VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

Coronary Syndrome in Children with Inflammatory Heart Disease

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Vilnius, 2023

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Summary

This narrative review analyzes the existing literature on coronary artery syndrome in children with inflammatory heart disease, with a particular emphasis on Kawasaki disease. It delves into the underlying immunological and genetic mechanisms contributing to its pathogenesis, and outlines evaluation strategies. Additionally, it discusses therapeutic interventions, risk stratification for coronary aneurysms, and a preventive follow-up plan to minimize subsequent cardiac complications.

Kawasaki disease, known as the leading cause of acquired heart disease in children, brings with it serious complications, the most significant being coronary artery involvement. These complications predominantly present themselves as coronary artery dilatation, potentially progressing to the formation of coronary artery aneurysms. This issue raises serious concern due to the risk of life-threatening complications such as thrombosis, myocardial infarction, and even sudden cardiac death.

The severity and duration of coronary artery inflammation affect the likelihood of developing coronary artery syndrome. Promoting treatment initiation with intravenous immunoglobulin and aspirin within 10 days of the illness onset can reduce the risk of coronary artery abnormalities. However, some patients may not respond to this initial standard treatment and thereby require adjuvant therapy. Patients with resistance to intravenous immunoglobulin and those identified as having a high risk of developing coronary artery aneurysms may benefit from adjuvant treatment.

The thesis aims to provide a review of the current literature on coronary artery abnormalities in children with Kawasaki disease, while also identifying potential innovative diagnostic and therapeutic targets that could be integrated into future treatment approaches.

Keywords

Kawasaki disease, Corticosteroids, Aspirin, Intravenous immunoglobulin, Coronary artery aneurysms, Echocardiogram.

1. Introduction

Kawasaki disease (KD) is a systemic vasculitis that primarily affects medium-sized arteries and is the leading cause of acquired heart disease in children worldwide, with a risk of developing coronary artery aneurysms in approximately 25% of cases if left untreated [1]. In January 1961, the first case of a vasculitis was reported and later acknowledged and confirmed by Tomisaku Kawasaki, a Japanese pediatrician, in 1967, based on profiling 50 patients who exhibited a similar phenotype of the disease [2].

The global incidence of Kawasaki disease varies among different regions, with annual incidence rates per 100,000 children <5 years old ranging from 100 to 300 in Japan and northern Asia regions and ten times higher compared to the United States, where the incidence is about 25 per 100,000 children [1,3]. The disease affects mainly children below the age of five years and is more prevalent in males, with a ratio of 1.5:1 [1,4].

Despite the fact that the incidence of Kawasaki disease has been increasing worldwide, the etiology remains unknown. A variety of etiologies have been hypothesized, including environmental factors such as bacterial and viral infection [5] and genetic factors [6]. Recent studies have reported the role of the five immune genes that are potentially involved in the pathogenesis of Kawasaki disease.

Kawasaki disease-related databases (GSE18606, GSE68004, and GSE73641) have been downloaded and integrated into samples from 173 Kawasaki patients and 101 regular patients using the Gene Expression Omnibus Database. CIBERSORT was used to detect 22 samples with immune cells that were submitted to differentially expressed gene (DEG) analysis and weighted gene co-expression network analysis (WGCNA). The identification of five immune genes, including CXCL8, CCL5, CCR7, CXCR3, and CCR1, that contribute to the pathogenesis of the disease was facilitated by the co-expression networks and Cytoscape 39's cytoHubba tool [7].

The classical symptoms during the acute phase of the illness include fever (> 39C) lasting for more than five days, bilateral conjunctivitis, oral mucositis and/or erythematous tongue ("strawberry tongue"), polymorphous rash, unilateral cervical lymphadenopathy, and changes in the extremities, such as edema and/or peeling of hands and feet [8]. The diagnosis is mainly

clinical and further classified into complete and incomplete Kawasaki disease. Supportive laboratory tests include markers of systemic inflammation such as elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), increased white blood cell count (WBCs), hypoalbuminemia, elevated liver enzymes, elevated platelet count, and anemia [9,10].

Patients suspected of having Kawasaki disease should undergo 2-dimensional (2D) echocardiography, as coronary artery abnormalities can manifest as dilatation or aneurysms of varying sizes, numbers, and characteristics [9].

The mainstay treatment for Kawasaki disease involves administering high-dose intravenous immunoglobulin (IVIG) and aspirin; however, recent studies have found that corticosteroids, along with intravenous immunoglobulin and interleukin-1 (IL-1), like anakinra, when employed as adjunctive therapy, prevent the occurrence of coronary artery aneurysms in Kawasaki disease [11,12].

The aim of this thesis is to delve into the underlying mechanisms of coronary artery pathology in Kawasaki disease with the goal of identifying potential prognostic and therapeutic targets that could be incorporated into future treatment approaches.

