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Review Article

Kawasaki Disease: Epidemiology, Etiology, Pathology, Symptoms, Clinical Features, Diagnosis, Treatments

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ABSTRACT

Kawasaki Disease is a disease of blood vessels, arteries and capillaries which predominantly occur in the children below the age of five years. It is vasculitis which if left untreated can lead to coronary artery aneurysm. The etiology of the disease is still not very well understood. Remittent fever is the major symptom for clinical finding of the disease. Various controversies are being undergone for the current diagnostic procedures, but Cardiac imaging has shown the best outcomes. Treatment type are based on how the patient reacts to the primary medication dose of Intravenous Immunoglobulin (IVIg) and should be induced within the first week of prevalence of disease to decrease the risk of cardiac involvement. Due to COVID pandemic situation, paediatric population could be on high risk of the Kawasaki disease which needs greater attention. With recent advancements herbal therapies have also become a part of the drug regime for the disease.

Keywords: Kawasaki Disease; Coronary artery aneurysm; Cardiac imaging; IVIg; Vasculitis

INTRODUCTION

Kawasaki Disease (KD) or Mucocutaneous Lymph Node Syndrome is vasculitis of unspecified origin which chiefly affect children and infants [1]. It affects all the races but has an incline toward the Asian population [2]. Indication of remittent fever, sclera inflammation, dryred lips, strawberry-red tongue, swelling of the hands and feet can be characterised as symptoms for the disease [3]. Majority of individuals affected by the disease are susceptible to cardiac involvement such as myocarditis, tachycardia, improper functioning of the lower chamber of heart, pericarditis, heart valves leakage [3]. In severe cases an individual may also come across extreme cardiac conditions which result in the coronary artery inflammation, fracture in aneurysm which in turn can turn fatal [4]. The etiology of the disease is still not specific but a few indications suggest its cause to be toxins produced by *Staphylococcus aureus* or *Streptococcus pyogenes*, according to a surrogate hypothesis which is assisted by the diagnosis of auxiliary infection in patient; in which the host affected by the infectious agents triggers a common pathway leading to KD [1]. Cardiac imaging is one of the best means to diagnose KD, the echocardiogram provides exceptional imaging of the valve functioning alongside gives coronary artery dimensions, evaluation of myocardial function, pericardial effusion [5]. Certain clinical evaluations are performed which indicate the leucocytosis, rising platelet levels, anaemia after the onset being between 2-3 weeks, they also show an increase in the inflammatory markers [6]. Compared with White children, Black children with KD had higher Intravenous Immunoglobulin (IVIG) refractory prevalence, more severe inflammation, more ancillary treatments, and longer hospitalizations [7]. The ideal treatment is suggested to be given within the first 7 days after the confirmation of KD to notably reduce the risk cardiac damage [8]. IGIV products (immune globulin intravenous [human]) are FDA approved drugs for the treatment of the disease. Corticosteroids can also be used as primary therapy while giving the first dose of IGIV or as secondary therapy if the patient develops resistance to IGIV. Administration of biologic drugs [9] and plasmapheresis [10] are also two effective alternative therapies for IGIV resistant KD patients. Current studies have shown that supporting herbal therapies or natural compounds can be used as an adjuvant therapy for KD [11]. Ouldali et al. [12], has established a relationship between the infection of SARS CoV2 and the occurrence of KD.

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LITERATURE REVIEW

Epidemiology

Since the occurrence of first case of KD, the KD epidemiologic studies have shown fresh patterns in the incidence of it [13]. The disease affects all races but has a tendency of affecting the Asian population to a wider extent [2]. The prevalence of KD in the Europe and United States has been found to be 10-30 times less than that of Northeast Asian countries. Epidemiologic studies have concluded that affected population average age is two years, phenomenon of occurring beyond this age is sparse [14]. In regard to the male female ratio, it affects the male more by a ratio of 1.5 to 1. Various studies and surveys have shown conclusive evidence for the same (Table 1).

Table 1: 21st Nationwide survey of 2009 and 2010.

Survey	Total population	Male	Female
21st nationwide survey (2009)	10,975	6,249	4,726
21st nationwide survey (2010)	12,755	7,266	5,489

KD is prevalent all over the globe but a few parts have higher incidences whereas some sections show a handful of cases [2]. For the epidemiological studies of KD, there are many survey data has been conducted across the globe and has been published in different years (Figure 1) [2,13,15-17].

