Etiology Models of Antibody Triggered Histamine Intolerance Inducing Kawasaki Disease and Multisystem Inflammatory Syndromes Diseases

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Abstract

The SARS-CoV-2 virus induces multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A) in a small subset of individuals. MIS-C and MIS-A symptoms overlap with Kawasaki Disease (KD). While many viruses and a few bacterial pathogens have been proposed as likely causative agents, the pathogenesis of KD remains unknown. The pathogenesis of MIS-C, MIS-A, and KD remain unknown. Herein, this article proposes that antibodies to pathogens, with levels higher than primary immune response level, are activating granulocytes and mast cells resulting in release of inflammatory molecules including histamine. Further, this article proposes that KD, MIS-C, and MIS-A are caused when elevated histamine levels exceed an individual's histamine tolerance level (i.e., Histamine Intolerance following elevated pathogen antibody levels). This model establishes a framework for why only a small subset of individuals develop KD, MIS-C, and MIS-A following much larger pathogen outbreaks and accounts for the delayed onsets observed.

Introduction

Kawasaki Disease (KD) is a form of vasculitis with unknown cause that results in a fever and mainly affects children under 5 years of age. Children and infants typically develop KD following pathogen outbreaks with an onset delay of several weeks. The number of children developing KD are considerably fewer compared to the number of individuals affected by the pathogen outbreaks. Multiple pathogens have been proposed as the cause of KD[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24]. However, the pathogenesis of KD remains unknown.

Previously, I have proposed that KD is caused by elevated antibody levels (higher than typical primary immune response antibody levels) to pathogens activating mast cells to cause KD[25][26]. Further, I also previously proposed that both MIS-C and MIS-A are both instances of KD associated with the SARS-CoV-2 pathogen[25][26]. Herein, this article extends this model and predict that KD, MIS-C, and MIS-A all induce Histamine Intolerance (HIT) syndrome in affected patients when elevated histamine levels exceed the individual's tolerance threshold. Multiple factors can influence an individual's tolerance threshold for histamine including drugs[27], foods (cocoa, spinach, tomatoes, beer, wine, cheeses, meat, soy,

yogurt, fermented foods, etc.[27][28]), gastrointestinal microbiome[27], and stage of menstrual cycle[28]. Histamine is metabolized extracellularly by the enzyme diamine oxidase (DAO), and intracellularly by histamine N-methyltransferase (HMNT), and aldehyde oxidase (AOX1). Both, individual genetic variants and temporal expression levels of these genes may alter an individual's rate of histamine degradation. This article proposes that KD, MIS-C, and MIS-A patients have prolonged elevated histamine levels that is the direct cause of most of the overlapping symptoms between these three diseases. Individuals with normal histamine metabolism are considerably less like to develop KD, MIS-C, and MIS-A and individuals with lower histamine tolerance at the time of infection are at higher risk for developing these diseases.

Discussion

The etiology and pathogenesis of KD remains unknown. Efforts to identify definitive single causative pathogen agents are countered by associations with other pathogen agents. Why KD has a delayed onset of weeks following pathogen outbreaks with a low incidence rate is also unknown. Mast cells have low affinity Fc receptors for IgG antibodies. Previously, I have proposed that KD, MIS-C, and MIS-A are caused by pathogen antibodies levels higher than primary immune responses triggering histamine release from mast cells[25][26]. KD is considered by some to be distinct from MIS-C and MIS-A because only younger children are affected by KD; this may be an arbitrary distinction when compared to the over 448 million COVID-19 cases worldwide associated with SARS-CoV-2 infections. The remaining unanswered question by this model remains why some individuals develop KD, MIS-C, and MIS-A and not others. This article expands this model that these three diseases are caused when the histamine levels exceed the tolerance level of the patient (e.g., Histamine Intolerance). The symptoms for these diseases overlap those for Histamine Intolerance and anaphylaxis (Table 1). Foods, drugs, microbiome, and menstrual cycle can all alter an individual's histamine tolerance threshold. This hypothesis provides a framework for why some patients develop KD, MIS-C, and MIS-A and other at risk individuals to not develop these diseases. Elevated histamine levels may be the direct cause of KD, MIS-C, and MIS-A disease symptoms (Table 1). Elevated histamine is known to cause rashes, abdominal pain, diarrhea, vomiting, conjunctivitis, dizziness, etc. (Table 1). Cardiac symptoms associated with β-imanazolylethylamine, a derivative of histamine, were described by Dale & Laidlaw[29]. These cardiac responses include altered blood-pressure, constriction of coronary arterioles, constriction of pulmonary arterioles, vasodilation in limbs, altered heart rate, and heart failure varying by dose and animal species[29]. These cardiac symptoms are also observed in some individuals with Histamine Intolerance[30]. I have previously proposed that vasoconstrictions caused by contracted cardiac capillary pericyte cells can result in pressure induced aneurysm and associated cardiac symptoms[25].