1.1 Literature search strategy

For this thesis, I conducted a narrative review and devised a literature search strategy, outlined as follows:

1. Databases searched: A search was conducted on numerous online databases including PubMed, Cochrane, Google scholar, ScienceDirect and Embase. The sources ranged from 2011 to 2023. The selection of articles was based according to their relevance to the research topic.
2. Search String: ("Kawasaki disease" OR "mucocutaneous lymph node syndrome") AND ("Corticosteroids" OR "steroids") AND ("Aspirin" OR "acetylsalicylic acid") AND ("Intravenous immunoglobulin" OR "IVIG") AND ("Coronary artery aneurysms" OR "coronary artery abnormalities") AND ("Echocardiogram" OR "cardiac ultrasound").

2. Mechanism and Pathology

The etiology of the Kawasaki disease remains unclear, but it is postulated to be a result of an aberrant response to infectious triggers in genetically predisposed individuals, common in children of Asian descent, particularly Japanese ancestry [13].

Several studies have been undertaken to unravel the underlying mechanisms of coronary artery involvement in the pathogenesis of Kawasaki disease by emphasizing the role of genetic and immunological factors [14].

2.1 Protein Biomarkers and Their Role

Through the application of isobaric tags for relative and absolute quantitation (iTRAQ) analysis and western blot, several studies have identified five key proteins associated with coronary artery abnormalities in Kawasaki disease [7]:

(1) Mannose-binding lectin 2 (MBL2); (2) Complement factor H (CFH); (3) Kininogen 1 (KNG1); (4) Serpin family C member 1 (SERPINC1); and (5) Fibronectin 1 (FN1).

CFH and MBL2 have a unique role in the body as they control the proteolytic cleavage of C2 and C4. When levels of CFH and MBL2 drop, it results in an increase in C3b levels and a decrease in C2 and C4 separation, leading to innate inflammation, coronary artery pathology, and thrombosis. On the other hand, KNG1 and SERPINC1, which are present in coronary artery aneurysms (CAA), exhibit properties that reduce inflammation and prevent blood clotting. Decreased levels of these proteins result in inflammation and damage to the vascular endothelium, leading to artery dilatation and aneurysms. Fibronectin 1 (FN1), an extracellular glycoprotein, plays a crucial role in wound healing and processing. Decreased levels of this protein are found in both coronary artery disease (CAD) and CAA [7,15-18].

2.2 Gene Polymorphism

An important gene in the development of coronary artery lesions in Kawasaki disease is the inositol 1,4,5-trisphosphate 3-kinase (ITPKC) gene, which functions as a negative regulator of calcium channels and T cell activation. Genetic polymorphisms in the ITPKC gene can lead to mRNA splicing defects and hyper-activation of calcium channels. An important mutation, ITPKC3G/C, causes premature mRNA splicing, which results in an immature and truncated

protein. This mutated protein leads to a continuous phosphorylation process, triggering the release of calcium into the cytoplasm. This sequence of events culminates in the activation of calcineurin, which in turn triggers the transcription of genes involved in T cell activation and the release of inflammatory cytokines. Consequently, this leads to inflammation of the coronary artery and the formation of aneurysms, highlighting the significant role of the ITPKC gene in the pathogenesis of Kawasaki disease [19-21].

2.3 Regulatory T cells (Tregs) and miRNAs

The role of the transforming growth factor-beta (TGF-beta) gene in T cell activation and ventricular remodeling is particularly important. It is involved in several cellular processes, such as cell proliferation, migration, apoptosis, angiogenesis, calcification, and fibrosis. The gene activity is regulated by the FURIN and EMILIN (elastin microfibril interfacer-1) proteins. Alterations in certain genes can result in continuous transcription and remodeling of coronary endothelial cells, contributing to coronary artery aneurysm formation [22].

A recent study investigated the role of platelet and vascular smooth muscle cell (VSMC) interactions in Kawasaki disease. Using genome-wide miRNA and droplet digital PCR, the researchers enrolled 242 KD patients and 75 individuals with confirmed coronary artery involvement. The main findings were that KD patients showed significant induction of the microRNA miR-223, which promotes vascular smooth muscle cell (VSMC) de-differentiation and wound healing. However, in patients with severe coronary artery aneurysms, there was a lack of miR-223 induction, leading to persistent VSMC de-differentiation and severe coronary abnormalities. Using a mouse model, the absence of miR-223 caused extensive arterial damage, which could be mitigated by the transfer of platelets, administering miR-223 mimics, or using the platelet derived growth factor-beta (PDGFR-beta) inhibitor. In patients with Kawasaki disease who develop coronary artery aneurysms, blood samples reveal a decrease in miR-223 levels. This deficiency triggers a significant release of matrix metalloproteinases 9 (MMP9), a protein that can damage the coronary artery endothelium, leading to dilatation and aneurysm formation. Furthermore, miR-223 levels were found to increase with age, explaining the higher susceptibility to coronary pathology in children under five years old. The detection of microRNA miR-223 can help identify KD patients at greatest risk of coronary involvement, and targeting miR-223 or VSMC PDGFR-beta could offer a potential therapeutic strategy for KD

[23].

