SN Comprehensive Clinical Medicine (2021) 3:1076–1080
https://doi.org/10.1007/s42399-021-00872-w

COVID-19

Potential New Treatments for Kawasaki Disease, Its Variations, and Multisystem Inflammatory Syndrome

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Accepted: 19 March 2021 / Published online: 25 March 2021

Abstract

The causation of Kawasaki disease has been a medical mystery for over 54 years. However, the causations of Kawasaki disease, its variations, and COVID-19-associated Multisystem Inflammatory Syndrome have been recently explained to involve high replication rate viral infections. In a subset of patients, the extensive antigen-antibody immune complexes that are not quickly cleared by phagocytosis will create a type III hypersensitivity immune reaction. The subsequent release of proteases and other enzymes and the expression or exposure of new immunogenic antigens due to protease attacks on basement membranes of epithelial cells or endothelial cells in blood vessels will induce new autoantibodies and cause Kawasaki disease, its variations, and COVID-19-related Multisystem Inflammatory Syndrome. There is now increasing evidence that a viral infection of a large surface area of tissue, such as the respiratory tract, gastrointestinal tract or blood vessels, and a resultant type III hypersensitivity immune reaction is the most plausible explanation for the causations of Kawasaki disease, its variations, and COVID-19-related Multisystem Inflammatory Syndrome. Furthermore, an improved understanding of these causations also suggests several potential new treatments which can be more effective.

Keywords Kawasaki disease; · Virus infections; · Respiratory infections; · Multisystem Inflammatory Syndrome; · Hypersensitivity reactions; · Inflammation

Introduction

The SARS-CoV-2 virus and the human symptoms of SARS-CoV-2 viral infection have already been extensively reviewed [1–3]. The symptoms of Kawasaki disease in general and related diseases associated with SARS-CoV-2 observed in some patients having a current or previous SARS-CoV-2 infection have also been reviewed [4–7]. A useful first step in finding potentially effective treatments for a disease is to determine how the disease is caused.

Some explanations for the initiation of autoimmune diseases, such as Kawasaki disease, have been proposed involving immunodeficiency disorders [8]. However, unlike Kawasaki disease possibly induced by a single infection, these disorders are more typically genetic and result in repeated episodes of infections in general [8]. Until now, the causation or pathogenesis of Kawasaki disease and related diseases including Multisystem Inflammatory Syndrome (MIS) have not been explained [4–6, 8].

But there was one paper that provided a proposed step-by-step explanation for Kawasaki disease, incomplete (atypical) Kawasaki disease or COVID-19-related Kawasaki disease symptoms now known as MIS, even during or after a single viral pathogen infection [7]. It was proposed that in some individuals such diseases could result from uncleared antigen-antibody immune complexes that caused a type III hypersensitivity reaction [7]. Proteases and other released enzymes and the expression of immunogenic antigens by the proteases and other enzymes, such as the exposure of new immunogenic antigens from basement membranes of endothelial cells in blood vessels, can induce new autoantibodies that start Kawasaki disease or related Kawasaki disease symptoms [7]. Table 1 summarizes the hypothesized steps leading to Kawasaki disease, its variations, or COVID-19-related Kawasaki disease symptoms (MIS).

This article is part of the Topical Collection on *Covid-19*

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Table 1 Main steps in the pathogenesis of Kawasaki disease, its variations and MIS

1. Host is infected by a very virulent pathogen, e.g., a coronavirus or influenza virus
2. Innate immune system and adaptive immune system T cells cannot stop the infection
3. Adaptive immune system B cells eventually produce antibodies against the viral pathogen
4. Antigen-antibody immune complexes are formed in great numbers
5. Antigen-antibody immune complexes are not quickly phagocytized
6. Antigen-antibody immune complexes activate receptors of several immune cells which release inflammatory cytokines that increase the permeability of blood vessels - a Type III hypersensitivity immune reaction is now initiated
7. Antigen-antibody immune complexes deposit in capillary tissues and induce microvascular thrombosis and adjacent tissue inflammation
8. Tissue inflammation triggers the complement system, including complement cytokines C3a and C5a releases
9. C3a and C5a attract neutrophils and proinflammatory M1 macrophages that release more proinflammatory cytokines, proteases and other enzymes
10. Proteases destroy basement membrane proteins, such as collagen and elastin, used by lungs and blood vessels in organs, skin and other luminal tissues
11. These proteases or other enzymes by themselves, or by their processing of substrate proteins, express or expose new antigens that induce new autoantibodies that bond with antigens to make new antigen-antibody immune complexes.
12. The original pathogen infection eventually ends as a result of antibody neutralization, or it continues.
13. If the host cannot eliminate the new antigen-antibody immune complexes, steps 6-11 could be repeated.

