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KAWASAKI DISEASE

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Abstract: Kawasaki disease has an unknown etiology. It is an acute febrile systemic vasculitis that mainly affects infants and young children, causes coronary artery aneurysms, and can lead to long-term cardiovascular complications, with intravenous immunoglobulin and aspirin being the treatment of choice in many countries. If the patient does not respond, a double dosage of immunoglobulin is given, and various alternative second and third-line therapy options have been suggested in recent years. Even though KD is commonly seen in young children, it can also be observed rarely in adolescents and adults. Early diagnosis and treatment of Kawasaki disease are difficult due to a lack of specific diagnostic techniques and biomarkers. This review has summarized pathophysiology, clinical manifestations, etiology, epidemiology, genetic correlations, interventions to prevent coronary aneurysms, and advances in treatment options. Because treatment of post-COVID-19 multisystem inflammatory syndrome in children is entirely drawn from KD therapy approaches.

Index Terms-Kawasaki disease, coronary artery aneurysms, unknown etiology, immunoglobulin, lack of specific diagnostic techniques, post-COVID-19 multisystem inflammatory syndrome.

1. INTRODUCTION

Mucocutaneous lymph node syndrome is another name for Kawasaki disease (KD). It is an autoimmune disease linked to acute febrile systemic vasculitis and primarily affects newborns and young children under the age of five (Kawasaki, 1967; Newburger et al., 2004). The etiology associated with the diseases remains unclear. It predominantly affects the coronary arteries. Dr Tomisaku Kawasaki in Japan was the first to recognize the condition in 1967 (Watanabe et al., 2022; Brogan et al., 2019). Both in China and Western countries, it is rapidly becoming the primary cause of heart disease in children (Xie et al., 2020). Even though KD is commonly seen in young children, it can also be observed rarely in adolescents and adults. The CAA risk is more at extremes of age than in children aged 1-9 years. However, the risk of developing CAA is higher in infants than in adolescents. This is because of delayed diagnosis and initiation of treatment (Manlhiot et al., 2009). The probability of developing hepatitis, arthralgia, and cervical lymphadenopathy is higher in adults than in children. At the same time, aseptic meningitis and thrombocytosis are significantly less in children than in adults (Wolff et al., 2007). KD is at present of special attention because KD-like disease is seen in young children suffering from the post-COVID-19 multisystem inflammatory syndrome, and its treatment is resulting from KD therapy options so far (Hoste et al., 2021). In this view, we have summarized the current understanding of KD genetics, epidemiology, pathophysiology, and treatment strategies.

2. CLASSIFICATION OF KD

Complete KD represents all major clinical manifestations. KD is referred incomplete when a child had a fever for > 5 days with < 4 out of 5 principal clinical signs. Incomplete KD, diagnosis, and treatment are challenging for clinicians (McCrindle et al., 2017). KD is atypical when there are one /more atypical signs of Kawasaki disease like retinal vasculitis, pulmonary (e.g., pneumonia), CNS (e.g., meningoencephalitis and facial palsy) involvement, uveitis, myositis, arthritis, and nephritis. Diagnosing Kawasaki disease is more difficult in the case of atypical signs. Pulmonary sequelae of KD can be very tough, even for astute clinicians (Singh et al., 2017). Systemic artery aneurysms are reported in < 3% of KD patients.

3. EPIDEMIOLOGY

The Kawasaki disease incidences are highest in China, Taiwan, Japan (Makino et al., 2018), and South Korea. While it was much lower in the Middle East and Latin America, European countries, Australia, India (Elakabawi et al., 2020) and the UK. In recent years, the incidences increased in Asian countries, mainly Japan and Taiwan. KD occurrence in Northeast Asian countries is ten to thirty times higher than in the USA and Europe (Brogan et al., 2019; Xie et al., 2020; Lee et al., 2022; Kim, 2019). In Japan, one in hundred children develops the illness by age five; however, the lowest incidence is seen in sub-Saharan Africa (Elakabawi et al., 2020).