3. Clinical presentation of the condition

3.1 Kawasaki disease

Kawasaki disease is an acute, self-limited systemic vasculitis of mainly medium-sized arteries, particularly the coronary arteries [24]. KD is a febrile illness that mainly affects children younger than 5 years old, with a male gender predominance at a ratio of 1.5:1 [1,14]. There are two forms of the condition, complete and incomplete.

3.1.1 Complete Kawasaki disease

The clinical presentation of complete type of Kawasaki disease is involves the presence of a fever lasts for more than 5 days along with typical signs and symptoms, including a fever (>39 C) that lasts for more than five days and meets at least four of the five following signs and symptoms: (1) bilateral non-exudative conjunctivitis; (2) erythema of the lips and oral mucosa; (3) rashes; (4) changes in the extremities; and (5) cervical lymphadenopathy [24,25].

3.1.2 Incomplete Kawasaki disease

Incomplete Kawasaki disease (iKD) is more common in infants <6 months old, and children older than 10 years present with a prolonged fever lasting five or more days along with two or three of the aforementioned classical signs and symptoms. In infants, signs of irritability are observed [26].

3.2 Cardiac Manifestations

During the acute episode of Kawasaki disease, children commonly present with a hyperdynamic precordium and tachycardia. These symptoms are indicative of myocardial inflammation and decreased cardiac output, which can lead to poor perfusion and potentially result in congestive heart failure. In rare cases, murmurs and a gallop rhythm can be observed in children, suggesting myocarditis or left ventricular dysfunction. Pericarditis may be present, and clinical signs of pericardial tamponade or a pericardial rub may be apparent, although it is very rare and typically mild and transient [1,11]. Valvular dysfunction, specifically affecting the mitral and aortic valves, has also been observed in children with KD during the acute episode [1].

3.2.1 Coronary artery abnormalities

Coronary artery abnormalities, such as dilatation or the formation of aneurysms, can be considered a specific supportive criterion for the diagnosis of KD, particularly in cases of incomplete KD. These abnormalities are defined based on the luminal dimensions of the coronary arteries, which can be detected by echocardiography [1,9]. Dilatations often resolve within 4-8 weeks, although in some cases it may persist or worsen [1]. Patients with severe coronary artery involvement, such as large or giant aneurysms, are at higher risk of developing major adverse cardiovascular events, such as stenosis, thromboses, and myocardial infarction [27,28]. Those patients may not exhibit any cardiac signs and symptoms unless myocardial ischemia occurs due to severe disturbances in coronary artery blood flow or thromboses. In infants, the clinical signs and symptoms of myocardial ischemia can be atypical and nonspecific, making diagnosis and treatment more challenging [1].

4. Diagnosis

4.1 Clinical Evaluation

4.1.2 Clinical Criteria for Complete Kawasaki disease

According to the 2017 AHA guidelines, the diagnosis of Kawasaki disease relies primarily on clinical manifestations. A diagnosis of complete Kawasaki disease can be made when a patient has a fever (> 39 C) lasting for five or more days and meets at least four of the five following clinical criteria [1]:

- Bilateral conjunctival injection without exudate.
- Changes in the lips and oral cavity, including injected pharynx, strawberry tongue, and/or lip cracking and/or erythema.
- Polymorphous rash.
- Cervical lymphadenopathy, usually unilateral and at least one lymph node ≥1.5 cm in diameter.
- Changes in the extremities, such as redness, swelling, and/or peeling of the hands and feet, or periungual desquamation.

If more than four of the principal clinical criteria are present, distinctly when redness and swelling of the hands and feet are present, the diagnosis of KD can be established earlier with only four days of fever. However, differential diagnosis is crucial because other conditions may present with similar symptoms. If a child has an unexplained fever lasting more than five days along with the principal clinical signs and symptoms, other conditions should also be considered [1,9].

The presence of aneurysms, identified by echocardiography, can be definitive for a Kawasaki disease diagnosis. On the other hand, coronary artery dilatation is typically not seen until after the first week of the disease and therefore, does not rule out KD, especially in the early stages of the condition [1].

4.1.3 Evaluation of Suspected Incomplete Kawasaki disease

Incomplete Kawasaki disease (iKD) is a diagnostic challenge, particularly in infants and those lacking oral and eye mucosal changes [1]. Children and infants with incomplete form of Kawasaki disease, increase the risk of delayed diagnosis and subsequent complications such as coronary artery abnormalities. Diagnostic echocardiography should be considered in infants younger than 6 months with unknown causes of fever for > 7 days and laboratory evidence of systemic inflammation and irritability [1,29]. An echocardiogram may reveal signs of coronary vasculitis, which would support a diagnosis of KD. However, the absence of suggestive findings, does not necessarily rule out KD [1,29-31].

The 2017 AHA guidelines provide a framework for considering the diagnosis of incomplete Kawasaki disease (Figure 1). The guidelines suggest that the diagnosis of iKD should be considered in all children and infants with unexplained, prolonged fever, those who exhibit less than four of the principal clinical manifestations, and laboratory or echocardiographic findings suggestive of KD [1].