Discussion

Why Does Kawasaki Disease Target Infants/Pediatric Patients Usually Only Once?

Infants and children under age 6 are the predominant targets of typical/atypical Kawasaki disease [5, 6]. There are logical fundamental immune response reasons why infants and young children suffer Kawasaki disease and its variations. Steps 2, 3, and 4 listed in Table 1 can explain why infants and young children are targeted, usually only one time. A first-time infection with an extremely virulent pathogen, such as a pulmonary virus like a coronavirus, will only be met with an initially mediocre T cell and B cell responses, but if the first-time infection is survived, this will lead to memory T cell, memory B cell, and long-lived plasma cell population subsets derived after affinity maturation to have a higher antibody affinity for the pathogen's antigens that will protect against a subsequent infection [9, 10]. If an individual experiences re-infection with the same or antigenically similar pathogens, memory T cells, particularly memory CD8 T cells in the case of viral pathogens, and memory B cells and long-lived plasma cells by higher affinity will more quickly target pathogen antigens and significantly reduce pathogen titers in infected lungs and other organs [9, 10]. This increased proficiency in targeting pathogens would either enable memory T cells, particularly memory CD8 T cells in the case of viral pathogens, to possibly handle a pathogen re-infection entirely by themselves without the need for antibodies; or enable memory B cells and long lived plasma cells to produce more effective antibodies to quickly target previously seen antigens of a pathogen re-infection. In either case, this more quickly targeted immune response would reduce pathogen titers and avoid the creation of a massive number of antibodies and a massive number of antigen-antibody immune complexes described in step 4 of Table 1. This would then pre-emptively avoid the later immune response steps listed in Table 1 that would cause Kawasaki disease or its variations. In summary, the peculiar and mysterious infection characteristics of Kawasaki disease, its variations and MIS can be logically explained by considering the implications of each step listed in Table 1.

What Pathogens Could Trigger Kawasaki Disease?

For almost 40 years, there have been several papers suggesting that viruses were involved with Kawasaki disease, and several viral candidates have been proposed [11]. One paper discusses the involvement of ~20 viral pathogens, including Epstein-Barr virus, bocavirus, human coronavirus HCoV-NL63, human coronavirus HCoV-229E, human coronavirus SARS-CoV-2, influenza virus, adenovirus, human parvovirus B19, Torque teno virus, etc. [11]. The linkages of human coronavirus HCoV-NL63 and coronavirus HCoV-229E to Kawasaki disease support the premise that high replication rate virus infections of a large area of tissue can trigger Kawasaki disease, since these viruses, like SARS-CoV-2, cause respiratory tract infections [12].

Other papers also provide strong evidence of virulent viral causation of Kawasaki disease. A recent paper statistically links the incidence of Kawasaki disease in a region of Paris, France, over a period of 15 years, to outbreaks of both an influenza A H1N1 virus infection in 2009 and the recent SARS-CoV-2 infection [13]. This paper provides strong evidence of a viral infection pathogenesis for Kawasaki disease, especially involving respiratory viral infections such as influenza and SARS-CoV-2, although the paper does not discuss the details of Kawasaki disease pathogenesis.

Another paper notes a seasonal and temporal clustering of Kawasaki disease cases in Japan over a very long time period, going back to specific outbreaks of Kawasaki disease in Japan in 1979, 1982, and 1986, and these cases also support an infectious disease causation [14]. This paper discusses infection involvement of over a dozen viral species, including Epstein-Barr virus, an unknown RNA virus, human coronavirus HCoV-NL63, adenovirus, human parvovirus B19; and

even some bacterial and fungal species, such as *Yersinia pseudotuberculosis, Mycobacterium* and *Candida albicans* involved in starting an immune response that leads to Kawasaki disease [14]. The link of the virulent human coronavirus HCoV-NL63 to Kawasaki disease is especially supportive evidence to the premise that high replication rate respiratory viruses that infect a large area of tissue can cause Kawasaki disease, since this virus, like SARS-CoV-2, causes major respiratory tract and gastrointestinal tract infections [12, 15].