4. ETIOLOGY

The etiology of the KD is unknown; however, epidemiological studies reveal that seasonal changes in the wind and environmental agents are responsible for an inflammatory process in hereditarily predisposed persons (Rodo et al., 2014). However, stimuli are supposed to be of viral origin and penetrate the body through mucosal surfaces in the lungs (Rowley, 2018). A human coronavirus was often identified in the KD patients' respiratory secretions (Esper et al., 2005). In some patients, staphylococcal shock syndromes were observed (Faulkner et al., 2005). Several early studies in Japanese children with KD compared with sex and age-matched control patients displayed reduced commonness of antibodies to the Epstein–Barr virus capsid antigen (Iwanaga et al., 1981; Kikuta et al., 1990; Kikuta et al., 1988). While the protein epitopes appear to be involved in hepacivirus, further investigations are needed to establish the definite gene sequence from which this peptide arises (Rowley et al., 2019). Based on serological and PCR examinations, microorganisms like *Candida albicans, Mycobacterium ss, Mycoplasma pneumonia, Lactobacillus casei, Bacillus cereus, Yersinia pseudotuberculosis, Staphylococcus aureus, Streptococcus pyrogens,* Unidentified RNA virus, Human coronavirus HCoV-NL63, Adenovirus, Human parvovirus B19, Human bocavirus (HBoV), Human immunodeficiency virus, measles virus, respiratory syncytial virus, enteroviruses, dengue Virus, A variant of Torque teno virus *Acinetobacter boumanni, E Coli*, Bocavirus, *Aspergillus* spp contribute to the pathogenesis of KD (Singh et al., 2017; Nakamura et al., 2019; Gamez-Gonzalez et al., 2018). In the genetically predisposed subset of KD patients, an unknown RNA virus infecting the bronchial epithelium typically causes asymptomatic infection. The virus endures in inclusion bodies, with alternating respiratory shedding, and enters the bloodstream through macrophages targeting coronaries. Coronaries are damaged, but CD8 T cells and antigen-specific IgA plasma cells respond. More than 95% of patients post-infection develop immunity to the virus and protect against relapse. The spread of the virus is either from those a previously infected contact or with asymptomatic primary infectivity in winter-spring (Rowley & Shulman 2018). Both prenatal and postnatal exposure to nitrogen oxide, nitric dioxide, nitric oxide, carbon monoxide, and pollutant standards index increased the KD incidences (Kuo et al., 2022).

5. POSSIBLE MECHANISMS OF KD PATHOGENESIS

Superantigens and pathogen/microbe-associated molecular patterns are produced by various infectious pathogens. T cells, including potentially auto-reactive T cells, are activated non-specifically by sags. Through cellular pattern recognition receptors (Dectin-1/-2 NOD1, TLRs,) MAMPs/ PAMPs also stimulate immune cells [monocytes, dendritic cells, and macrophages] & endothelial cells. This stimulation causes a systemic inflammatory response by increasing the production of pro-inflammatory cytokines/chemokines and NOS/ ROS. MAMPs/ PAMPs, on the other hand, activate the complement lectin pathway via soluble PRRs (mannose-binding lectin-2, ficolin-1). This activation can cause inflammatory vascular damage by attracting innate inflammatory cells and injuries ECs. Individual genetic backgrounds determine the intensity of the inflammatory response, resulting in a small number of children developing KD in response to infectious triggers (Figure 1) (Nakamura et al., 2019).

