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Special Article

Kawasaki Disease: An Update

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Overview

Kawasaki disease (KD) is the most common cause of vasculitis affecting children. Although the inflammatory response is found in medium and small vessels throughout the body, the most common site of end organ damage is to coronary arteries, making KD the leading cause of acquired heart disease in the developed world.[1] KD affects children of all nationalities and its incidence appears to be increasing world wide. KD is a syndrome complex still in search of an aetiology. As such, KD is defined by diagnostic criteria which include: prolonged fever, polymorphous skin rash, conjunctival injection, oral mucosal changes (redness and swelling of the lips, oral pharynx or tongue), extremity changes (redness and swelling of the hands or feet) and cervical lympadonopathy. These clinical finding demonstrate the classic signs of inflammation: redness, heat, and swelling and are due to inflammation of the small and medium size blood vessels in the body. Even though the clinical findings due to this multisystem inflammation is well described, the events leading to immune activation and the path from generalised inflammation to localised coronary artery damage is not known. Even with early and appropriate institution of high dose intravenous immunoglobulin (IVIG) together with aspirin during the acute phase of KD, 5% of affected children continue to develop coronary artery aneurysms.[2] When adjusted for body surface area, this number increases to 20-30% of children.[3] Many important questions remain unanswered in Kawasaki disease including the nature of the aetiologic agent, the pathogenesis, and optimal therapeutic interventions. In this paper I will review the recent advances in our understanding in these areas and discuss their potential clinical implications.

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Aetiology

Kawasaki disease has been linked to many different aetiologic agents ranging from bacteria such as Proprionibacterium, Staphylococcus, Streptococcus and Chlamydia to viruses such as Epstein Barr virus, Parvovirus and Retroviruses,[4-15] but no one positive agent has been consistently demonstrated. The epidemiology of KD suggests an infectious origin. It is an endemic disease with epidemics every two to three years, it has a seasonal predominance in late winter and early spring, and there is geographic clustering of outbreaks with cases within clusters sharing similar clinical features. With each new geographic outbreak another infectious agent or family or infectious agents is reported to be associated with Kawasaki disease. Most recently intense interest and debate has centered on a novel human coronavirus found by one group of investigators in the respiratory secretions of some children with KD. Esper et al[16] report a new coronavirus named New Haven Coronavirus (HCoV-NH). Reverse transcriptase polymerase chain reaction (RT-PCR) was used to detect HCoV-NH in 8 of 11 (72.7%) of children with KD but only one of 22 (4.5%) of control specimens. Other investigators have not been able to confirm this data (reported at the 8th International Kawasaki Disease Symposium, San Diego, February 2005). The inconsistencies in reproducing the findings of a single aetiologic agent echo the outbreak dependent nature of this syndrome. The longer the search for a single infectious agent responsible for KD, the longer the list of diverse infectious agents found. A more likely explanation is a shared property common to multiple infectious agents

resulting in the same pathogenic process leading to the clinical syndrome we know as KD. One such common feature of many infectious agents is the presence of superantigenic activity.

Superantigens

Superantigens (SAG) encompasses a family of proteins that are able to cause a dramatic immune response that is T-cell dependent. Of the wide variety of micro-organism share the ability to produce a superantigen and many of these microbes have been implicated in the pathogenesis of KD. The term "superantigen" was first introduced in 1989 to describe a group of antigens that differed in many ways from a typical protein or peptide antigen.[17] SAGs are a group of intermediate sized proteins able to associate with major histocompatibility complex class 2 molecules (MHC II),[18,19] and share the ability to stimulate large proportion of T cells by binding to the variable (V) region of the TCR beta chain. A large number of micro organisms isolated from outbreaks of KD are represented on the list of SAG producing micro-organisms. These include Staphylococci, Streptococci, Mycobacterium, Mycoplasma, Yersinia, Lactobacillus,[20-22] retroviruses,[23,24] Epstein Barr virus,[25,26] rabdoviruses,[27,28] and candida albicans.[29]

T-cell recognition of superantigens differ from that of conventional antigens. The molecular interaction between the T-cell receptor and that of the superantigen does not occur with lock and key specificity but occurs outside the binding pocket for a conventional peptide for both the TCR and the MHC molecules involved. In fact the interaction is with a non-variable portion of the V region of the TCR beta chain (TCR Vβ). Additionally, SAGs do not require antigen processing, are not loaded onto the peptide binding cleft of the MHC, and are not classically self MHC restricted.[21,30,31] Since humans and other mammals only have 20 to 50 TCR Vβ families and superantigens typically bind to several TCR Vβ families, SAGs can stimulate up to 30% of the entire T cell repertoire causing a massive immune response. Therefore, the footprint of a SAG immune response is disproportionate representation of SAG reactive TCR Vβ families otherwise know as TCR Vβ skewing.

