

Unravelling the Enigma of Kawasaki Disease: Navigating Diagnostic Uncertainty

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Abstract

Kawasaki disease is still a rare pediatric disease with a multifactorial origin and genetics. There is an overall global burden of the disease, especially in the pediatric population in Asian countries. The disease is named after a Japanese paediatrician, Tomisaku Kawasaki. Research efforts are extensive and focus on finding the cause and molecular origin of Kawasaki disease. This chapter aims to elucidate the molecular and immunological basis of a rare paediatric disease with, to date, an unknown aetiology. Kawasaki disease initially presents with characteristic clinical symptoms, followed by the development of coronary artery lesions in a small percentage of cases. Some patients develop coronary artery lesions, whereas others do not. Both mild and severe forms of the disease are observed. Current research focuses on identifying biomarkers to predict the early development of coronary artery lesions in children with Kawasaki disease. Kawasaki-like features of the disease have been described, such as multisystem inflammatory syndrome in children (MIS-C) or Kawasaki-like syndrome, which do not clearly exhibit the classical clinical presentation of Kawasaki disease. In such cases, Kawasaki disease may not fully conform to its typical definition. A clear classification and a clear diagnosis of each patient are of utmost importance.

Keywords: Kawasaki disease; cardiac disease; coronary artery lesions; multisystem inflammatory syndrome; pediatric disease.

1. Introduction

Kawasaki disease (KD) is a leading cause of acquired cardiac disease in children in developed countries. The development of coronary artery lesions (CALs) in 15–25% of

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untreated patients has made KD a leading cause of acquired heart disease in developed countries. The first reported case presented was in 1961, and the first article to describe the clinical manifestations in 50 patients was published by Dr Kawasaki in 1967. The historical context of KD was updated by Dr Kawasaki in 2014, in which he was able to share insights and highlight many of the cardiac manifestations of the disease not initially recognised in the original case series (Jone, 2024). In Germany, approximately 9 out of 100,000 children under five years of age are affected each year, while the incidence of Kawasaki syndrome in Japan in the same age group is around 185 out of 100,000. Severe and lethal cases are described in the literature (Sabsabee et al., 2026; Xue et al., 2026; Zhou et al., 2026; Hailegiorgies, 2026). In this study, 75% of all patients are younger than five years old, with children in their second year of life being particularly susceptible. Boys are affected by the disease about one and a half times more often than girls. In the northern hemisphere, there are more cases in winter and spring than in summer and autumn, while in tropical regions, there is no seasonal pattern. In Germany, compared to the classical Kawasaki syndrome, a multisystem inflammatory syndrome associated with COVID-19, an unspecified "Kawasaki-like" syndrome, a multisystem inflammatory syndrome in children (MIS-C), a pediatric inflammatory multisystem syndrome (PIMS), a cytokine storm temporally associated with COVID-19 is described (Jiao et al., 2023). MIS-C is a rare but severe pediatric condition (Noval Rivas & Arditi, 2023). "Since April 2020, a novel syndrome resembling Kawasaki syndrome has been observed in the USA and some European countries, named MIS-C. MIS-C may be linked to infections by the SARS-CoV-2 virus. In May 2020, the WHO called for monitoring and research on MIS-C. By mid-May 2020, 103 children with symptoms resembling Kawasaki syndrome had been treated in the state of New York alone. Of these children, 60% tested positive for COVID-19 caused by the virus, while antibodies against SARS-CoV-2 were detectable in the remaining 40%. The age group most affected is 5 to 14 years old. Unlike acute COVID-19, which is often mild or asymptomatic in children, MIS-C presents as a severe hyperinflammatory condition, typically occurring 2–5 weeks after infection (Scaltrito et al., 2025). In a recent study from a cohort from Brazilia, genetic analyses of patients with MIS-C, severe COVID-19, and Kawasaki disease revealed rare potentially damaging variants in 29 individuals" (Reis et al., 2023). "A total of 50 variants were found in 38 different genes, including known variants in IFNA21 and IFIH1 genes, as well as new variants in genes previously linked to MIS-C (KMT2D, CFB, and PRF1)" (Reis et al., 2023). "Additionally, variants in genes newly associated with MIS-C, such as APOL1, TNFRSF13B, and G6PD, were identified" (Reis et al., 2023). "Gene ontology analysis highlighted thirteen major pathways, including the complement system, hematopoiesis, immune system development, and type II interferon signalling, which had not been previously reported in MIS-C (Reis et al., 2023). To that point, Kawasaki is not Kawasaki. A clear classification and a clear diagnosis of each patient are of utmost importance. Seasonal patterns of Kawasaki Disease (KD) incidence have been well-documented, but it remains unclear whether these patterns are driven by changes in climate or other seasonal factors" (Abrams et al., 2018). "In another study published in 2018, researchers analysed KD incidence data from Japanese nationwide epidemiologic surveys (1991-2004) and climate data from 136 weather stations of the Japan Meteorological Agency to investigate the relationship between KD incidence and *deviations from expected temperature and precipitation*" (Abrams et al., 2018). "Researchers used Poisson-distributed generalised linear regression models to examine the effects of temperature and precipitation on KD incidence in the same month as KD