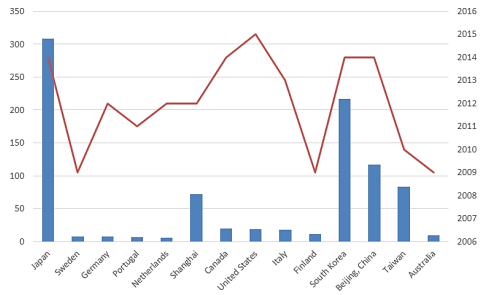

Figure 1: Incidences across the globe. Note: ( ) incidence (per 100,000 less than 5-year-olds); ( ) year.

Etiology

KD is a disease mainly affecting then younger age mostly affecting the coronary arteries. Rarely does it lead to myocardial infarction and sudden death [13]. The etiology is still unknown. Dr. Kawasaki had proposed the initial descriptive information on the disease in 1960s and since then various theories have been submitted in regard to the etiology [14,18,19]. But etiology of the KD still having challenges which are the potential area of the KD research.

Pathology

Medium-sized arteries, extra-parenchymal muscular arteries show pathological changes but the coronary arteries are majorly affected, the extents till which the coronary arteries are affected decide the fatality of the disease [8]. The main vascular abnormalities experienced by the arterial walls are:

- Necrotizing arteritis,
- Subacute/chronic vasculitis, and
- Luminal myofibroblast proliferation

The Medium-sized arteries, extra-parenchymal muscular arteries and the coronary arteries undergo decay of the wall lining of the vessel which leads to the activation of the lumen which causes inflammation of the arteries due to the accumulation of neutrophils in cells as a result of the lumen release [4]. The arteries enlarge as the wall of the arteries weaken due to the neutrophil elastases which interrupt the process of recoil of vessel wall by the disruption of elastic laminae [20]. Subacute/chronic vasculitis and luminal myofibroblast proliferation are closely related and can be detected from the week of arrival of fever till years later (JCS 2013) [21]. KD patients become more vulnerable to aneurysm formation as the polymorphism in TGFb pathway which plays a role in the pathological cycle of KD. Along with this myocardial ischemia can also occur due to LMP as they tend to narrow the lumen [8].

Symptoms

The primary symptom which marks the onset of the disease is remittent fever, which on antipyretic administration stays unaffected. The fever may persist ranging from 5 days to 3 weeks at a temperature range off 101°F -103°F. Cases of fever ranging up to 3 weeks are rare (JCS 2013) [21]. KD patients start developing reddish rashes in the perineal region after a week of persistent fever the rashes then emerge to become a maculopapular rash [22]. The skin of the foot and hands starts shedding by the second week of being infected. Alongside of fever majority of the children also suffer from bilateral conjunctivitis which refers to the whitening of the iris [14]. The oropharyngeal region shows inflammation of mucous membranes which leads to cervical lymphadenopathy, strawberry tongue and dry-cracked lips [3]. About 1/3rd of the patient experience gastrointestinal problems such as diarrhoea, irritability, vomiting, hydrops. Numerous other symptoms such as arthritis (joint pain and stiffness), myalgias (muscle pain), arthralgias (joint pain) [1]. Various other clinical findings were discovered in different regions of the body like neurological, gastrointestinal, cardiovascular [23]. Other laboratory findings such as arthritis, hydrocele, hepatomegaly have also been seen in various cases [4] (Figure 2).

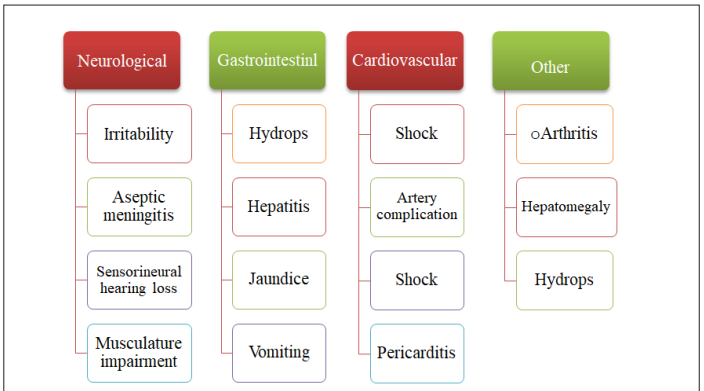

Figure 2: Clinical features of KD.