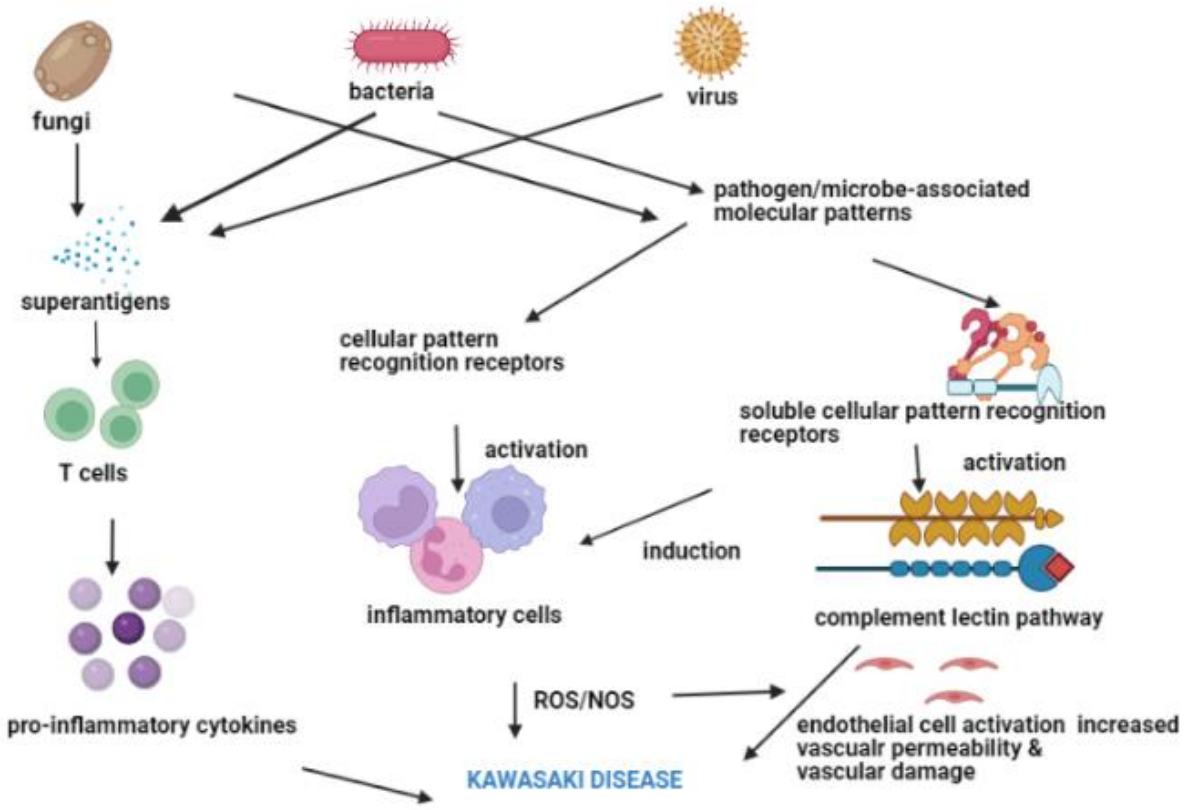

Fig. 1 Pathogenesis of kawasaki disease

6. SIGNS AND SYMPTOMS

General clinical symptoms include high fever that persists for 5 days or even longer, diffuse erythematous polymorphous rash, changes in the oral cavity and lips, strawberry tongue, sometimes with perineal desquamation, cervical lymphadenopathy, ocular conjunctival hyperemia, reactivation of the bacillus Calmette– Guerin injection site, and edema over feet and hand all these manifestations were observed in the 1st week of KD. In the 2nd week, peeling of the skin is also seen in KD patients (Figure 2). If not diagnosed and treated in time, about 25% of the patients develop occlusion, coronary stenosis, coronary artery dilatations, inflammation, and coronary artery aneurysms, which are the major severe complications of KD and even death; all these critically affect patients' lives and health (Newburger et al., 2004; Watanabe et al., 2022; McCrindle et al., 2017; Dietz et al., 2017; Newburger et al., 2016). The cardiovascular events resulting in childhood extended to adulthood, and the KD is no longer considered self-limiting (Noval Rivas & Arditi, 2020). About 60% of patients diagnosed with KD experienced vomiting, diarrhoea, and abdominal pain at the onset of acute illness (Yaniv et al., 2005; Colomba et al., 2018). Other symptoms like hydrops of the gall bladder, myocarditis, peripheral arthritis, paralysis of the extremities, sterile pyuria, mitral valve regurgitation or pericardial effusion, reduced level of consciousness, paralytic ileus, cough, transverse grooves across the fingernails, retropharyngeal edema, infiltrate on chest radiograph, CSF pleocytosis, palsy of facial nerve, rhinorrhea, seizures (Singh et al., 2017; Kobayashi et al., 2020). Peripheral gangrene is rare but seen in some KD patients (Jindal et al., 2019).