onset and the preceding 1 to 6 months, while controlling for geographic variations and seasonal trends. The results showed that KD incidence was negatively associated with temperature in the previous 2 to 5 months and positively associated with precipitation in the previous 1 and 2 months” (Abrams et al., 2018). “The model that best predicted variations in KD incidence used climate data from the previous 2 months (Abrams et al., 2018). Specifically, a 100 mm increase in total monthly precipitation was associated with an increased KD incidence, while a 1°C increase in monthly mean temperature was associated with a decreased KD incidence” (Abrams et al., 2018). “These findings suggest that temperature and precipitation in the preceding months have a significant impact on KD incidence, independent of other seasonal factors” (Abrams et al., 2018). *The pathogen that triggers this disease is still unknown 40 years after its first description.* Epidemiological findings suggest a significant genetic component in the aetiology, and some *candidate genetic variations* that confer susceptibility to KD or risk for coronary artery lesions have been identified. However, most of these associations need further confirmation through replication studies with larger cohorts. Multiple theories have been proposed to explain the cause of Kawasaki disease. It is believed that genetic factors play a significant role in predisposing individuals to KD, with certain genetic variations increasing susceptibility to the disease and the development of coronary artery lesions. The higher prevalence of KD in Asian countries compared to non-Asian countries further supports the genetic influence on the disease. In addition to genetic factors, an infectious cause has also been suggested but not confirmed for KD. Studies have shown that specific epidemics of KD in Japan have seasonal patterns and mimic viral or bacterial infection symptoms. Some research has linked adenovirus infection to the onset of KD, with the virus potentially triggering an immune response that leads to coronary artery damage. Antibodies associated with KD have been found to identify inclusion bodies in tissues, suggesting a viral origin for the disease. These inclusion bodies contain viral RNA and proteins that have not been fully identified. The interaction between genetic predisposition and *infective triggers* likely contributes to the development of KD and its associated complications, the most serious of which are coronary artery aneurysms. “A review *candidate gene* association study from a genome-wide approach that highlights the importance of the *Ca²⁺/nuclear factor of activated T-cells pathway* in the pathogenesis of KD. KD is a systemic vasculitis syndrome that primarily affects infants and children. Intravenous gamma globulin (IVIG) therapy has significantly reduced the occurrence of CALs, but approximately 15% of patients do not respond well to treatment and are at higher risk for CALs. Two main strategies for identifying disease genes are the candidate gene approach and the genome-wide approach” (Rhim et al., 2022; Pilania et al., 2018; Gupta, 2022). Candidate gene studies have focused on genes with known functions or roles in disease pathophysiology. HLA genes, TNF- α , VEGF, MMPs, and genes related to the immune system have been investigated for their association with KD. However, most of these studies have yielded conflicting results and require further validation in larger cohorts. Genome-wide approaches, such as linkage studies and LD mapping using SNPs, have provided new insights into the genetic basis of KD. A recent genome-wide linkage study identified *several chromosomal loci* associated with KD, with the *12q24 region* showing the most significant linkage. LD mapping using SNPs identified an LD block on chromosome *19q13.2* containing three SNPs significantly associated with KD. Further functional analyses revealed that the *ITPKC gene* within this LD block plays a crucial role in the

Ca²⁺/NFAT pathway in T cells and is associated with KD susceptibility and CAL formation (Bittmann, 2024).