The most fatal factor can be the weakness of the coronary arteries which are responsible for the supply of oxygen rich blood to the heart [14]. The inflammation of the artery can be caused due to dilation or bulging which is only show by 3%-20% of the affected population [23]. The severity of the condition rises when blood clots develop or burst (JCS 2013) [21]. The condition which should be taken the most care of is the cardiac condition as the involvement of the heart can lead to complications initially and with time can be fatal and cause the death of the patient [1].

Diagnosis

Due to the absence of pathognomonic laboratory test the clinical aspect of diagnosis is mostly considered. The first and foremost symptom of KD is fever persisting for at least 4-5 days, which is also the characteristics feature of it [8]. Alongside of remittent fever some of the other distinctive features of the disease include red-cracked lips, strawberry tongue, rashes in the groin area eventually and then gradually over other both parts, swelling of the lymph nodes, shedding of the skin from the tips of hands and toes [14]. With further symptoms case-control observational studies are also conducted which look into the patient's medical history, daily exposure, family history, allergies etc. [24]. These parameters have further observational parameters for proper diagnostics [8].

1. Patient medical history

- Ethnic origin
- Birth history
- Diseased condition
- Vaccination
- Medical conditions

2. Allergies

- Environmental sensitivity
- Food related sensitivity
- Drug related sensitivity
- Immunological

3. Family history

- Parents medical history
- Parents diseased condition

4. Routine Subjection

- Contact with people, pets.
- Daily food intake

Some of the laboratory test also provide additional information for the diagnosis of the disease such as most of the patients suffering from KD have immature form of white blood cells which lead to leukocytosis [4]. Thrombocytosis is also observed in a few cases at the end of first week off illness. In serious cases the platelet count may rise up to 1,000,000/ mm^3 [24]. Also, in a few tests the haemoglobin concentration in RBC is within the average range but the RBC count is below the normal range (normochromic normocytic anaemia) [6]. An elevation is seen in the Erythrocyte Sedimentation Rate (ESR) which is an important inflammatory marker. There is also increment in the serum concentration of some of the acute phase reactant proteins such as C-reactive protein, a1 antitrypsin [1]. Transaminase, plasma g-glutamyl transpeptidase and cerebrospinal fluid protein levels have also show net elevation in 20%-50% of the diagnosed individuals. Renal involvement occurs in rare cases which may show hypoalbuminemia and hyponatremia [25] (Table 2).

Table 2: Clinical findings in KD.

Finding	Increase	Decrease
White blood cells		P
Red blood cells		P
Platelets	P	
C-reactive protein	P	
ESR	P	
a1 antitrypsin	P	
CSF protein	P	
Transaminase	P	
Plasma transpeptidase	P	
Albumin		P
Sodium levels		P
Troponins	P	
B-type natriuretic peptide	P	
Cholesterol	P	
Apolipoprotein A1	P	
High-density lipoprotein	P	

Note: P=Present

For the initial diagnosis of the disease there are different set of guidelines provided by two organisations. According to these sets of guidelines, the classification of the disease have been made on the condition of the disease along with the risk of cardiac involvement. Cardiac imaging is proven to be one of the most valid methods for finding out if any cardiac damage is done [26]. Echocardiography along with giving information about the coronary artery features it also produces results which gives details about the cardiac functioning [25]. The imaging should especially be performed for the left coronary artery, Left Anterior Descending artery (LAD), left circumflex coronary artery, Right Coronary Artery (RCA), and posterior descending coronary artery along with all the other arteries [27]. The evaluation of the coronary artery conditions are based on their size which have set limits. Z scores are also checked which are a limit set for checking the range of normal coronary artery dimension, artery dimensions below or above the range can cause abnormalities and are used for diagnosis [5]. The limits are set under two different guidelines [4].

Kawasaki Disease Research Committee guidelines (Japanese guidelines), 2003. The Japanese guidelines suggest the presence of 5 out of 6 following symptoms [21,22].

1. Fever continuing for more than 5 days

2. Bilateral conjunctival congestion

3. Oropharyngeal region inflammation- Red-cracked lips, strawberry tongue

4. Polymorphous exanthema

5. Acute non purulent cervical lymphadenopathy

6. Reddening of palms, toes and groin area eventually leading to desquamation of membrane of the toes and hands.

Patients check marking 5 out of the above 6 symptoms come under the Level A certainty and are diagnosed with Typical KD. Atypical KD or Level B certainty is diagnosed when the patients 2-D echocardiography or cardio angiography results show signs of aneurysms and dilation of coronary artery. For the diagnosis of incomplete KD the patient can show either of the two [5].