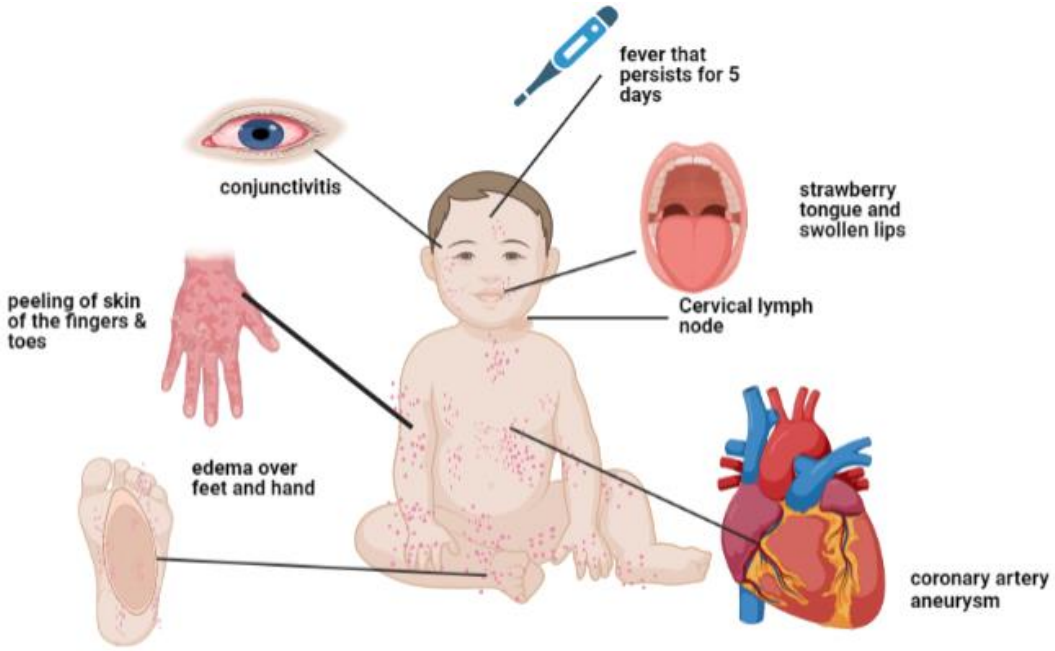

Fig. 2 Signs and symptoms of KD

7. PATHOPHYSIOLOGY

The histological outcome reveals that coronary arteritis begins six to eight days after inception and develops into pan-vasculitis on about day tenth of acute Kawasaki disease. Aneurysms progress on or around day twelfth and are escorted by demolishing the internal elastic media & lamina. In acute KD vasculitis, Smooth muscle cells are seen in the intima and are believed to involve in vasculitis development. LR11-a member of the low-density lipoprotein receptor family is noticeably articulated in vascular smooth muscle cells in the intima of atherosclerotic lesions. Secreted soluble LR11 (sLR11) and membrane-bound LR11 are connected with the migration of SMCs from the media to the intima. It indicates the role of LR11 in vascular lesions development (Figure 3) (Watanabe et al., 2022).

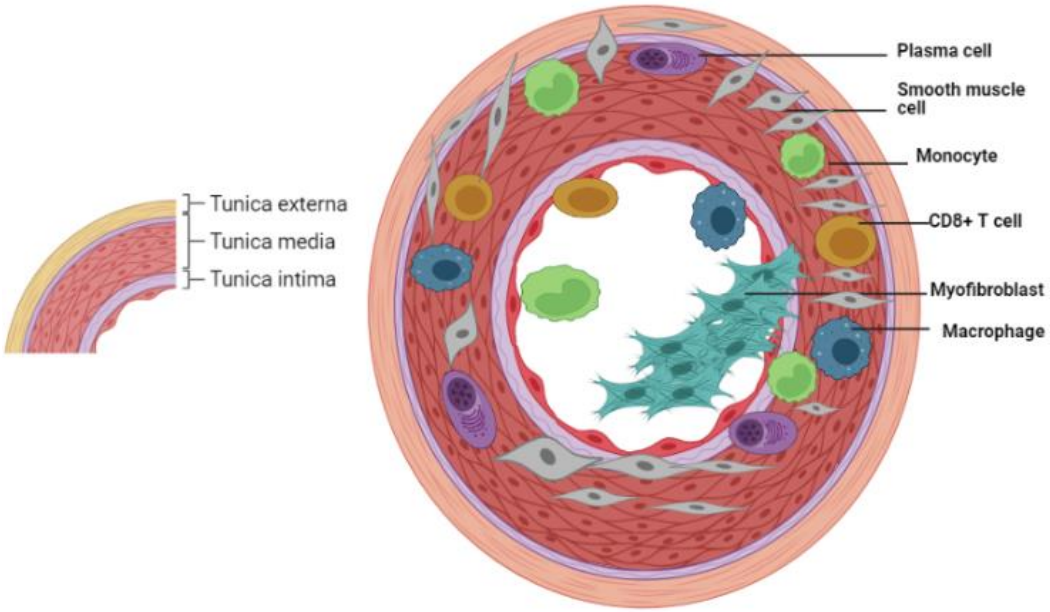

Fig. 3 Kawasaki disease vasculitis (Watanabe et al., 2022)

Matrix metalloproteinases play a vital part in both inflammation & tissue remodelling processes (Siefert & Sarkar, 2012). The enhanced levels of MMP9 and MMP3 are known to involve in the migration of vascular SMCs and the development of neointimal cells in KD patients. The MMP levels are associated with the development of coronary artery aneurysms (Johnson et al., 2011; Popper et al., 2007; Matsuyama, 1999).