An experiment was conducted to induce immune complex vasculitis in piglets using horse serum infusions to simulate Kawasaki disease (Philip et al., 2004). Twenty-one male piglets of different ages were divided into two groups: one receiving horse serum (HS) infusions and the other receiving normal saline (NS) infusions. Echocardiographic examinations were performed before and after infusions, and histopathologic studies were conducted after 14-60 days (Philip et al., 2004). The HS group showed skin rashes, coronary artery dilation, and vasculitis, while the NS group did not develop vasculitis. The main changes observed in the coronary vasculitis included intimal proliferation, smooth muscle cell necrosis, and vacuolization (Tian et al., 2022). Piglets that received three HS infusions had more skin rashes than those receiving two infusions. This study suggests that piglets can be used as an experimental model for immune complex vasculitis involving the coronary arteries, with skin rashes resembling Kawasaki disease, which aspects are evaluated in further studies (Philip et al., 2004; Philip et al., 2023; Menikou et al., 2019; Philip, 2014). The *genetic basis of KD is complex and multifactorial*, with both candidate gene and genome-wide approaches contributing to our understanding of the disease. Identification of susceptibility genes and pathways involved in KD pathogenesis may lead to new therapeutic and preventive strategies for this enigmatic disease.

2. Tomisaku Kawasaki

Tomisaku Kawasaki (February 7, 1925 – June 5, 2020) was a Japanese pediatrician. He is known for identifying and describing Kawasaki disease, a condition named after him. Kawasaki was born in 1925 as the youngest of seven children. Despite his initial interest in plants during his youth, he pursued a career in medicine at the urging of his mother. He began his medical studies at Chiba University immediately after the end of World War II and eventually specialized in pediatrics. Due to his family's financial struggles, he sought assistance and was offered a position at the Red Cross Hospital in the Hiroo district of Tokyo, where he worked for forty years. Around ten years into his tenure at the hospital, Kawasaki encountered his first patient with symptoms that did not fit any known disease, a four-year-old boy. Presenting the case at an internal hospital conference, other doctors initially suspected scarlet fever, but a consensus on the diagnosis was not reached. Over the next six years, Kawasaki identified more patients with similar symptoms. He published his observations of the disease in a Japanese medical journal in 1967, sparking widespread interest and leading to the establishment of a government committee in 1970 to study the condition. His hypothesis of a distinct disease was confirmed, and he was awarded the Asahi Prize in 1989 for his research. Kawasaki went on to lead the Kawasaki Disease Research Center from 1990, served as a visiting professor at Kurume University, and taught in the United States. He received numerous accolades, including the top prize from the Japanese Pediatric Society. Kawasaki passed away in June 2020 at the age of 95 in Tokyo (Bittmann, 2024).

3. Biomarker for Kawasaki Disease and Kawasaki-Associated Cal

3.1 Filamin C and Meprin A

In 2012, American researchers were able to identify markers in the urine of affected children that make the disease easier to diagnose quickly and accurately (Kentsis, 2012). These biomarkers are filamin C, excreted in urine from necrotic heart and skeletal muscle cells, and meprin A, an enzyme involved in the inflammatory response (Kentsis, 2012). The diagnosis based on these markers was made in a study with 107 patients with 98% accuracy (Kentsis, 2012). It is about the protein filamin C, a component of heart and skeletal muscle, which, as one might suspect, is excreted in the urine from necrotic cells of the vessel wall in the disease. The second marker is Meprin A, which, as an enzyme, is likely to be involved in the inflammatory reaction in vasculitis. The researchers were able to detect it in higher concentrations in the diseased coronary arteries in a mouse model of the disease. The researchers investigated the diagnostic value of the two markers in 107 patients suspected of having Kawasaki disease, which was clinically confirmed in 53 patients. The two markers were able to distinguish diseased from non-diseased children with 98% accuracy.