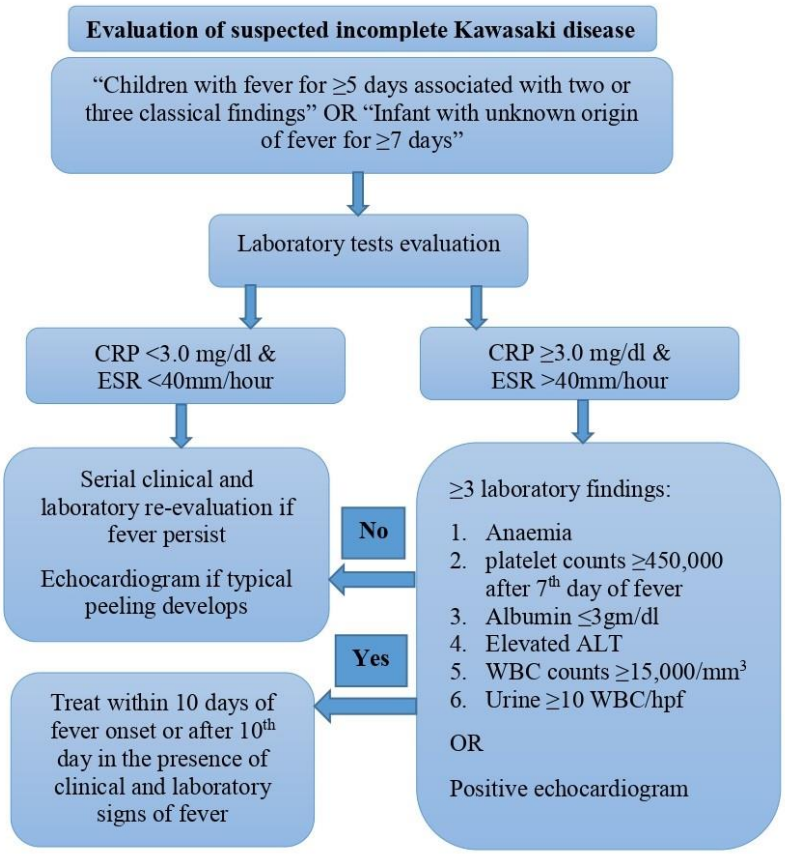

Figure 1. Evaluation of suspected incomplete Kawasaki disease [1]

Figure 1. Evaluation of suspected incomplete Kawasaki disease [1]: positive echocardiography indicates if any of 3 conditions are met: (1) Z score of left anterior descending artery or right coronary artery ≥2.5; (2) presence of coronary artery aneurysm; (3) ≥3 other suggestive features like decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5. Positive laboratory signs represent elevated CRP (C-reactive protein), ESR (erythrocyte sedimentation rate). ALT- alanine transaminase; and WBC-white blood cells.

This algorithm is meant to guide clinicians in determining the need for treatment in patients with suspected iKD. However, the algorithm is not designed to differentiate Kawasaki disease from other febrile illness [23].

4.2 Laboratory Findings

Kawasaki disease, despite lacking a definitive diagnostic laboratory test, can be supported through a range of laboratory investigations, especially in the context of patients exhibiting atypical clinical manifestations of the disease.

The 2017 American Heart Association (AHA) guideline proposes that nonspecific laboratory findings of raised inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count, should be considered as potential indicators for evaluating incomplete KD [1].

In the acute phase of KD, a complete blood count often reveals leukocytosis with a count exceeding 15,000/mm3 and a predominance of neutrophils. Supplementary laboratory findings may reveal anemia by age, with hemoglobin levels falling below the age-specific reference range, hypoalbuminemia (< 3.0 mg/dl), hyponatremia (< 130 mmol/L), platelets count > 450,000/mm3 after day 7 of illness, and elevated liver enzymes [1,8,10,28]. Urinalysis often shows sterile pyuria (>10 WBC/HPF) [1].

Thrombocytosis is a common occurrence in patients with Kawasaki disease, typically manifesting within the second to third week of the disease course. The platelet count may continue to increase in the subacute phase of the illness, but typically resolves by 4 to 6 weeks after onset [1,28,32]. Thereby escalating the risk for development of coronary artery abnormalities [8,32].

4.2.1 Cardiac Biomarkers

N-terminal pro Brain Natriuretic peptide (NT-proBNP), has been identified as potentially useful in detecting myocardial involvement in some patients with KD, particularly during the acute phase when NT-proBNP levels are known to increase [1,33]. Furthermore, elevated levels of NT-proBNP are associated with the development of coronary artery aneurysms and can serve as a predictor for intravenous immunoglobulin resistance in patients with KD [33].

Moreover, several studies and meta-analyses have provided evidence supporting the use of NT-proBNP as a diagnostic marker [33-36]. While NT-proBNP may have limitations due to its non-specificity and the absence of definitive threshold values, its potential usefulness justifies further research to explore its value in diagnostics and treatment protocols together with other clinical criteria and laboratory findings [33-38].