Remarkably expressed miR-145 levels in vascular SMCs have been involved in their conversion to proliferating neointimal cells (Rangrez et al., 2011; Parmacek, 2009) and control the transforming growth factor- β signalling pathway (Shimizu et al., 2013). Cardiomyocyte apoptosis seen in KD is due to enhanced levels of miR-23a, which blocks the autophagy of macrophages and promotes inflammatory responses (Si et al., 2018; Long et al., 2017).

Myocarditis has been observed in patients (50–70%) using technetium-99 WBC scans and gallium citrate scans (Kao et al., 1993). Myocarditis has been considered the "hidden face of the moon" in KD (Dahdah, 2010). In infants, myocarditis is associated with lethal arrhythmias, and in some cases, it can lead to long-term risk factors and myocardial fibrosis (Orenstein et al., 2012; Burns, 2009).

KD affects medium and small-sized vessels, mainly the coronary arteries. However, aneurysms and dilatations can arise systemically and can be seen in the iliac, renal, brachial, subclavian, and axillary arteries, including the abdominal aorta (Takahashi et al., 2017; Miyake et al., 1995; Canter et al., 1981; Amano et al., 1980). In post-mortem studies of KD patients, it was observed that involvement of renal artery & acute kidney damage involved in glomerulonephritis with intra capillary alterations and accumulation of immune complex consisting of immunoglobulin A and complement component 3 (Takahashi et al., 2010; Watanabe, 2013; Watanabe, 2018) .

A protein epitope targeted by the antibodies (monoclonal antibodies) reaction to KD offer a way to explain the pathogenesis of KD (Rowley et al., 2020). The initial administration of IVIG less than four days after the onset of symptoms of elevated ESR, lactate dehydrogenase and reduced platelet and haemoglobin counts, polymorphous rash, swelling of the extremities, cervical lymphadenopathy, and oral mucosa changes are the risk factors for intravenous immunoglobulin resistant in KD. The male sex was reported to have more risk of developing KD than females (Li et al., 2018; Hedrich et al., 2018).

8. GENETICS OF KD

Knowledge about genes involved in KD pathogenesis will help in diagnosis and treatment. In East Asian countries and transmigration regions, the KD is due to genetic components rather than environmental factors. Several genes have been linked with HLA (human leukocyte antigen) linkages and non-HLA linkages in disease vulnerability in KD. HLA is distributed differentially between diverse races and ethnicities (Kumrah et al., 2020). Polymorphism in IgG increases the risk of KD and CAAs (Ramphul & Mejias, 2018). Caspase-3, inositol 1, 4, 5-trisphosphate 3-kinase C, and Ca^{+2} release-activated Ca^{+2} modulator genes were observed as susceptibility genes for KD (Onouchi, 2017). Modified transforming growth factor β signalling (TGFB2, SMAD, TGFBR2, & MMP) were also responsible for KD pathogenesis (Kumrah et al., 2020).

Mechanistically, ITPKC polymorphism may be directly responsible for hyperactivity of the T cell, and significantly it could encourage NLRP3 inflammasome activation and augment IL-18 & IL-1β production (Alphonse et al., 2016). In patients with KD, improved CD40L expression on CD4+ T cells and platelets was observed, which was linked with enhanced development of coronary artery lesions (Wang et al., 2003). Mannose-binding lectin-A& C deposits were seen in aortic roots in mouse models (Nakamura et al., 2014). Infectious and autoimmune disease developments have been linked with the polymorphisms in genes encoding the Fcγ receptors (Manger et al., 1998; Brun et al., 2002; Bredius et al., 1994). Genes like ORAI1, BLK (B- cell lymphoid kinase), CD40, FCGR2A, TGFbR2, SMAD3, ADAM17, and MMP-11 are responsible for higher risk of KD (Chaudhary et al., 2019). Ying et al., using a human transcriptome array, identified a decrease in CDR2, DDX24, DUSP2, and BCL11B levels in KD. The noticed CDR2 is a novel suppressed gene. The DDX24 associated with forming CAL contributes to a better understanding of CAL pathogenesis in KD (Huang et al., 2022). Defective FOXP3 levels mediated through SMAD3 and NFAT pathways were observed in acute KD patients (Olivito et al., 2010; Tone et al., 2007).

Elakabawi et al. identified DNA hypomethylation by imbalanced DNA methyltransferases, and Teneleven translocation activities are assumed to be a primary reason for the disease pathogenesis. Huang et al., in their experiment, observed a significant reduction in the mRNA levels of DNA methyltransferases 1 & 3A and a substantial elevation in Teneleven translocation2 levels in KD patients (Elakabawi et al., 2020). Recent investigations have also suggested the function of NT-proBNP in assessing patients with KD, particularly in incomplete or atypical KD (Reddy et al., 2016; Cho et al., 2011; Lin et al., 2015).