3.2 N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP)

“N-terminal pro-brain natriuretic peptide (NT-proBNP) has emerged as a potential biomarker for predicting coronary artery lesions (CAL) in Kawasaki disease (KD), the most common acquired heart disease in children” (Zheng et al., 2020). “The marker is useful to identify myocarditis, because 90 per cent of KD patients will have myocarditis before coronary arteritis occurs. A meta-analysis aimed to evaluate the diagnostic value of NT-proBNP in detecting CAL during the acute phase of KD” (Zheng et al., 2020). “A systematic search of multiple databases identified eight relevant studies for inclusion. This analysis revealed an overall sensitivity of 0.84 and specificity of 0.71, with an area under the summary receiver operating characteristic curve of 0.8582” (Zheng et al., 2020). “When using a threshold of approximately 900 ng/L, the sensitivity and specificity were 0.82 and 0.72, respectively, with an SROC of 0.8868. The study provides valuable insights into the utility of NT-proBNP as a predictive biomarker for CAL in KD” (Zheng et al., 2020).

3.3 Matrix Metalloproteinases (MMPs)

“A further study aimed to investigate the role of matrix metalloproteinases (MMPs) in coronary artery lesions (CAL) in children with Kawasaki disease (KD)” (Tian et al., 2022). “Serum samples were collected from healthy children, febrile children, and KD patients with or without CAL. Standard blood parameters were analysed, and MMP-2 and MMP-9 levels were measured using ELISA. KD patients received intravenous immunoglobulin (IVIG) therapy, and changes in MMP levels before and after treatment were compared. The study found that KD patients exhibited signs of abnormal immunoregulation compared to febrile and healthy controls. While clinical parameters did not differ significantly between KD patients with or without CAL, MMP-2 and MMP-9 levels were significantly higher in KD patients with CAL (Tian et al., 2022). IVIG treatment effectively reduced MMP levels, especially in patients with CA” (Tian et

al., 2022). “Correlations were observed between MMP levels and clinical parameters such as fever duration and white blood cell count. *Elevated MMP levels* were associated with coronary artery aneurysms in KD patients, indicating their potential as biomarkers for CAL in KD patients” (Tian et al., 2022).

Platelet-to-lymphocyte ratio (PLR) seemed to be a biomarker for predicting coronary artery lesions (CAL) in Chinese children with Kawasaki Disease (KD) (Li et al., 2023). A study included 3,664 Chinese children with KD, of whom 1,328 developed CA (Li et al., 2023). The meta-analysis showed a sensitivity of 0.78, specificity of 0.71, overall diagnostic odds ratio of 8.69, and an area under the curve of 0.82 for PLR in predicting CAL. PLR in combination with other indicators had higher sensitivity, specificity, and area under the curve. Sensitivity analysis confirmed the stability of the results, but significant publication bias was observed. PLR was shown to have a predictive value for CAL in Chinese children with KD (Li et al., 2023). MMP can be reduced by IVIG and added Doxycycline (Bittmann, 2024).

3.4 miRNAs

“Kawasaki disease (KD) can lead to coronary artery lesions (CAL) in children” (Li et al., 2019; Xiong et al., 2022). “Previous research has identified *miRNAs* as potential biomarkers for distinguishing KD patients from non-KD patients” (Li et al., 2019; Xiong et al., 2022). “A recent study aimed to investigate whether these biomarkers could predict CAL formation in KD patients” (Li et al., 2019). “A meta-analysis, miRNA mimic transfection, in vitro cell model, and microarray assays were conducted. Results showed that miR-182-5p and miR-183-5p levels were higher in KD patients with CAL compared to those without CAL. Machine learning analysis confirmed the predictive value of CAL formation with an auROC value of 0.86. Treatment of neutrophil cells with miR-182-5p mimic enhanced their infiltration of endothelial layers composed of human coronary artery endothelial cells” (Li et al., 2019). “Microarray analysis revealed activation of genes enriched in the leukocyte transendothelial migration pathway with *miR-182-5p overexpression*. MiR-182-5p enhances in vitro leukocyte infiltration by activating the leukocyte transendothelial migration pathway in CAL formation in KD” (Li et al., 2019).