Candidate Adjunctive Treatments Suggested by Model

This model of pathogen antibodies hyper-activating mast cells suggests that the current treatment of intravenous immune globulin dilutes pathogen antibodies off of mast cell Fc receptors eliminating or reducing histamine release from mast cells. The current treatment of high dose aspirin mechanism of actions includes COX inhibitor and mast cell stabilizer with one or both affects potentially reducing histamine release from mast cells. The model that KD, MIS-C, and MIS-A are

caused by ADE triggering Histamine Intolerance suggests candidate treatments for evaluation in patients. These candidate adjunctive treatments for further evaluation include supplemental DAO, high dose famotidine[31][32][33][34], cetirizine[35][36], and dexchlorpheniramine[35] given apparent efficacy in treating COVID-19 patients.

Summary

The etiology model is presented that Kawasaki Disease (KD), Multisystem Inflammatory Syndrome in Children (MIS-C) and Adults (MIS-A) are caused by pathogen associated antibody dependent enhancement of disease hyper-activating mast cells that elevate histamine levels to cause Histamine Intolerance. This model provides possible mechanisms of actions for current treatments and suggests several adjunctive treatments (DAO and antihistamines) for evaluation in these patients.

Consent statement/Ethical approval

Not required.

Declaration of interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authorship

The author attest they meet the ICMJE criteria for authorship.

Tables

Table 1. Symptoms overlaps between histamine intolerance, anaphylaxis, multisystem inflammatory syndrome in children and adults, and Kawasaki Disease.

Symptom	Histamine Intolerance	Anaphylaxis	MIS-C & MIS-A	Kawasaki Disease
Ongoing fever	N	N	Y	Y
Abdominal pain	Y	Y	Y	Y
Conjunctivitis - Bloodshot eyes	Y	Y	Y	Y
Diarrhea	Y	Y	Y	Y
Dizziness or lightheadedness	Y	Y	Y	Y
Skin rash	Y	Y	Y	Y
Vomiting	Y	Y	Y	Y
Dyspnea (trouble breathing)	Y	Y	Y	Y
Persistent chest pain or pressure	Y	Y	Y	Y
New confusion		Y	Y	
Inability to wake or stay awake	Y	Y	Y	Y
Cyanosis - Pale, gray, or blue-colored skin, lips, or nail beds		Y	Y	Y
Cervical lymphadenopathy (swollen lymph nodes in neck or elsewhere)			Y	Y
Sore throat		Y	Y	Y
Extremely red, swollen tongue "strawberry tongue"	Y	Y	Y	Y
Swollen, red skin on palms of the hands and soles of the feet			Y	Y
Irritability	Y	Y	Y	Y
Joint pain	Y	Y		Y
Aneurysm			Y	Y
Inflammation of the heart muscle, lining, valves			Y	Y
Arrhythmias, tachycardia	Y	Y	Y	Y
Myalgia	Y	Y	Y	Y

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