1. Four out of six above mentioned symptoms are present but no sign of CAA

2. When patient has coronary aneurysms along with three of the above six symptoms.

According to the Japanese guidelines the criteria is set on the age of the child and dimension of the internal lumen of the coronary artery (Table 3).

Table 3: Japanese criteria for KD diagnosis based on age.

Age (years)	Limit (mm)
0-4	3
5 or above	4/1.5 time or larger artery segments in comparison to adjacent irregular coronary lumen

Z scores are given to various arteries as with age the dimension of the arteries also vary, z scores are mainly body surface adjusted coronary artery dimensions [26]. These are given to only a few important arteries which are left main coronary artery, left anterior descending artery, and right coronary artery [27]. Division of the aneurysms are as small, medium and large (JCS 2013) (Tables 4 and 5).

Table 4: Japanese criteria for KD diagnosis based on size.

Size	Internal diameter (mm)
Small	Less than 5
Medium	5-8
Large	Greater than 8

Table 5: AHA criteria for KD diagnosis.

Size	Internal diameter (mm)
Small aneurysm	2.5-5
Medium aneurysm	5-10
Large aneurysm	Greater than or equal to 10
Only dilation	2-2.5
No involvement	Less than 2

American Heart Association (AHA) guidelines, 2004.

The second set of guidelines are set by American Heart Association which say that for the presence of the disease the following conditions should be fulfilled [24].

1. 5 days of persistent fever

2. Four out of the five below mentioned clinical findings

i. Oropharyngeal region inflammation- Red-cracked lips, strawberry tongue

ii. Polymorphous exanthema

iii. Acute non purulent cervical lymphadenopathy (>1.5 cm diameter)

iv. Reddening of palms, toes and groin area eventually leading to desquamation of membrane of the toes and hands.

v. Bilateral bulbar conjunctival injection without exudates

Diseases which show matching findings should not be present such as [14,21]. Scarlet fever, Measles, Adenovirus, Stevens-Johnson syndrome, Toxic shock syndrome, Epstein-Barr virus, Rocky mountain spotted fever, Leptospirosis. The AHA also classifies the disease as typical and atypical. For the disease to be typical KD, the patient has fever persisting for 5 days and also has 4 out of thee 5 clinical features and if the patient does not match with 4 of 5 of the findings but has 3 of them along with CAA it is characterised under typical KD [5]. Atypical or incomplete KD is when the patient shows only two or three clinical findings out of the five along with fever for 5 days or more [26]. The z scores given according to AHA for the diagnosis are as follows Padilla et al. [7], had performed a cohort study to determine whether black children with KD exhibit disparities in prevalence, sequelae and response to intravenous gamma globulin (IVIG) treatment. International Classification of Diseases codes were used to identify children with KD admitted to a tertiary center in the southeastern US. Subjects diagnosed and treated according to American Heart Association criteria. Compared with White children, Black children with KD had higher IVIG refractory prevalence, more severe inflammation, more ancillary treatments, and longer hospitalizations. Blacks presented with higher C-reactive protein level and erythrocyte sedimentation rate and lower hemoglobin, albumin, and sodium levels [24]. Blacks had a higher proportion of persistent Coronary Artery (CA) abnormalities than Whites at second follow-up echocardiogram (14.5% *vs.* 6.3%; P=.03), and at third follow-up echocardiogram (21.2% *vs.* 6.9%; P=.01) [28]. This study found a greater persistence of CA abnormalities in black children compared with white children, with no differences in follow-up times.

Treatment

An alternative therapy for hypogammaglobinaemia or some other immuno deficiency disorder is done through the introduction of Intravenous Immune globulin (IVIg), collected from the purified plasma of various donors [8,14,24]. As inflammation is caused which leads to thrombosis in aneurysms, thus IVIg is given to solve the problem of tissue and systemic inflammation [29]. After the diagnosis of the disease the first line of treatment is the induction of intravenous immune globulin and aspirin therapy [25]. IVIg is known to have various mechanisms of action such as competitive binding of neonatal FC receptor (FcRn), Inhibitory Fc Receptor (FccRIIB) on macrophage activation, Adhesion molecule blockage and cytokines, chemokines and activated complement but the exact mechanism is not completely known (JCS 2013) [21].