4.3 Cardiovascular Evaluation

4.3.1 Electrocardiogram

In the acute phase of Kawasaki disease, electrocardiogram (ECG) findings may include PR-interval prolongation, and QT-interval prolongation, non-specific ST and T-wave changes [1,39]. QT dispersion abnormalities may persist for several months, and the persistence of repolarization abnormalities during follow-up may indicate a higher risk of ventricular arrhythmia, even in the absence of obvious echocardiographic abnormalities. [39,40]. ECG findings such as ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina are indicators for acute coronary syndrome.

4.3.2 Echocardiography

Echocardiography is crucial for monitoring cardiac complications in the acute phase of Kawasaki disease in children. Although two-dimensional echocardiography is the preferred imaging method, a normal examination cannot completely rule out a diagnosis of KD. However, if there are any changes in the echocardiography, the diagnosis becomes more certain. It is advisable to perform frequent echocardiography examinations during the initial days of the disease and repeat them at the time of discharge and after two weeks. It is important to note that a normal baseline echocardiogram within the first 7 days does not necessarily rule out the possibility of the later development of coronary artery aneurysms [1,26]. Guidelines recommend echocardiography in Kawasaki disease at baseline, 1 to 2 weeks, and 4 to 6 weeks after treatment to monitor coronary artery abnormalities [1].

4.3.3 Classification of Coronary artery aneurysms

The American Heart Association (AHA) 2017 and Japanese Circulation Society (JCS/JSCS) 2020 classified aneurysms, utilizing the Z-score (Table 1) [1,13]:

Table 1. Classifications of coronary artery aneurysms in American Heart Association and Japanese Circulation Society guidelines [1,13]

A) American Heart Association (AHA) 2017 classification [1]:

1. No involvement: Z score always <2
2. Dilation only: Z score 2 to <2.5; or if initially <2, a decrease in Z score during follow-up of ≥1
3. Small aneurysm: Z score ≥2.5 and <5
4. Medium aneurysm: Z score ≥5 and <10, or absolute dimension <8 mm
5. Large aneurysm: Z score ≥10, or absolute dimension ≥8 mm

B) Japanese Circulation Society (JCS) 2020 Classification [13]:

1. Acute Phase (<30 days):

1.1 For patients under 5 years old:

- Small aneurysm: ≤4mm inner diameter of coronary artery
- Medium aneurysm: >4mm to ≤8mm inner diameter of coronary artery
- Large aneurysm: >8mm inner diameter of coronary artery

1.2 For patients above 5 years old:

- Small aneurysm: Z score ≥2.5 to <5
- Medium aneurysm: Z score ≥5 to <10
- Giant aneurysm: Z score ≥10

2. Severity classification after 1 month:

1. No dilation change: No change in the dilation of coronary arteries including the acute phase
2. Transient dilation (in the acute phase): mild transient dilation that normalizes by 1 month after onset
3. Regression: complicated with coronary artery lesion beyond 1 month from onset, and bilateral coronary artery findings completely normalize during follow-up, and did not fall into group 5
4. Remaining coronary aneurysms: coronary aneurysms on one or both sides on coronary angiography but do not fall into group 5
5. Coronary artery stenotic lesion: Coronary angiography shows a stenotic lesion in the coronary artery
    - Without ischemic findings in various tests
    - With ischemic findings in various tests

Table 1. Classifications of coronary artery aneurysms in American Heart Association and Japanese Circulation Society guidelines: compares the American Heart Association (AHA) 2017 and Japanese Circulation Society (JCS) 2020 guidelines for classifications of coronary artery aneurysms in Kawasaki disease [1,13]. While the American Heart Association uses Z-scores and absolute dimensions to categorize aneurysm size, the Japanese Circulation Society uses either inner diameter or Z-scores, depending on patient age. Additionally, the JCS incorporates dilatation changes, condition regression, remaining aneurysms, and stenotic lesions, thereby reflecting the disease time course and severity.

Studies have shown that the clinical outcome of patients with giant coronary artery aneurysms (CAAs) with a Z-score of >10 or measured values of >8 mm is worse compared to those with

small aneurysms of <5 mm in size. Patients with large or giant aneurysms are at a higher risk of serious complications such as thrombosis, myocardial infarction, and sudden cardiac death [1].

4.3.4 Other Cardiovascular Imagining Modalities

Advanced imaging modalities such as transesophageal echocardiography (TEE), invasive angiography, cardiac magnetic resonance imaging (CMRI), and computed tomography angiography (CTA) are generally not used as the initial diagnostic procedure for acute illness due to their invasiveness or radiation exposure [1,11]. While echocardiography is considered the gold standard for detecting coronary aneurysms in the acute phase of Kawasaki disease within the first six weeks, more advanced imaging modalities may be necessary in some cases to evaluate the vascular system for accurate risk stratification [41].

