae seen as strawberry tongue, diffuse erythema of the oral mucosa or oropharynx (18). Different inflammatory markers like CRP, TNF-α, Leptin, geharlin and B-type Natriuretic peptide (BNP) can help in early diagnosis of the disease. Blood reports of patients of KD will invariably show anemia and leukocytosis (19). Thrombocytosis, Hypoalbuminemia, increased levels of liver enzymes and sterile pyuria can be associated (20-22). An ECG as well as Echocardiography may help rule out the existence of any early coronary artery involvement. Furthermore, we have to rule out KD with other diseases having similar presentations such as scarlet fever (present with fever with chills rash and sore throat), juvenile rheumatoid arthritis, toxic shock syndrome, Stevens Johnson syndrome and Rocky Mountain spotted fever (tik born) (23).

TREATMENT:

It is highly suggested to begin the treatment straight away if the patient fits in the clinical diagnostic criteria for Kawasaki disease. It is managed by intravenous immunoglobulin and High dose of aspirin. A study reported that administering corticosteroids with intravenous immunoglobulin as primary treatment has a superior outcome on decreasing the jeopardy of coronary artery disease as compared to the use of intravenous immunoglobulin alone (24-25). The intravenous immunoglobulin can avert the formation of coronary artery aneurysms. It has a dose-dependent outcome. A single dose of 2 g/kg is given within ten days of sickness or afterward if the patient has signs of inflammation, constant fever or aneurysm on echocardiography. Immunoglobulin can also be given in a dose of 1gm/kg/day for 1-2 days or 400mg/kg/day for 4-5 days. The intravenous immunoglobulin can sway the T cell bustle and decrease the synthesis of antibodies and cytokines responsible for the symptoms of Kawasaki disease (26).

High dose Aspirin alleviates inflammation and prevents the risk of thrombosis. It can decrease pain and inflammation of joints. It can also reduce fever. The AHA has suggested a dose of 80 to 100 mg/day divided into four daily doses till the patient is afebrile for 48 to 72 hours (27). Then the dose is decreased to 3 to 5 mg/ kg/day as a single dose for 6 to 8 weeks. If the patient develops coronary artery aneurysm it should be given for longer than this duration. Patients of refractory Kawasaki disease with coronary aneurysm can be treated with aspirin along with antiplatelet drugs. Bigger aneurysms can be treated with heparin followed by oral anticoagulant warfarin. It is also been proposed and suggested that KD can be treated with cyclosporine A and methotrexate. Cyclosporine A is a calcineurin inhibitor that targets the Ca2+/NFAT signaling pathway (28). It leads to a decrease in inflammatory response as per various studies. Anti cancer drugs such as Methotrexate can inhibit enzymes involved in purine metabolism leading to accumulation of adenosine in the cells. Since the mechanism of action and its role in Kawasaki disease are not completely known, the AHA has not given any suggestion for its use in Kawasaki disease (29).

CONCLUSIONS:

KD still remains an inadequately understood disease; it can be managed with appropriate treatment and follow-up. The goal of treatment is prevention of post KD cardiac complication and death. A quick diagnosis and early treatment can enormously help in improving the prognosis and in lessening the complications of Kawasaki disease. Modern diagnostic tools like BNP, as a biomarker for quick diagnosis and early use of gamma globulin and aspirin as treatment of the KD can certainly be useful in combating the disease and preventing the dreaded complications of this disease.

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