Superantigens and Kawasaki Disease

Evidence of a SAG-mediated pathogenic process in KD include identification of microbes producing SAGs from affected children, isolation of SAG protein from affected children or finding the hallmarks of SAG activation in the immune system of affected children. Investigators have isolated SAG producing bacteria from children with acute KD, with a focus on TSST-1 producing staphylococcus aureus and pyrogenic exotoxin producing streptococcus (SPE).[32-35] Given the rapid kinetics of a SAG-mediated process, tiny amounts of bacterial SAG needed to start the immune response, and that neither the presence of SAG nor the organism that produced the protein is needed to perpetuate the immune response, isolation of the offending SAG or SAG-producing organism can be difficult. Thus, many investigators have concentrated their efforts in finding evidence of SAGs from their tell-tale trail of immune activation. The hallmark of the SAG mediated T-cell response is TCR Vβ skewing with expansion followed by deletion of reactive TCR Vβ families. Skewing of TCR Vβ2+ T cells is the finding most commonly seen in children with KD reflecting the TCR Vβ footprint of TSST-1 and streptococcal pyrogenic exotoxin-B and C (SPE-B and SPE-C).[36-39] Additional evidence and support of a SAG-mediated process is evidenced by the polyclonal nature of the reactive T cells,[40,41] an infiltration of the cardiac tissue by the same polyclonal SAG reactive TCR Vβ families.[42] Additionally, SAG reactive T cells proliferate then progress to a period anergy post exposure to a SAG. Decreased T cell proliferative response in cytokine production in TCR Vβ reactive families are features of anergic lymphocytes that have been found in children after acute KD.[43] Other investigators have found increased titres of specific anti-superantigen antibodies including those directed against TSST-1,[44] SPE-A,[35] SPE-C[34] in children with KD.

Conventional Antigens and Kawasaki Disease

Other investigators have focussed their energy on identifying one specific pathogen or family of pathogens responsible for disease. One group have identified oligoclonal IgA antibodies present in cardiac tissue from 3 fatal cases of KD.[45] Prevalent IgA genes from affected coronary tissue were cloned and synthetic human antibodies produced. These synthetic antibodies were used as detecting antibodies in immunohistochemical assays on tissue from other fatal cases of KD. Positive staining was found in respiratory epithelium of 10 out of 13 KD cases and none of 9 control cases as well as a subgroup of macrophages in various inflamed tissue from 17 children with KD.[46] The authors conclude that a conventional antigen driven

response leads to KD and the respiratory tract is the site of entry for this pathogen.[47] Although the debate continues regarding the mechanism of immune activation, most investigators agree on the intense nature of the immune response. KD fits in a spectrum bridging infection and autoimmunity. The utility of the immune system primarily rests on its ability to distinguish between self and non-self. Inability to respond to infectious non-self may lead to overwhelming infection and the consequence of recognising self is autoimmune disease. KD fits nicely in this spectrum, with infectious non-self initiating the immune response which persists and evolves into immune damage toward self. The persistence of the inflammatory response may hold the answer for a final common pathway in understanding the pathogenesis of KD. A unifying model[48] proposes that a microbe with superantigenic activity initiates the massive activation of the developing immune system. A subpopulation of the SAG-responsive T-cells is rescued from programmed cell death because of interaction with an antigen presenting cell presenting a conventional peptide antigen providing costimulation. This peptide antigen may be derived from self or an infectious mimic of self. The immune response is perpetuated locally where the self-antigen is found, in this case the coronary vessel wall. A SAG-initiated immune response last 10 to 14 days. Untreated, the acute phase of KD lasts approximately 10 to 14 days. T-cells rescued by peptide antigens mediate a persistent low grade inflammatory response. Children with KD continue to have evidence of systemic inflammation for up to 6 weeks into the course of KD, and evidence of ongoing microvascular inflammation in affected cardiac tissue is present for up to 23 years.[49] Self-antigens in the coronary artery direct the localised inflammatory response resulting in damage and aneurysm formation. This hypothesis accounts for all findings cited by proponents of both the superantigen and conventional antigen aetiology camps.