In cases where echocardiographic evaluation is limited due to factors such as thrombi or stenosis or if the resolution is inadequate in older children and adolescents, the following advanced modalities could be indicated [11]:

- CT coronary angiogram is performed to determine the size of giant aneurysms detected in the proximal or distal coronary segments by echocardiography, assess the distal segments, and detect the presence of thrombi or stenosis in the coronary arteries.
- Cardiac MRI is performed in patients with a risk level above 3 or in patients with suspected associated myocarditis.
- Cardiac catheterization is typically reserved for patients with a positive evaluation of myocardial ischemia or if there are clinical or echocardiographic changes suggestive of acute coronary disease.

5. Management

5.1 Standard Therapy

5.1.1 Intravenous Immunoglobulin

Once a diagnosis of KD is confirmed, it is well established that prompt administration of IVIG during the acute phase can effectively decrease inflammation and minimize the risk of developing

coronary artery abnormalities [1,10,11,30]. The recommended dosage is a single infusion of 2g/kg given intravenously over a period of 12 hours, preferably within the first 7 days of illness onset [1,10,11]. It is unclear whether IVIG treatment is effective after day 10 of illness. In cases where children are diagnosed late or have incomplete KD, IVIG treatment should be considered if there is unexplained persistent fever, the presence of aneurysms, or ongoing systematic inflammation indicated by elevated ESR or CRP levels [10,11].

5.1.2 Aspirin

The current guidelines suggest a combination of aspirin and intravenous immunoglobulins during the acute phase of KD. The recommended dose of aspirin is 80mg/kg per day, divided every six hours, and continued for 14 days. After the fever subsides, the dose of aspirin is typically reduced to an antiplatelet dose of 3-5 mg/kg per day and continued for 6–8 weeks or until there is no evidence of coronary artery abnormalities on echocardiography [1,30]. For patients with persistent coronary aneurysms during the convalescent phase, it is recommended to continue low-dose aspirin (3-5 mg/kg per day) until the aneurysms have resolved. It is important to consider the individual risk-benefit ratio when deciding on long-term aspirin therapy (3-5 mg/kg per day) for patients with regressed CAA [30].

5.2. Adjunctive Therapies

The primary treatment for KD is intravenous immunoglobulin combined with high-dose aspirin. However, some patients do not respond to this initial therapy, necessitating adjunctive treatments to reduce the risk of complications.

5.2.1 Corticosteroids

Corticosteroids have long been considered for use in Kawasaki patients due to their potent anti-inflammatory and immunosuppressive properties, with the aim of preventing the potential risk of coronary artery aneurysm development. However, the use of corticosteroids as a first- or second-line treatment remains a topic of debate, as studies have reported conflicting results based on factors such as patient selection (all patients versus high-risk patients) and ethnicity [41].

Recent studies, including a systematic review and meta-analysis, have reinforced the effectiveness of corticosteroids as part of the initial treatment strategy for KD, particularly for high-risk patients who are prone to developing coronary artery aneurysms and those who are

resistant to IVIG therapy. This approach has shown significant benefits, such as a reduced risk of coronary artery abnormalities and coronary aneurysms, faster resolution of fever, shortened duration of clinical symptoms, and faster normalization of lab parameters. These studies have highlighted that adding corticosteroids to IVIG therapy as an initial treatment for high-risk patients with KD can reduce the risk of CAA without increasing the incidence of adverse events. [42,43].

5.2.2. Infliximab

Infliximab, an antibody that targets tumor necrosis factor-alpha (TNF-α), has been employed as an adjunctive therapy for Kawasaki disease patients who are either prone to resistance to intravenous immunoglobulin or who have not shown a response to the initial IVIG regimen [1]. Its application as a complementary treatment to primary therapy is reported to be safe; however, it does not improve coronary outcomes. Administering infliximab was linked with shorter hospital stays and reduced fever duration, but not with an incidence of coronary artery abnormalities or adverse events [11]. The suggested regime is 6 mg/kg given intravenously over a span of 2 hours, with 1-2 doses given (if two doses are used, they should be administered weekly) [1,11,41].

5.2.3. Anakinra

Anakinra is a recombinant human interleukin-1 receptor antagonist (IL-1RA) that blocks the biological activity of interleukin-1 (IL-1), which is a pro-inflammatory cytokine, by competitively inhibiting its binding to the interleukin-1 (IL-1) receptor, thereby down-regulating the IL-1 mediated inflammatory response [1,41].

Recent case reports and clinical trials have demonstrated the successful use of anakinra in patients with KD highly refractory to conventional treatment [12,44-50]. Anakinra has been associated with a decrease in the duration of fever and serum marker levels as well as improved short-term coronary outcomes; therefore, it should be considered for the rescue of patients that do not respond to conventional treatment [11,12,44-50].

Maggio et al.,[46] reported KD in siblings following parvovirus infection. The younger sibling developed incomplete KD and a coronary artery aneurysm despite treatment with IVIG. Anakinra administration led to improved clinical conditions and a reduction in aneurysm size.