9. INFLAMMATORY BIOMARKERS

Biomarkers give an insight into ongoing inflammation; however, they have inefficient use in arriving at an exact diagnosis. Inflammatory markers are highly fuzzy as these levels are also prominent in various infective and inflammatory ailments. Most commonly employed inflammatory markers that lack specificity in Kawasaki disease include total leucocyte counts (TLC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). In the acute phase of KD, markers of platelet activation and inflammation include elevated levels of procalcitonin, low mean platelet volume (MPV), platelet-derived microparticles (PDMP), and platelet distribution width (PDW). Low albumin and peripheral blood eosinophilia (PBE) are associated with resistance to IVIG (Chaudhary et al., 2019). In inflammatory diseases, serum ferritin is an acute-phase reactant. Serum ferritin is implied to be a supportive biomarker for estimating IVIG-nonresponsive KD, coronary artery anomalies (CAAs), and the tendency of macrophage activation syndrome (Qiu et al., 2021).

10. CELLULAR MARKERS

Cellular markers downregulated in the acute phase of KD are Th1 & Th2 cells that regulate cellular and humoral immunity by secreting IL-2, IL-10, IL-4, IL-6 IL-5, and IFN- γ, Cytotoxic T cell CD8 T cells, TGF- β, TNFa all these are involved in inflamed coronary arteries and CAA. CD14 plus monocytes that produce IL-1, IL-6, TNFa, and early activation marker for T cells; CD69 plus CD8T cells upregulated in acute KD. In addition to Th17 proportions, Treg cells are decreased, (Tem) effector memory T-cells and central memory T-cells (Tcm), IFN-Y, myeloid & plasmocytoid dendritic cells, and IL-2, IL-10, IL-6, IL-4, IL-17A/F, ROR-gt, CXCL10 (IP-10) are elevated. Th2-related chemokine CCL-2 activated in acute KD (Chaudhary et al., 2019). Cytokines IL-10, IL-6, and IFN-γ contribute to developing IVIG non-responsiveness and coronary aneurysms (Li et al., 2019). Mako et al. reported G0S2 (G0/G1 switch gene 2) and its antisense HSD11B1-AS1 involvement in inflammation of innate immunity in KD and a novel essential target lncRNA (long non-coding RNA) for the diagnosis of patients with KD (Okabe et al., 2022).

11. PROTEOMIC BIOMARKERS

Higher values of NT-proBNP, cardiac troponin I (cTnI)r periostin, thrombospondin 1& 2, gamma-glutamyl transferase, clusterin, Alanine transferase, fibrinogen β & γ chains, periostin, CD5 antigen-like precursor, nitric oxide synthases (iNOS), leucine-rich alpha-2-glycoprotein, angiotensinogen, lipopolysaccharide-binding protein (LBP), tenascin- C and suppression of tumorigenicity 2(sST2) were implied in acute KD. In the urine of KD patients, immune cytokine protease meprin A, talin, filamin, complement regulator CSMD3, and immune pattern recognition receptor muclin levels were increased markedly (Chaudhary et al., 2019).

12. DIAGNOSIS

The timely diagnosis of KD is vital for recognizing coronary artery abnormalities by echocardiography and assessing a variety of biomarkers by blood tests (Lee et al., 2022). Sudhakar et al., through computed tomography angiography, reported the involvement of aneurysms in all four coronaries left anterior descending, right coronary, left main, and the left circumflex coronary arteries (Sudhakar et al., 2022).

The multiple differential diagnoses to rule out Kawasaki includes toxic shock syndrome, Stevens-Johnson syndrome, streptococcal scarlet fever, viral infection, juvenile idiopathic arthritis, drug hypersensitivity, and staphylococcal scalded skin syndrome (Newburger et al., 2004).

MRI is helpful in the assessment of coronary artery abrasion and myocardial association in all phases of KD. There is no radiation exposure with MRI. Yet, young children would frequently require to be sedated, and the process is time-consuming. Interpretation of MRI images needs vast knowledge and expertise (Pilania et al., 2018).

The American heart association 2004 classification was a principal advance as it anticipated employing Z-scores for measuring CAAs. Application of body surface area for Z-score evaluation increased the consistency of reporting of CAAs and is significant for making therapeutic decisions (Elakabawi et al.,2020).