The Immune Response in Kawasaki Disease

The immune response in KD is wide ranging involving both innate and adaptive immunity. Evidence of activation for different components of adaptive immunity are present during the acute phase of KD with studies demonstrating activation of T cells and B cells. There is significantly increased pro-inflammatory cytokine production. The elevated serum levels of TNFα and IL-1 are characteristic of the acute phase of KD, and can mediate the clinical and laboratory features seen in this phase of the illness.[50-53] The most commonly studied pro-inflammatory cytokine is TNFα. Many groups have found elevated levels of TNFα in children with acute KD irrespective of coronary outcome. Several groups have studied promoter polymorphisms controlling TNFα production as a possible genetic link involved in susceptibility to KD[54] or as a risk factor in development of coronary artery lesions.[55] Unfortunately no associations have been found. The important pathogenic role of TNFα is exemplified by the use of anti-TNF monoclonal antibodies such as Infliximab as salvage therapy in children with refractory KD.[56] The use of TNF blockade must be considered cautiously, given the infectious triggers implicated in disease onset. We have found that 33% of all children at KD diagnosis have a proven infection. These children are indistinguishable from those without proven infections and share similar clinical and laboratory features as well as response to treatment and coronary outcome thus liberal use of TNF blockade must be cautioned.[57] The dramatic immune response seen in KD has lead to investigation of mechanisms involved in regulation of this response. Interestingly regulator T-cells appear to be decreased in children with KD.[58] Affected children have decreased levels of CD4+, CD25+ T_{reg} and Fox-P3, a transcription factor associated with this subgroup of regulatory T cells, in the peripheral circulation compared to controls. This suggests that there is a decreased regulatory or suppressive activity which may contribute to the exaggerated immune response seen in the acute phase of KD. Investigators have also found specific polymorphisms in their promoter of the CD14 toll-like receptor gene associated with poor coronary outcome in KD.[59] Other groups investigating the innate immune response have also found mannose binding lectin, which is associated with neutrophils, may also be involved in the immune response in KD. Mutations in mannose binding lectin are increased in children with KD compared to health controls and may be associated with poor coronary outcome.[60] There is also an interesting link between mannose binding lectin genotype and vascular stiffness following KD.[61] S100A12 (EN-RAGE) is a neutrophil derived factor, which has garnered much interest in many autoimmune diseases recently. This marker of innate immunity is also increased during the acute phase of KD and decreases after IVIG therapy.[62,63] Movement of the systemic immune response to the vascular tissue is also of interest and the role of leukocyte migration signals in this have been studied. Increased levels of chemokines and chemokine receptors,[64] as well as localised increased expression of adhesion molecules[65] in the coronary artery lesions during evolution of KD have also been found.

Clinical Implications

Increased physician awareness of KD has lead to early diagnosis and treatment of children presenting with the classic signs and symptoms of the disease. Questions regarding clinical management now address timing of the therapeutic intervention and management of children with atypical/incomplete KD. The question of early treatment with IVIG in children presenting with all the classic criteria of KD, but less than 5 days of fever remain in debate. All studies done to date have found that therapeutic intervention before day 5 or after day 5 if fever do not affect coronary outcome.[66,67] A recent large Japanese study[68] with 4,731 children treatment between days 1 to 4 of fever, compared to 4,020 treated between days 5 and 9 of fever, found a slightly increased rate of IVIG re-treatment in those treated early, but most importantly, this study as in previous studies, found no difference in coronary outcome between the two groups. As such the current American Heart Association (AHA) recommendation suggests in the presence of 4 of 5 classic criteria for KD the diagnosis can be made and the treatment initiated on day 4 fever with the first day of fever counting as day 1.[69]