In a case series by Kone-Paul et al.,[47] anakinra was administered to 11 KD patients (nine with complete KD and two with incomplete KD) who deteriorated despite primary and secondary treatment regimens. The use of anakinra led to the resolution of fever and inflammation and a reduction in aneurysm size in these patients.

Guillaume et al.,[48] presented the case of an 18-year-old boy with typical KD who developed aneurysms despite treatment with IVIG and methylprednisolone. The initiation of anakinra on the 25th day of illness led to a reduction in C-reactive protein levels and the size of aneurysms.

The case studies reviewed suggest that anakinra could be a promising therapeutic option for managing refractory KD and preventing the progression or development of aneurysms. However, larger-scale, controlled studies are necessary to confirm these findings and establish the optimal dosage and duration of treatment with anakinra in patients with KD.

5.3 Management and Prevention of Thrombosis

5.3.1 Antiplatelet Therapy

The use of antiplatelet agents, such as aspirin (acetylsalicylic acid) and clopidogrel (a thienopyridine), is standard therapy for patients with coronary aneurysms. For small coronary artery aneurysms, low-dose acetylsalicylic acid (ASA) alone is usually adequate. But when it comes to moderately large or giant aneurysms, combination therapy is preferred. For patients with moderate aneurysms, ASA may be combined with a thienopyridine like clopidogrel [1,11,41].

5.3.2 Anticoagulation Therapy

For patients with large or giant aneurysms who are at a higher risk of thrombosis due to abnormal flow conditions and stasis, a combination of antiplatelet and anticoagulant therapy is often employed. This commonly includes low-dose ASA along with warfarin (with an International Normalized Ratio or INR target of 2.0 to 3.0) or low-molecular-weight heparin (LMWH). Warfarin's use may be challenging in infants; thus, LMWH is often preferred. LMWH may also be used in older children when INR cannot be adequately controlled [1,41].

The anti-inflammatory properties of LMWH could provide added advantages during the acute phase of Kawasaki disease, although transient low levels of antithrombin during acute illness can

affect the antithrombotic action of LMWH [1,41]. To ensure that anticoagulation is adequate, activated factor Xa levels are monitored. The therapeutic range is typically between 0.5 and 1.0. If these levels are not reached despite appropriate dosing of LMWH, the next step is to assess antithrombin levels. This is particularly important in patients with coronary artery aneurysms due to Kawasaki disease, where achieving the correct balance of anticoagulation is critical. If antithrombin deficiency is detected, fresh-frozen plasma or antithrombin supplementation can be considered [1]. These interventions can help raise antithrombin levels, potentially enhancing the effectiveness of LMWH. However, they must be used with care due to the increased risk of bleeding, and it is critical to continue monitoring both activated factor Xa and antithrombin levels as well as for any signs of bleeding or thrombosis.

5.3.3 Thrombolytic Therapy

Tissue plasminogen activator (tPA), specifically alteplase, is the first-choice thrombolytic therapy in children with coronary artery aneurysms and subsequent thrombosis. However, tPA is contraindicated in patients with active bleeding or who have recently undergone surgery or trauma [1,35]. Alteplase, used cautiously in this context, has various dosing regimens, including a low-dose protocol combined with abciximab, a platelet aggregation inhibitor [1]. Unfractionated heparin (UFH) is continued at an age-appropriate dose during alteplase administration, which can be given as an intermittent or continuous infusion or targeted locally towards the thrombus [11,32]. After treatment, imaging is used to reassess the thrombus, and careful patient monitoring is essential due to the risk of both major and minor bleeding events [1]. The use of alteplase requires individualized dosing, meticulous monitoring, and a multidisciplinary medical team experienced in pediatric anticoagulation management.

5.4 Prevention of Thrombosis

The 2017 American Heart Association (AHA) guidelines for the prevention of thrombosis during the acute phase of Kawasaki disease recommend the following [1]:

- **Low-dose ASA (Aspirin):** For patients without evidence of coronary artery changes, it is recommended to administer low-dose ASA (3–5 mg/kg per day) until 4 to 6 weeks after the onset of illness.

- **Systemic Anticoagulation:** For patients with rapidly expanding coronary artery aneurysms or a maximum Z score of ≥10, it is reasonable to administer systemic anticoagulation with low molecular weight Heparin (LMWH) or warfarin (with an international normalized ratio target of 2.0–3.0) in addition to low-dose ASA.
- **Triple Therapy:** For patients at an increased risk of thrombosis, for instance, those with large or giant aneurysms (≥8 mm or Z score ≥10) and a recent history of coronary artery thrombosis, “triple therapy" may be considered. This involves ASA, a second antiplatelet agent, and anticoagulation with warfarin or LMWH.

6. Long-Term management

Cardiac complications are the most serious concern for patients with Kawasaki disease. These complications primarily manifest as coronary artery aneurysms, which can lead to myocardial infarction or ischemic heart disease [1,24]. The 2017 American Heart Association (AHA) guidelines provided a comprehensive framework follow-up plan to facilitate early detection and prevention of these cardiac complications (Table 2).