3.5 NLRC4 Methylation

“Understanding its molecular mechanisms is essential for diagnosis and the development of effective treatments. NLR Family Card Domain Containing 4 (NLRC4) encodes key components of inflammasomes that act as pattern recognition receptors” (Yu et al., 2024). “A recent study from 2024 aimed to investigate the potential of NLRC4 methylation as a biomarker for KD” (Yu et al., 2024). “Pyrosequencing was used to analyse NLRC4 promoter methylation in blood samples from 44 children with initial complete KD, and 51 matched healthy controls” (Yu et al., 2024). “Methylation at five CpG sites within the NLRC4 promoter region was assessed. These changes were reversed after intravenous immunoglobulin treatment. ROC curve analysis showed that the mean NLRC4 gene methylation had a high diagnostic capability for KD. NLRC4 promoter methylation was negatively correlated with central granulocyte percentage, age, mean haemoglobin quantity, and mean erythrocyte volume” (Yu et al., 2024). “It was also positively correlated with lymphocyte percentage and lymphocyte absolute value. The study

revealed the role of peripheral NLR4 hypomethylation in KD pathogenesis and IVIG treatment response. NLR4 methylation could potentially serve as a biomarker for treatment monitoring, although its exact functions require further elucidation” (Yu et al., 2024).

3.6 Expression of Eosinophilic Subtype Markers in Patients with Kawasaki Disease

“Eosinophils may increase in the acute phase of Kawasaki disease (KD) both before and after intravenous immunoglobulin (IVIG) therapy” (Chang et al., 2022). “Research has explored the link between KD and allergic diseases, highlighting the role of eosinophils in type 2 inflammation. Recent studies have identified two distinct subtypes of eosinophils: lung-resident eosinophils (rEOS) and inflammatory eosinophils (iEOS). A case-control study aimed to investigate the marker expression of eosinophilic subtypes in KD patients. Transcriptome arrays indicated the importance of rEOS in KD, as evidenced by lower IL10RA, higher SELL, and SERPINB1 gene expression” (Chang et al., 2022). “In contrast, the iEOS representative gene CD101 was not elevated in KD. IL10RA expression was higher in KD patients, particularly those without coronary artery lesions (CAL), compared to febrile controls. SELL expression was higher in CAL patients before treatment and remained elevated after six months compared to febrile controls. This important study seems to be the first to show increased SELL expression in KD patients compared to febrile controls after six months of treatment” (Chang et al., 2022). “The findings suggest dynamic differences in eosinophilic involvement between KD patients with and without CAL, warranting further investigation into the role of eosinophilic subtypes in KD patients” (Chang et al., 2022).

3.6.1 The Role of Superantigens in Kawasaki Disease

“The immune activation seen in acute KS is similar to diseases caused by bacterial superantigens” (Xiong et al., 2022). “Staphylococcal TSS toxin-1 (TSST-1) and streptococcal pyrogenic exotoxins (Spes) are well-known superantigens that stimulate T cells” (Xiong et al., 2022). “These bacterial toxins bind directly to amino acid residues outside of the peptide binding groove and selectively activate T cells expressing T-cell antigen receptor (TCR) b-chain variable gene segments (Vb-TCRs). Nominal peptide antigens only activate a small number of T cells” (Xiong et al., 2022). “To investigate if acute KS is caused by superantigens, researchers analysed the T cells for Vb-TCR expression” (Xiong et al., 2022). “Acute KS was linked to *Vb2 T-cell expansion*, while cells from control subjects did not show this expansion” (Xiong et al., 2022). During the recovery phase of KS, the percentages of Vb2-positive cells returned to normal levels. This *increase in Vb2-positive T cells* is similar to the changes seen in TSS. Subsequent reports have also noted Vb2 expansion in KS (Xiong et al., 2022). Additionally, studies have observed increased Vb2 T cells in the small intestines of children with acute KS. Analysis of Vb2 gene segment sequences from patients with acute KS revealed no evidence of clonotypic expansion, supporting the idea of superantigen stimulation (Xiong et al., 2022).