The initial dosing should be administered by the first day of fever and latest by the tenth day. 2 g/kg of IVIg is given along with high dose of aspirin as the first medication. When the first dosing of IVIg and ASA were given different results were shown with different administration.

i. In 1983, IVIg was administered in 14 patients and reports showed that IVIG high dosing (400 mg/kg for 5 days) showed significant results as none of the administered patients showed signs of any coronary artery aneurysms also they reduced the time of illness in the patient [30].

ii. Further randomized controlled trials were conducted for ASA alone in 47 patients with a dose 30-50 mg/kg/day administration. About 23% of the patients showed abnormal results in echocardiography at the end of 30 days [25].

iii. 46 patients were subjected to IVIg and ASA administration out of which only 2% showed coronary artery abnormalities [8].

iv. A comparison study was also conducted on 84 patients between IVIg plus ASA with dose regime of IVIg 400 mg/kg/day for 4 days and high-dosing of 80-120 mg/kg/day of ASA. Reports between the second and seventh week of administration showed conclusive evidence showing a lower rate of coronary artery abnormalities in

patients given IVIg plus ASA [8].

v. A decrease rate from 25% to 5% in coronary artery aneurysms was a clinical finding in 1980 when the dose is given to the patient within the first week to 10 days from the onset of fever of IVIg plus ASA [24].

Various laboratory trials were conducted for the apt dose calculation for the treatment of the disease for which various Japanese and North American studies took place which eventually ended on a single infusion of IVIg (2 g/kg) (Tables 6 and 7).

Table 6: Survey results of Japanese RCT.

Criteria	RCT 1	RCT 2
Patients	160	136
Days	5	3
Dose	3 doses:- 1. 50-100 mg/kg 2. 200 mg/kg 3. 400 mg/kg	400 mg/kg
Result	400 mg/kg showed positive results for CAA	23% still had fever. Better result than only ASA administration.

Table7: North American survey.

Criteria	RCT 1	RCT 2
Patient	47	549
Dose	400 mg/kg-1 g/kg	2 g/kg
Days	4	Four-infusion protocol
Result	Faster clinical recovery in single infusion	Chance of CAA reduced, low fever rate

According to the study conducted by a North American group they were working on the reduction of days for the dose administration. 2 different studies were conductedThe final dosing according to the AHA guidelines was concluded to be 2 g/kg on behalf of various analysis and studies [30]. A 1995 meta-analysis when concluded the result of CAA after 30 and 60 days no evident change was seen when a single infusion of a dose higher than 1 g/kg was induced. The lower dose induction did not show similar results [31]. According to the Cochrane review, the outcome was quite similar to that of the meta-analysis. Which concluded that not much of difference was seen with a different dose regime [6]. Also, one study which was conducted ahead of the above studies showed that the single infusion of higher dose (2 g/kg) proved to be economically friendly than the low dose regime for 5 days (400 mg/kg) [32].

IVIg infusion also shows a few complications

i. In the first 48 hours of administration of IVIg the patient may suffer from slight fever [33].

ii. Various cases of KD management show a risk of haemolytic reaction, for the prevention of any type of hemolytic reaction the dose of IVIG is administered over a span of 8-12 hours. Various reasons are predicted for the hemolysis [32].

• Patients having blood group A, B, AB have a higher possibility hemolysis.

• High dosing of IVIg is also a risk factor

iii. Infusion reaction may also occur, the patient is premedicated with diphenhydramine or various antihistamine medication [34].

iv. Coronary artery lesion is a risk factor in patients which show persistent fever after the administration of the first dose of IVIg. About 15% of the patient show persistent fever, to overcome this problem a dose of 2 mg/kg of IVIg is given after a duration of 48 hours from the first dose (JCS 2013) [21].

Corticosteroids have also used in the management of KD as primary and secondary treatment. When the dose of corticosteroids is accompanied along with the first dose of IVIg it is termed as primary treatment but when the patient starts showing resistance to IVIg it is used as the secondary line of treatment [1]. A study was conducted in Japan for the use of corticosteroids in therapy because earlier studies on corticosteroids showed a negative effect on coronary artery but eventually lead to a positive result in children [30]. The Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy in Kawasaki Disease (RAISE trial) was conducted in which the patients were administered with IVIg standard dose along with prednisolone (2 mg/kg/day) [33]. The final findings were found to give a positive result on the CAA [35,36]. Along with the decreased risk of CAA the combination therapy also resulted in the decrease in the frequency of fever and z-scores were normalised [32]. The corticosteroid can be provided orally and intravenously [29]. Prednisolone is administered orally with low dose regime of 0.5-2 mg/kg/day and the intravenous administration is of methylprednisolone of a high dose of 30 mg/kg [14].