Children presenting with fever of 5 or more days in less than 4 of the classic symptoms are termed to have incomplete or atypical Kawasaki disease. Incomplete is a more appropriate term as these children do not present with atypical features, rather they simply do not present with the full clinical picture typical of the disease. Management of these children continue to be an area of clinical concern. Increased recognition of children with incomplete KD and the implications for coronary outcome have lead to new guidelines for the management of these children. The AHA have proposed algorithms to guide clinical management of children suspected of having KD.[69] The management algorithms proposed by the AHA committee of experts represents informed opinion rather than evidence. In the absence of a gold standard for diagnosis of KD there is difficulty in devising evidence based guidelines. These guidelines stress a high index of suspicion for KD in any child presenting with prolonged fever and incomplete clinical features of KD and introduce a set of supportive laboratory findings for KD. These include elevated inflammatory markers (ESR and CRP) together with other supportive laboratory features such as hypoalbuminenia, anemia, increased platelet count, increased white blood cell count, elevated transaminases, and sterile pyuria. The AHA recommends performing an echocardiogram as well as continued clinical observation, re-evaluation and treatment as warranted.[69]

Therapy

High dose IVIG administered during the acute phase of KD is recognised as the most efficacious therapy.[70,71] Recently a meta-analysis confirmed that high dose IVIG, (2 g/kg) administered before day 10 was the optimal therapeutic regiment.[72] Despite appropriate treatment with IVIG approximately 5% of children with KD continue to develop coronary artery aneurysms and 1% develop giant aneurysms.[2] The number with coronary artery abnormalities increases to 20-30% of children with KD when adjusted for body surface area.[3]

High dose aspirin was the sole therapy for KD in the early years prior to IVIG. During the acute phase high dose aspirin continues to be administered together with IVIG in both North American and Asia. The dose of aspirin varies from country to country but high dose aspirin together with IVIG appear to have an additive anti inflammatory effect. Traditionally, aspirin is used at high doses for its anti inflammatory effects and at low doses for anti-platelet effects. North American institutions tend to use 80 to 100 mg/kg/d as their dose range for high dose aspirin in the acute phase and Japanese institutions use 20 mg/kg/d as their high dose regiment. In North America high dose aspirin is continued until the child is afebrile for 48 to 72 hours and then reduced to anti-platelet dose (3 to 5 mg/kg/d) at that time. In Japan 20 mg/kg/d is continued for 6 weeks and then stopped. There are no prospective randomised control trials looking at the effectiveness of the different dosing regiments for aspirin, and recently investigators have questioned the effectiveness of high dose aspirin during the acute phase of KD.[73] On a mechanistic level, high dose and not lost dose aspirin inhibits NFκB nuclear translocation.[74] NFκB is a critical transcription factor in signalling the downstream effects of TNFα and many other pro-inflammatory cytokines. Additionally, aspirin also inhibits AP-1, another transcription factor involved in inflammatory cytokines signalling. High dose aspirin also inhibits dendritic cell maturation and decreases expression of the co-stimulatory molecules[75] which are important aspects in augmenting the immune response. Aspirin also has a role inhibiting matrix metalloproteinase activity.[76]

The role of corticosteroids in the treatment of acute KD has garnered great debate. Although corticosteroids are the mainstay of therapy in systemic vasculitides, their use in KD is very limited. A cautious approach has been taken by physicians treating children with KD due to an early study suggesting potential deleterious effects of corticosteroids when used in the acute phase of KD.[77] Recently, investigators

have begun to study this immunosuppressive agent in more detail. One group found that inclusion of corticosteroids in the initial treatment of KD was associated with a significantly shorter fever duration and lower rate of coronary artery lesions.[78] These findings are supported by recent studies showing that steroids rapidly decrease systemic inflammatory markers and pro-inflammatory cytokines[79] with no adverse effect on coronary outcome.[80,81] A randomised, double-blinded, placebo controlled trial of corticosteroids together with IVIG during the acute phase of KD has just concluded in North America. The results of this study should lay to rest the debate regarding the clinical utility of steroids during the acute phase of KD.

As we review the literature we must note many of the limitations of the reported studies in KD. Small study numbers have limited power and may not have the ability to detect clinically important differences. Additionally, KD is a endemic disease with interspersed epidemics. The clinical phenotype may be outbreak dependent and contribute to the different results from different investigators at different times from different centers. Biologic specimens, especially affected coronary tissue, are not readily available and much data have been generated from a very limited number of autopsy specimens from these very extreme clinical presentations. Improving our knowledge and management of children with KD will only go forward from evidence gathered by collaborative studies with large enough study numbers to enable us to detect clinically important differences. A multi-centre, interdisciplinary approach will help us understand the disease from its various aspects and hopefully lead to a clearer understanding of the aetiology and pathogenesis of this disease, and improve the outcome in affected children.

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