4. Discussion

In January 1961, Dr Tomisaku Kawasaki encountered his first case of Kawasaki disease in a 4-year-old male patient with high fever, conjunctival hyperemia, lip abnormalities, and skin rash. Initially misdiagnosed, subsequent cases led to the recognition of the disease. Dr Kawasaki published a paper in 1967 detailing 50 cases, which gained recognition years later. Funding was secured in 1970 for further research, leading to the establishment of diagnostic guidelines.

Cases with coronary aneurysms were identified, prompting advancements in diagnostic imaging techniques (Bittmann, 2024).

Kawasaki syndrome, also known as mucocutaneous lymph node syndrome (MCLS), is an acute, febrile, systemic disease characterised by inflammation of small and medium arteries (necrotising vasculitis) and systemic inflammation in multiple organs (Tong et al., 2026; Zheng et al., 2026). The exact cause is unknown, but it is believed to have an infectious, likely viral origin, possibly triggered by a genetic predisposition. The prognosis for patients with this syndrome is generally good, with potentially significant aneurysmal changes, particularly in the coronary arteries, detectable by echocardiography (Zhao & Miao, 2026). The mortality rate, mostly due to heart attacks, is around 1 per cent. In Germany, approximately 9 out of 100,000 children under five years old are affected each year, while the incidence of Kawasaki syndrome in Japan in the same age group is around 185 out of 100,000. The disease predominantly affects children under five years old, with boys being affected about one and a half times more often than girls. There is a seasonal variation in the northern hemisphere, with more cases in winter and spring compared to summer and autumn, while tropical regions show no seasonal pattern. The Kawasaki syndrome progresses through three phases: acute febrile period, subacute phase, and convalescent phase. The main symptoms include persistent fever, oral symptoms, conjunctivitis, rash, hand and foot changes, and enlarged cervical lymph nodes. Genetic susceptibility is a key area of investigation in Kawasaki Disease (KD) due to its varying occurrence among different ethnic groups and races. Epidemiological studies have shown the highest incidence in Japan, Korea, Taiwan, and Asian races in the USA. In Japan, siblings of KD patients have a ten-fold higher risk of developing KD, and children with a parental history of KD have a two-fold higher risk. These differences in familial and racial patterns suggest a significant genetic component in the development of KD. Initial studies focused on the *Human Leukocyte Antigen (HLA) genes*, specifically *HLA-DRB1*, *HLA B5*, *Bw51*, and *Bw44*, which were associated with KD susceptibility. Elevated cytokine levels can increase the risk of KD shock syndrome. The involvement of respiratory viruses in the disease's pathogenesis is still uncertain. COVID-19, caused by the SARS-CoV-2 virus, has been linked to a condition in children and adults that shares similarities with KD, known as MIS-C or Kawasaki-like syndrome. The role of cytokines in the development of KD or Kawasaki-like syndrome triggered by COVID-19 is a topic of debate. Autoantibodies targeting endothelial cells and the concept of immunothrombosis are emerging as potential mechanisms in the pathogenesis of KD. Diagnosing and treating KD and Kawasaki-like syndrome, a leading cause of acquired heart disease in developed countries, can be complex due to the lack of a standardised protocol. Ongoing research aims to identify candidate genes for KD to understand its genetic basis and etiopathogenesis. Genome-wide association studies have made progress