A few more therapies which are not very commonly used and are still under study are the use of Infliximab and Cyclosporin [29]. Cyclosporin, a calcineurin inhibitor, when studied in Japan and United States was proved to advantageous in patients who develop IVIg resistance [33]. A 5 mg/kg dose of a tumour necrosis factor inhibitor drug Infliximab is given which shows results in on the decrease of fever but no effect on CAA was observed (JCS 2013).

The dosing of ASA shows no significant effect on CAL. The dose is given over a period of 6 hours ranging from low to high dosing (30-50 mg/kg/day and 80-100 mg/kg/day respectively) (JCS 2013). A medium range of dosing of ASA is preferred as the effect of ASA has no relation with CAA thus to avoid toxicity [36]. Along with the ASA dosing a single dose of 3-5 mg/kg/day of antithrombotic is also induced [4]. Various practitioners give a high dosing of ASA in the beginning followed by a low dosing till the sixth week of normal cardiac imaging reports [14]. Some practitioners give high dosing of ASA till 48 hours whereas some give it for duration of 2 weeks [26]. In the sixth week, if the reports show normal echocardiograph, the low dosing is discontinued [37].

When a person acquires resistance to the IVIg various other dosing are given.

1. Second infusion of 2 g/kg/day of IVIg [33].

2. IVIg (2 g/kg/day)+Prednisolone (2 mg/kg/day) administered IV equally over a period of 8 hours until persistent fever then shifted to oral dosing until normal CRP [31,36]. The transcription of different inflammatory cytokines is inhibited and the transcription of anti-inflammatory cytokines and proteins is induced by these combinations [38].

3. Infliximab (IFX), a TNF-a monoclonal antibody, exert its anti-inflammatory role *via* inhibition of TNF-a or soluble TNF-a receptor, prevented the release of proinflammatory cytokine and interleukin, lowering the levels of IL-6 or CRP to reduce the severity of vasculitis [38]. Infliximab is administered over a period of 2 hours in a single IV infusion of 5 mg/kg body weight [32].

4. Cyclosporin is administered as IV infusion (3 mg/kg/day) and orally (4-8 mg/kg) over a span of 12 hours [32]. It inhibits the calcineurin-NFAT signaling pathway, reacts with IL-1β and increases the activity of T cells [38].

5. Anakinra is induced subcutaneously at a dose of 2-6 mg/kg/day [29]. It downregulates various IL-1ß-mediated inflammatory responses, and also act as a receptor antagonist which competitively inhibit the binding between IL-1 and the corresponding receptor thereby downregulating various IL-1 mediated inflammatory responses and IL-1 biological activity [24].

6. Cyclophosphamide dose of 2 mg/kg/day is given by IV infusion [37].

7. Biologic drugs are important agents for regulating TNF-α or IL-1 which triggered KD-related vasculitis. Owing to the role of TNF-α in the pathogenesis of coronary artery dilation and KD, using TNF-α inhibitors in the treatment of KD is possible [9].

8. Plasmapheresis (PE) can directly reduce the level of inflammatory cytokines and chemokines activated from the bloodstream, and prevent the occurrence of CAA in KD patients [39]. Colloid was used for the replacement of plasma during PE. Clinical study has reported PE as a treatment for both IVIG and IFX non-responsive KD patients with their fever symptoms relieved, and body temperature restored to normal after treatments [40].