Table 2. Risk classification of coronary aneurysms and follow-up recommendations for children with Kawasaki disease according to 2017 American Heart Association (AHA) guidelines [1]:

Risk Level	Pharmacological therapy	Physical activity	Follow-up plan
Level I No Involvement (Z Score <2)	• ASA 3–5 mg/kg until 6 weeks • No additional medical therapy after first 6 to 8 weeks	• Physical activity counselling at each visit. • Healthy lifestyle counselling every 1 year.	• ECG, Echocardiography, History and physical examination between 4 weeks to 12 months.
Level II Dilation only (Z score 2 to <2.5)	• Consider continuing ASA 3–5 mg/kg if dilation persists	• Physical activity counselling at each visit. • Healthy lifestyle counselling every 1 year.	• ECG, Echocardiography, History and physical examination between 4 weeks to 12 months. • If dilatation persists reassess every 2 to 5 years.
Level III Small aneurysm (Z score >2.5 to <5)	• Low-dose aspirin at 3-5 mg/kg/day until aneurysm regression documented • Consider statin administration	• Patient age <11years: No restriction after first 6-8 weeks. • Patients >11years: • Physical activity guided by biennial stress test, • Discouraged contact or high-impact sports as patients on antiplatelet	• ECG, Echocardiography, History and physical examination at 6 months if dilatation persists. • Cardiac stress imaging every 2 to 3 years, if dilatation persists 3 to 5 years.
Level IV Medium aneurysm (Z score >5 to <10, and absolute dimension <8mm)	• Low-dose aspirin at 3-5 mg/kg/day • Consider anticoagulation therapy (LMWH) or dual antiplatelet (clopidogrel) therapy if aneurysms persist; If aneurysms regress consider statins	• Avoid contact or high-impact sports; Physical activity recommended according to stress test or myocardial perfusion scan outcome	• ECG, Echocardiography, History and physical examination at 3,6,12 months, if dilatation persists then every 6 to 12 months. • Cardiac stress imaging every 1 to 3 years, if dilatation persists 2 to 5 years.
Level V Large and giant aneurysm (Z score >10, or absolute dimension >8mm)	• Long-term low-dose aspirin and warfarin or LMWH if giant aneurysm persists; Consider use of tPA, β-blockers, statins and ACE inhibitors	• Avoid contact or high-impact sports; • Physical activity recommended according to stress test or myocardial perfusion scan outcome	• ECG, Echocardiography, History and physical examination at 3,6,9,12 months, if dilatation persists then every 3 to 6 months. • Cardiac stress imaging every 1 to 3 years, if dilatation persists 2 to 5 years.

Table 2. Risk classification of coronary aneurysms and follow-up recommendations for children with Kawasaki disease according to 2017 American Heart Association (AHA) guidelines [1]: Level I - no coronary artery changes at any stage of illness; Level II- transient coronary artery ectasia that disappears within 6-8 weeks; Level III- one small-medium coronary artery aneurysm/major coronary artery; Level IV- >5 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without Obstruction; Level V- coronary artery obstruction. ASA- acetylsalicylic acid; ACE- angiotensin-converting enzyme; ECG- electrocardiogram; LMWH- low molecular-weight heparin; TPA- Tissue plasminogen activator.

7. Conclusion

This narrative review provides an overview of the current literature on coronary artery syndrome in children with Kawasaki disease.

The aim of this review was to explore insights into the pathogenesis of coronary artery development in Kawasaki disease and identify potential diagnostic and therapeutic targets that could be incorporated into prospective treatment paradigms.

The review has shown the potential utility of the N-terminal pro B-type natriuretic peptide biomarker for the identification of coronary artery aneurysms and for discerning resistance to intravenous immunoglobulin therapy, particularly during the acute phase when levels are typically elevated. Future research endeavors should focus on discerning the prognostic capabilities of this biomarker with a view to enhancing its sensitivity when assessing patients with Kawasaki disease.

Therapeutic strategies encompassing intravenous immunoglobulins, aspirin, corticosteroids, and adjuvant agents such as interleukin-1 receptor antagonists, specifically anakinra, were also explored in the review. Evidence suggests that anakinra can effectively minimize the likelihood of coronary aneurysms and manage refractory Kawasaki disease in pediatric patients.

Moreover, the microRNA miR-223 exhibits promise in identifying those Kawasaki disease patients at highest risk of coronary artery pathology. Utilizing miR-223 and platelet-derived growth factor-beta inhibitors as potential therapeutic targets may represent an innovative treatment strategy for Kawasaki disease patients with coronary artery aneurysms. However, it is important to note that till now it has only been examined in vitro; therefore, controlled studies and trials are required to establish the prognostic and therapeutic value of miR-223 and the platelet-derived growth factor-beta inhibitors.

These comprehensive investigations are expected to shed light on the intricate processes that govern the development of coronary artery syndrome in children with Kawasaki disease. Understanding these processes is critical, not only to enhance our knowledge of the disease but also to guide the design and implementation of effective, patient-specific interventions.

8. Reference

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