in identifying potential genetic loci associated with KD, including *genes such as inositol 1,4,5-triphosphate 3-kinase (ITPKC), caspase-3 (CASP3), B- lymphocyte kinase (BLK), CD40, and HLA. The ITPKC gene* codes for an enzyme involved in T cell signalling and has been linked to KD susceptibility and coronary artery abnormalities. CASP3 plays a role in cell death pathways and has been associated with KD risk. *FCGR2A, BLK, and genes in the TGF- β signalling pathway* have also been implicated in KD susceptibility and disease outcomes. Genomic data from different immune-mediated diseases can be combined to identify shared genetic risk loci (Carmona et al., 2022). A recent study focused on Kawasaki disease (KD) and IgA-vasculitis to understand the genetic contributions. Researchers analysed 1190 vasculitis patients and 11,302 healthy controls. In the discovery phase, they combined genome-wide data from 405 KD patients, 215 IgA V patients, and corresponding controls of European origin (Carmona et al., 2022). Top associated polymorphisms were replicated in additional cohorts (Carmona et al., 2022). A genetic variant, *rs3743841 in the NAGPA gene*, showed significant association in the cross-disease meta-analysis (Carmona et al., 2022). This variant had a strong association with IgAV (Carmona et al., 2022). Functional annotation revealed its regulatory role in gene expression (Carmona et al., 2022). Moreover, the assessment of *human Anti-Neu5Gc antibodies* in Kawasaki disease was the topic of an interesting study of 2013 (Padler-Karavani et al., 2013). N-glycolylneuraminic acid is an immunogenic sugar found in human sera, with varying levels and epitope-recognition profiles. These antibodies are implicated in inflammation-related diseases like cardiovascular diseases and cancer. Detecting anti-Neu5Gc antibodies can indicate disease risk and progression (Padler-Karavani et al., 2013). The study presented a simple method to measure these antibodies using mouse models with and without Neu5Gc (Padler-Karavani et al., 2013). This new method was applied to study anti-Neu5Gc antibodies in Kawasaki disease (KD), a childhood inflammatory condition affecting the coronary arteries (Padler-Karavani et al., 2013). The findings of the study suggested elevated anti-Neu5Gc antibody levels in acute KD patients with normal coronaries compared to those with complications (Padler-Karavani et al., 2013). Another findings of another study indicate that *IL-1 α and IL-1 β* , along with CD11c(+) dendritic cells and macrophages, play a crucial role in the development of Kawasaki disease (KD) vasculitis and coronary arteritis in mice (Lee et al., 2015). Bone marrow chimaera experiments suggest that MyD88 signalling is essential in both hematopoietic and stromal cells, while IL-1 signalling and response are necessary only in stromal cells, not in endothelial cells. Understanding the specific roles of IL-1 α , IL-1 β , and different cell types in the KD vasculitis mouse model could lead to more targeted therapies and a better grasp of the molecular mechanisms underlying KD immunopathologies (Lee et al., 2015). Treatment aims to reduce inflammation and prevent coronary artery aneurysms, typically involving high-dose immunoglobulins and aspirin. Kawasaki disease (KD) is an immune vasculitis of unknown origin characterised by transient inflammation. *The activation of the cGAS-STING pathway*, triggered by the *release of mitochondrial DNA (mtDNA)*, has been implicated in the onset of KD. However, its specific role in the progression of inflammation during the acute phase of KD remains unclear. In a study published in 2024, researchers measured mtDNA and 2'3'-cGAMP expression in serum from KD patients using RT-qPCR and ELISA (Wei et al., 2024). A murine model of KD was induced by injecting *Lactobacillus casei* cell wall extract (LCWE), and activation of the cGAS-STING pathway and inflammatory markers were assessed through various methods (Wei et al., 2024). Human umbilical vein endothelial cells (HUVECs) were treated with KD serum and modulators of the cGAS-