Based on elevated inflammatory parameters American Heart Association (AHA) has recommended a diagnostic algorithm for KD patients.

- A patient with two/three principal clinical signs may be diagnosed with Kawasaki disease if elevated C-reactive protein/ erythrocyte sedimentation rate along with 3 out of 6 laboratory anomalies such as pyuria leucocytosis, raised transaminases, thrombocytosis, low albumin, and anaemia.
- Diagnosis of KD with elevated ESR/CRP is considered in patients with coronary artery aneurysms with 2/3 principal clinical manifestations (Reddy et al., 2016; Cho et al., 2011; Lin et al., 2015).
- Shock has been described as an essential cardiovascular sequela; it has given significant concern in the 2017 modified guidelines as a shock in KD is considered to be associated with bacterial sepsis. These patients also develop quick resistance to IVIG as they are at a higher risk of myocardial dysfunction and coronary artery anomalies.
- Particular diagnostic guidelines are also mentioned about infants; according to these guidelines.
    a. Infants > six months old with irritability and persisted fever,
    b. Infants with mysterious aseptic meningitis and persisted fever,
    c. Infants/ children with cervical lymphadenitis and prolonged fever insensitive to antibiotic treatment,
    d. Infants or children with parapharyngeal phlegmon/ retropharyngeal and prolonged fever insensitive to antibiotic therapy,
    e. Infants or children with unexplained or culture-negative shock and prolonged fever should be given careful contemplation.
- In the presence of few signs of Kawasaki disease and when bacterial cultures are sterile/ if there is a response to antimicrobials, a probability of Kawasaki disease must be considered.
- Differentiating the conditions like lymphadenitis of KD and bacterial lymphadenitis, the guideline suggested computed tomography and ultrasonography as these two conditions are often confused.
- Echocardiography is obligatory in the acute stage of KD to screen for cardiac problems. Especially 2D echocardiography has been recommended in KD children. If any changes in echocardiography were observed, then secure the diagnosis.

The modified guidelines suggest the application of Z scores for measuring coronary artery (CA) dilation.

- Z-score of internal CA diameter greater than or equal to 2.5 SD units is considered coronary artery dilation.
- In case the inspector faces difficulty in using the Z score, traditional measurements of inner diameter ≥4 mm (greater than or equal to 5 years old) / ≥3 mm (less than 5 years old) might be employed for the diagnosis of CA dilation (Kobayashi et al., 2020).

13. TREATMENT

The coronary aneurysm is controlled by administering intravenous immunoglobulin (Xie et al., 2020). The primary treatment for a coronary aneurysm is with IVIG with aspirin; if patients are unresponsive, a second dose of IVIG is administered. Patients who are unresponsive to immunoglobulin should be treated with TNF- alpha blocker etanercept, infliximab, (Yamaji et al., 2019) corticosteroids (methylprednisolone) (De Graeff et al., 2018), and DMARDs including methotrexate, cyclophosphamide, plasmapheresis (Rowley & Shulman, 2018) and cyclosporine along with plasma exchange agents and anakinra. According to most of the nation's guidelines, IVIG is considered the first-line treatment in non-responsive and incomplete KD. However, adjuvant therapy is heterogeneous (Scherler et al., 2022).

IVIG inhibits IL-1β production by stimulating macrophages and activating IL-1Ra production (Iwata et al., 1987; De Souza et al., 1995). In KD, IVIG decreases the fabrication of inflammatory chemokines and cytokines and reduces the activation and amount of circulating macrophages, monocytes and neutrophils activated T cells by saturating Fc receptors (Rizk et al., 2015). Best adjunctive therapy in a high-risk group of patients with CAA on baseline echocardiography, individuals treated with corticosteroids/ infliximab along with IVIG had less development in CAA size than individuals treated with IVIG alone (Dionne et al., 2019).