The breadth of experimental evidence presented in the preceding papers implies that some virulent pathogens are the trigger that initiates Kawasaki disease. The most strongly linked pathogens cause respiratory tract, gastrointestinal tract, blood vessel infections, or other large surface area infections [12–14]. These types of infections can create extensive antigen-antibody immune complexes that cannot be quickly eliminated by phagocytosis in individuals having transient or permanent antigen-antibody immune complex clearance problems with their livers, spleens or complement systems.

Uncleared antigen-antibody immune complexes could then bind to receptors on innate immune cells and induce these immune cells to release several inflammatory cytokines, which in turn would begin a type III hypersensitivity immune reaction, with fever and increased blood vessel permeability [7]. The increased blood vessel permeability would allow antigen-antibody immune complexes to deposit in underlying tissues and induce localized inflammation and complement activation, including releases of complement cytokines C3a and C5a [7]. This in turn would attract additional neutrophils and proinflammatory M1 macrophages that would produce more inflammatory cytokines, proteases and other enzymes [7, 16]. These proteases and other enzymes would include acid proteases, cathepsins, and so forth, as well as neutral proteases including matrix metalloproteinases [16]. Proteases also have many other names, such as peptidases, proteolytic enzymes, proteinases, and so forth [16, 17]. Proteinases will be the primary term used below.

Basement membrane proteins of epithelial cells can be cleaved by some proteinases [7]. It has been long recognized that proteinases can cause extensive protein damage [17]. A proteinase anti-proteinase hypothesis was developed in the 1980's after studies on patients with inflammation-induced lung damage [17]. One of the conclusions of this hypothesis was that large populations of inflammatory immune cells will cause proteinase releases of matrix metalloproteinases, cysteine proteinases, and serine proteinases capable of overcoming lung tissue proteinase inhibitors and destroy extracellular matrix proteins in lung alveolar walls [17].

Therefore, the most probable proteinases involved in Kawasaki disease, its variations and related diseases including MIS are matrix metalloproteinases (MPPs), including MMP-1 through MMP-12; cysteine proteinases including the cathepsins B, S, H, L; and serine proteinases including neutrophil elastase, cathepsin G, proteinase 3, and so forth [17–19]. These proteinases and other enzymes will degrade protein substrates and these proteinases or other enzymes, or fragments of their protein substrates, will be able to express new immunogenic antigens to induce new autoantibodies to start Kawasaki disease, its variations or MIS [17–19].

There is experimental evidence to support this explanation, including neutrophil-associated cathepsin C and macrophage-associated cathepsins B, S, K or L detected in synovial fluids near arthritis degraded cartilage [20]. There is additional experimental evidence for involvement of a type III hypersensitivity reaction in causing autoimmune diseases like Kawasaki disease, its variations and MIS, and the involvement of neutrophil-associated proteinases and other enzymes themselves in expressing autoantigens and inducing autoantibodies in cases of antineutrophil cytoplasmic antibodies vasculitis [21, 22]. The experimental evidence includes detection of elevated serum levels of C3a and C5a, and autoantibodies against proteinase 3 and myeloperoxidase enzyme released from neutrophils, proving complement activation and that proteinases and other enzymes can express or expose autoantigens and eventually induce autoantibodies [21, 22].

It should also be noted that there is very strong evidence for the fundamental involvement of proteinases and other enzymes in Kawasaki disease provided by the chemical nature of effective drug treatments already used for Kawasaki disease. Ulinastatin is a trypsin enzyme inhibitor and inhibitor of neutrophil elastase and other proteinases that activate matrix metalloproteinases, and neutrophil elastase degrades tissue inhibitors of matrix metalloproteinases [23]. Ulinastatin directly and indirectly suppresses neutrophils and their secretion of proteinases, inflammatory cytokines and superoxide anions, and it has been long used for the treatment of Kawasaki disease, achieving clinical effectiveness for intensive initial treatments and even reducing Kawasaki disease coronary artery lesions [23]. Furthermore, angiotensin-converting enzyme (ACE) inhibitors are another enzyme inhibitor treatment for cardiovascular protection and Kawasaki disease, and ACE inhibitors are reported to have a direct inhibitory effect on matrix metalloproteinase-9 (MMP-9) [24].