STING pathway for comparative analysis (Wei et al., 2024). Mitochondrial function was evaluated using Mitosox staining, mPTP opening was quantified by fluorescence microscopy, and mitochondrial membrane potential (MMP) was determined with JC-1 staining (Wei et al., 2024). The results showed increased mtDNA and 2'3'-cGAMP expression in KD patient serum, along with elevated levels of pathway-related proteins and inflammatory markers in both in vivo and in vitro models (Wei et al., 2024). Transmission electron microscopy confirmed mitochondrial damage, and further experiments demonstrated that inhibition of mPTP opening reduced mtDNA release, inhibited cGAS-STING pathway activation, and alleviated inflammation (Wei et al., 2024). The findings suggest that mtDNA released through the mPTP plays a crucial role in *activating the cGAS-STING pathway*, leading to inflammation in KD (Wei et al., 2024). Targeting mtDNA release or the cGAS-STING pathway could be a potential therapeutic strategy for managing KD (Wei et al., 2024). Long-term monitoring is essential to detect and manage potential complications, especially coronary artery abnormalities. Most cases of Kawasaki syndrome resolve without complications, but long-term cardiac monitoring is recommended due to the risk of coronary artery involvement. Patients may experience reduced exercise tolerance as a long-term consequence of the disease. In rare cases, inflammation of the coronary arteries with aneurysm formation or stenoses that occur after years. Myocarditis or pericarditis in the acute phase, heart attack, arrhythmias and calcified, aneurysmatically dilated coronary vessels were described. The disease is commonly treated in a hospital setting. The therapy aims to reduce inflammation and prevent coronary artery aneurysms, which usually occur in the second to third week. It has been shown that therapy can reduce the occurrence of coronary artery changes from 25% to 2 to 4%. Therefore, starting therapy before the tenth day is crucial for a favourable outcome. The initial therapy includes high-dose immunoglobulins: 2 g/kg body weight in twelve hours as an infusion, possibly repeated after very early administration and unsatisfactory response. High-dose acetylsalicylic acid (ASA) until the acute inflammation subsides (30 to 100 mg/kg body weight/day) for 14 days is recommended. The dosage is controversially discussed. Whether cortisone-like medications are helpful for "therapy failures" is still a subject of research; they may at least show an additive effect. A cortisone pulse treatment was not better than a placebo (Bittmann, 2024).

Following the acute treatment, long-term treatment for thrombosis prophylaxis with acetylsalicylic acid 3 to 5 mg/kg body weight/day for approximately six to eight weeks is recommended, with further measures depending on the occurrence of coronary aneurysms. As long as an aneurysm exists, ASA should not be discontinued at the low dosage. If a large aneurysm with stenosis has formed, blood clotting may need to be inhibited with other medications such as phenprocoumon. Additionally, bypasses may be considered. A recent study stated that Melatonin, a safe and multifunctional neurohormone with anti-inflammatory and immunoregulatory properties, may offer potential as an adjuvant therapy for KD (Ramos et al., 2018). Further clinical studies are needed to explore melatonin's role in managing KD (Ramos et al., 2018).

The long-term course of the disease depends on whether changes occur in the coronary arteries. In about 25% of untreated children, one or more aneurysms develop. In this case, daily intake of a mild anticoagulant, such as acetylsalicylic acid (30-80mg/kg), is recommended for children. ASA will be continued in the presence of coronary artery disease. About half of these aneurysms resolve within a year. In about 20% of patients,

stenoses develop over the years, which, if left untreated, lead to a heart attack in almost half of the cases.

5. Conclusion

Kawasaki disease is still a rare pediatric disease with a multifactorial origin and genetics. Various studies reveal multiple genetic loci. It is believed to result from a combination of genetic predisposition and various environmental and immunological factors (Menikou et al., 2019). Certain susceptibility genes have been linked to an increased risk of developing KD and coronary artery complications. Additionally, interactions between genes and changes in DNA methylation are thought to be important factors in the development and outcome of KD (Menikou et al., 2019). Research efforts are enormous, especially in Asian countries, where the incidence of Kawasaki disease is much higher than in European countries or in the US.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

Disclaimer (Artificial Intelligence)

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Competing Interests

Author has declared that no competing interests exist.

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