In acute illness, aspirin is given to patients along with GI protection. Patients persisting after 6 weeks with a coronary aneurysm should maintain on long-term aspirin and those in later remodelling of the coronary aneurysm. To minimize the thrombosis in situ and myocardial infarction risk, switching of dose from high to low dose aspirin is recommended (Krumholz, 1996). Patients with a giant coronary aneurysm should maintain an aspirin low dose or clopidogrel and include an anticoagulant. A low rate of Coronary aneurysms is observed in patients administered with warfarin (McCrindle et al., 2017). However, it is difficult to use warfarin in very young children then; subcutaneous heparin-like enoxaparin is recommended, which, after administration, gets converted to warfarin (Su et al., 2014; Levin et al., 2014). Beta-blockers are prescribed in antiarrhythmic therapy and myocardial ischemia. Beta-blockers are recommended lifelong in patients with depressed ejection fraction and prior infarction. Statins are considered in persisting coronary aneurysms because of their anti-inflammatory potential (Suda et al., 2015). Patients who received immunoglobulin treatment after the tenth day of fever exhibit a more remarkable two-fold risk of aneurysm than with who received treatment before the tenth day of fever. The risk of aneurysms is more with delayed immunoglobulin treatment, particularly in giant and medium aneurysms (Van Stijn et al., 2022). Other treatments with IVIG for KD patients with peripheral gangrene may need additional therapy, including propranolol, dipyridamole, nifedipine, nitroprusside, urokinase, heparin, and prostacyclin. Peripheral gangrene is occasionally seen with the utilization of infliximab, cyclophosphamide & steroids in patients with peripheral gangrene. In spite of these measures, the peripheral gangrene development in patients with KD remains guarded, and most children require confiscation of fingers. Nevertheless, timely diagnosis and good therapy have seldom been reported to aid in saving the limb (Jindal et al., 2009).

Immunoglobulin resistance can be treated with combinational therapy (CT) of intravenous immunoglobulins with calcineurin blockers or anakinra, steroids, and TNF blockers. This combination is effective in controlling pro-inflammatory cytokines. Infliximab reduces fever duration and decreases inflammation markers (Tremoulet et al., 2014). Treatment with etanercept significantly reduced IVIG resistance only in patients older than one year old (Portman et al., 2019). The Kobayashi scoring system successfully predicted biomarkers involved in immunoglobulin resistance by combining laboratory test results and demographic variables in Japanese patients but failed in the North American children (Kobayashi et al., 2006; Sleeper et al., 2011). The combination of IVIG and prednisolone was beneficial in combating IVIG- resistance in Japanese patients as per the Kobayashi score, reduced fever onset, and development of coronary aneurysm (Kobayashi et al., 2012). Based on the Kobayashi score, administering IVIG combined with a calcineurin inhibitor- cyclosporin suppressed interleukins and T cell activation in Japanese patients. This treatment decreased the incidence of the coronary aneurysm but was associated with a high risk of relapse (Hamada et al., 2019). Anakinra, which inhibits the IL-1 pathway observed to be helpful in Europe and North American patients (Tremoulet et al., 2016; Kone- Paut et al., 2019).

Immunization with all vaccines should be delayed at least six months after an episode of KD therapy with IVIG (De Graeff, et al., 2018; Eleftheriou et al., 2013). Considerably live oral, and inactivated vaccines can be given at any instance after high dose immunoglobulins in KD patients. Of note, administration of inactivated influenza vaccine to patients with a background of Kawasaki disease on aspirin treatment is associated with known concerns and complications of Reye syndrome if the patient experiences infection with influenza. This vaccine must be administered at least two days after temporary stopping the administration of acetylsalicylic acid, which must then be substituted by clopidogrel for six weeks after giving the varicella vaccine because there is a minute hypothetical complication of Reye syndrome being stimulated by the attenuated varicella-zoster virus of the vaccine (Soni et al., 2020).

14. PREVENTION OF CARDIOVASCULAR RISK FACTORS

Patients who have ever had a coronary aneurysm should be advised to reduce the cardiovascular risk from an early age by eating a diet low in animal fat, maintaining of ideal weight, taking regular aerobic exercise, quitting smoking, reducing the risk of diabetes, periodic check-up for hyperlipidemia and hypertension (Brogan et al., 2019).

15. DISEASE PROGNOSIS

About five percent of all Kawasaki patients experience arterial aneurysms. The death rate is around 0.1%. While late diagnosis and therapy commencement are allied with therapy relapses and the advancement of coronary aneurysms, timely and adequate therapy is a key to accomplishment. Usually, cardiovascular complications for Kawasaki patients without CA luminal changes are similar to the general population. For all other patients, the relentlessness of luminal abnormality and potentially emerging squeal describe the individual risk. The possibility of relapses in KD is comparatively less and has been reported to be 3% in Japanese children (Hedrich et al., 2018).

16. CONCLUSION

KD-like symptoms were seen during the COVID-19 pandemic in children. The treatment is entirely drawn from the KD therapy approaches. In this review, we have emphasized the pathophysiology, possible etiology, various therapeutic approaches etc... This might be helpful in better understanding the disease and employing appropriate treatment and diagnosis techniques. As major drawbacks of the disease are the lack of specific biomarkers and diagnostic methods.

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