DISCUSSION

Supporting herbal therapies for treating resistant KD

Current studies have shown that herbal therapies or natural compounds can be used as an adjuvant therapy for KD [11]. For example, combination of IVIg along with triptolide (produced by the Thunder God vine, *Tripterygium wilfordii*) reduces the level of intracellular cell adhesion molecule-1 (ICAM-1) and TNF-α in KD mouse models [41]. Since 1990 till now, an study with various herbal products have been conducted and it concluded that the *Gypsum fibrosum, Radix Rehmanniae, Lonicera japonica Thunb. Forsythia suspense* and *Cornu Bubali* are the effective herbal medicines commonly prescribed for the treatment of KD [40]. Dan-Shen-Yin is widely used to treat coronary heart disease in clinical practice [42], studies have found that Dan-Shen-Yin reduced infarction size, the level of serum CRP, IL-6, TNF-α and malondialdehyde, and increased superoxide dismutase activity [42], which are closely correlated to the inflammatory level of KD. 'Qingre Liangxue Decoction' made of *Gypsum fibrosum, Rhizoma anemarrhenae, Lonicera japonica Thunb*. And other herbal products reduced the level of serum IL-33, TNF-a and platelet count, thus alleviated inflammation and hypercoagulability of KD patients [43]. All these clinical applications of herbal products both classical and IVIG-resistance cases of KD still worth further investigation.

Syndrome resembling KD in CoVID-19

Recent reports have described a secondary MIS-C after a prior COVID-19 infection that often has features of KD. KD was diagnosed during the COVID-19 pandemic and appeared to be differing from historical cohort of patients. Therefore, researchers classified these patients as Kawasaki-like disease [44]. From a clinical perspective, patients were older, and had respiratory and gastrointestinal involvement, meningeal signs, and signs of cardiovascular involvement [45]. From a biochemical perspective, they had leucopenia with marked lymphopenia, thrombocytopenia, and increased ferritin, as well as markers of myocarditis. Similar clinical features are shared by patients with COVID-19 [46]. Additionally, these patients had a more severe disease course, with resistance to intravenous immunoglobulin and need of adjunctive steroids, biochemical evidence of Macrophage Activation Syndrome (MAS) and clinical signs in keeping with KDSS [40].The proinflammatory effect of COVID-19 has been reported in adults with the most severe respiratory complications of COVID-19 [46,47]. Many of these patients have a constellation of features classified under the term cytokine storm, such as fever, lymphopenia, elevated transaminases, lactate dehydrogenase, D-dimer, and ferritin, in keeping with MAS [47-49]. Likewise, MAS is a form of cytokine storm, and might affect patients with KD [50,51]. All these elements supported the need to start adjunctive steroids. This treatment is effective and safe and should be considered by physicians treating patients with Kawasaki-like presentations in the context of the COVID-19 pandemic [44]. So, it can be reported as the immune response to SARS-CoV-2 is responsible for a Kawasaki-like disease in susceptible patients. Moreover, recently suggested that viral respiratory infections, including SAR-CoV-2, could be a prominent trigger for KD and indicates the potential timing of an increase in incidence of the disease in COVID-19 epidemics [12,52-65].

CONCLUSION

KD is a children-oriented disease which targets children below the age of 5 and causes the dimensional changes in their coronary arteries which may lead to fatal condition. The prevalence of the disease is more dominant in male than female. Also, it persists all over the globe but Japan shows majority of the cases. The initiation of the disease can be seen with a persistent fever of 5 days and various other symptoms which are observed such as redness in groin area, shedding of skin of hands and toes. The actual etiology of the disease is still under consideration but three main theories have given the most evident findings which are Environmental toxin theory, Autoimmune pathogenesis theory and Superantigen/bacterial toxin theory. The diagnosis of the disease is also not systematic, there is no set pattern of determination but various case-control studies are performed. Other diagnosis characteristics are the platelets levels, sedimentation rate and many other. Cardiac imaging has been proven to be of great use in the detection of any coronary artery defect. The Japanese guidelines and The American Heath Association have also set a few standards known as Z scores for proper diagnosis. When criteria have been matches the 2 g/kg dose of IVIG is induced along with ASA within the first ten days of onset of fever. Other therapies have also been used for the treatment such as using Corticosteroids, Infliximab, Cyclosporin, Anakinra. The results are seen when the Z scores come into the normal ranges according to the guidelines. The research is still on for the apt treatment for the disease and various are under clinical trials. Administration of biologic drugs and plasmapheresis are also two effective alternative therapies for IGIV resistant KD patients. Current studies have shown that supporting herbal therapies or natural compounds can be used as an adjuvant therapy for KD. These herbal products reduced the level of serum IL-33, TNF-α and platelet count, thus alleviated inflammation and hypercoagulability of KD patients. The association between SARS-CoV-2 and Kawasaki-like disease should be taken into account when it comes to considering social reintegration policies for the pediatric population. Health-care providers should be prepared to manage an influx of patients with severe KD, particularly in countries where the peak of COVID-19 has recently been reached.

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