New Treatment Approaches

In addition to the previously discussed drug ulinastatin, there are several other Kawasaki disease treatments that have been implemented [25–28]. These treatments include intravenous immunoglobulin with or without aspirin; plasma exchange (plasmapheresis) to remove inflammatory cytokines and chemokines; suppressing segments of the patient's immune system with corticosteroids, including prednisone, prednisolone, methylprednisolone or dexamethasone; and use of

methotrexate, cyclosporine, or cyclophosphamide, with consider side-effects and risks [25–28]. Additionally, there has been use of monoclonal antibodies, such as infliximab or abciximab, to bind TNF-α to prevent release of pro-inflammatory cytokines; use of the monoclonal antibody canakinumab to bind to IL-1β; use of etanercept for a receptor blockade of TNF-α receptors; and use of anakinra to inhibit the binding of IL-1 and its receptor [25–28]. However, an improved understanding of Kawasaki disease causation suggests several new treatment approaches.

Several new treatment approaches are strongly suggested by the involvement of the complement cytokines C3a and C5a [7]. These cytokines will attract neutrophils and proinflammatory M1 macrophages that will secrete proinflammatory chemokines, cytokines, prostaglandins, and proteinases and other enzymes [7]. Therefore, quickly deactivating C3a and C5a can reduce the attraction of neutrophils and macrophages that release the proteinases and other enzymes that express or expose autoantigens that induce the autoantibodies. Fortunately, there are several anti-cancer drugs already available to deactivate C3a and C5a [29, 30]. There is a FDA-approved monoclonal antibody complement inhibitor for C5 called ecoluzimab, and another C5 complement inhibitor called pexelizumab [29]. There are C3 complement inhibitors, including AMY-103, which blocks C3a and C5a, and compstatin [29, 30]. There are also C3a receptor antagonists including SB290157, and C5a receptor antagonists including PMX-53 [29, 31]. C5a inhibitors, including the C5 and leukotriene B4 inhibitor nomacopan, ecolouzimab, and an anti C5a monoclonal antibody inhibitor IFX-1, can also reduce inflammation, coagulation and lymphocyte exhaustion caused by high viral loads, so there are potentially significant benefits from their use for treating Kawasaki disease [29–33].

In addition, several new treatment approaches are strongly suggested by the involvement of proteinases and other enzymes that express or expose autoantigens that induce autoantibodies [7]. If the specific proteinases involved can be identified, their proteinase inhibitors are very likely already known and these proteinase inhibitors can reduce the expression or exposure of new autoantigens [34]. Aprotinin is an FDA-approved monomeric polypeptide that acts as a nonspecific serine proteinase inhibitor, and this also reduces the blood levels of the metalloproteinases [34]. At least 37 serine proteinase inhibitors, also known as serpins, have been identified; C1 esterase inhibitor (C1INH) inhibits complement C1s and C1r and many enzymes including plasma kallikrein; α1-antitrypsin (α1AT) inhibits neutrophil elastase; and antichymotrypsin (ACT) inhibits inflammation and extracellular matrix remodeling [35].

Selected proteinase inhibitors can be injected to inhibit protease attacks, preferably without causing significant disruption to normal mammalian proteases. Appropriate inhibitors for a proteinase can be determined from the MEROPS database of proteinases, their substrates and their inhibitors [36]. As of late 2017, there were 5267 proteinase identifiers and 868 inhibitor identifiers cataloged in the MEROPS 12.0 database, including each proteinase's substrate [36].

Conclusion

Especially virulent viral pathogens that infect extensive amounts of tissue, such as lung tissue, can ultimately induce the adaptive immune system to produce large amounts of antigen-antibody immune complexes, especially in a first-time infection. Some immuno-compromised patients will be unable to quickly phagocytize these antigen-antibody immune complexes and this event will possibly induce a type III hypersensitivity immune reaction, leading to either Kawasaki disease or its variations, or in the case of COVID-19, lead to Kawasaki disease or related diseases including Multisystem Inflammatory Syndrome. A type III hypersensitivity reaction induces macrophages and neutrophils to release proteinases (e.g., matrix metalloproteinases, cysteine proteinases, and serine proteinases) and other enzymes that will create systemic inflammation and express or expose autoantigens that lead to autoantibodies. However, an improved understanding of Kawasaki disease, its variations, and related diseases including Multisystem Inflammatory Syndrome also suggests several potential new treatments for these diseases which could be more effective.

Acknowledgements There are no acknowledgements.

Author Contribution The author is the sole contributor, and no other person made any contributions.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Ethics Approval The author confirms that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Conflict of Interest The author declares no competing interests.

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