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REVIEW

The role of infection in Kawasaki syndrome

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Summary *Objectives:* To analyse the evidence suggesting a possible infectious origin of Kawasaki syndrome (KS).
Methods: PubMed was searched for all of the studies published over the last 15 years using the key words "Kawasaki syndrome" or "mucocutaneous lymph node syndrome" and "infectious disease" or "genetics" or "vasculitis" or "pathogenesis".
Results: Various levels of evidence support the hypothesis that KS is a complex disease triggered by an infection due to one or more pathogens. Viruses or bacteria may be the *primum movens*, although no specific infectious agent can be considered definitely etiological. A number of genetic polymorphisms have been identified in subjects with KS, but none of them can currently be considered a real marker of susceptibility.
Conclusions: Various data suggest that KS is intimately related to infectious diseases and that its clinical expression is influenced by predisposing genetic backgrounds, but our knowledge of the infectious agent(s) involved and the genetic characteristics of susceptible children remains only partial. Further studies are needed to address the many still open questions concerning the disease.

Introduction

Kawasaki syndrome (KS), originally called "mucocutaneous lymph node syndrome" in 1967,[1] is an acute multisystem vasculitis that causes generalised inflammatory cell tissue injury starting in the vascular endothelium and is mainly encountered in children aged less than five years regardless of their ethnicity.[1] The injuries are particularly severe in the coronary arteries, which are frequently affected by dilatations, aneurysms or fistulae, especially in patients who do not receive prompt treatment with intravenous immunoglobulins and anti-inflammatory doses of acetylsalicylic acid.[2] Now that rheumatic fever is largely controlled, KS has become the leading cause of acquired heart disease among children in industrialised countries.[3]

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As no specific diagnostic test is available, KS is identified on the basis of a constellation of non-specific clinical signs. According to the American Heart Association guidelines,[4] which are shared by most scientific communities throughout the world, a diagnosis requires prolonged fever lasting more than five days and at least four of the following signs: 1) diffuse oral cavity inflammation (including pharyngeal infection), dry fissured lips, and a strawberry tongue); 2) bilateral non-purulent conjunctivitis; 3) heterogeneous skin rashes; 4) angioedema of the extremities (including peripheral erythema, oedema, or induration of the hands or feet); and 5) non-purulent cervical lymphadenopathy exceeding $\geq$1.5 cm in diameter. In what are known as "incomplete" cases, one or more of these clinical signs may be absent but a diagnosis can still be made if there is echocardiographic evidence of coronary artery abnormalities. Furthermore, a broad range of unusual clinical finding have been reported as defining the "atypical" variant of KS, including aseptic meningitis, peripheral facial nerve palsy, uveitis, gastrointestinal complaints, acalculous gallbladder hydrops, urethritis, testicular swelling, pulmonary nodules, liver impairment with jaundice, and even hemophagocytic syndrome.[5] Laboratory investigations (listed in Table 1) can only support the diagnosis of KS, but they still need to be validated before they can be used in everyday clinical practice.

However, although the clinical features of KS are usually recognisable, its underlying immune mechanisms are still being investigated. Most experts consider it to be the consequence of an abnormal immunological response evoked by one or more widely distributed infectious agents in genetically susceptible individuals, but it still remains a medical enigma.

The main aim of this review is to analyse the available evidence suggesting that KS may have an infectious origin. PubMed was used to search for all of the studies published over the last 15 years using the key words: "Kawasaki syndrome" or "mucocutaneous lymph node syndrome" and "infectious disease" or "genetics" or "vasculitis" or "pathogenesis". More than 1300 articles were found, but only those published in English or providing evidence-based data were included in the evaluation.

What is known about Kawasaki syndrome and infections

Various levels of evidence support the hypothesis that KS is a complex disease initiated by an infection due to one or more pathogens (Table 2). However, no strict and unmistakable correlation between specific infectious agents and the development of the disease has ever been identified.

Table 1 Laboratory findings supporting a diagnosis of Kawasaki syndrome.

1. C-reactive protein $\geq$3.0 mg/dL
2. Erythrocyte sedimentation rate $\geq$40 mm/h
3. Albumin $\leq$3.0 g/dL
4. Age-relative anaemia
5. High alanine aminotransferase levels
6. Platelet count $\geq$450,000/mm^3 in the subacute phase of the disease
7. White blood cell count $\geq$15,000/mm^3
8. White blood cells/high-power field $\geq$10 in urinalysis

Microbiological data

A number of bacterial and viral infectious agents have been sporadically isolated from KS patients. The most frequently implicated bacteria are *Staphylococcus aureus*,[6] *Streptococcus pyogenes*,[7] and atypical pathogens,[8–10] and the viruses associated with KS over recent years are Epstein–Barr virus,[11] adenovirus,[12] parvovirus B19,[13] herpesvirus 6,[14] parainfluenza type 3,[15] measles,[16] rotavirus,[17] dengue virus,[18] and human immunodeficiency virus.[13] Varicella,[19] 2009 H1N1 pandemic influenza[20] and Coxsackie B3 virus[21] have also been described in patients with KS, but they were equally found in the blood or body fluids of both patients and healthy subjects. Moreover, no relationship was reported between KS and the circulation of the commonest respiratory viruses.[22]

The most recent and numerous studies of KS-related viruses have postulated the etiological role of human coronavirus (HCoV) NL63 and bocavirus,[23–25] but this has not been confirmed by subsequent studies.

In order to evaluate the importance of HCoV-NL63 in KS, Shimizu et al. established a multi-institutional collaborative research project to test respiratory samples using real-time polymerase chain reaction (RT-PCR), and found that only one out of 48 KS patients (2%) was positive[26]; Dominguez et al. found exactly the same prevalence in nasopharyngeal wash samples from KS patients and healthy controls over a period of seven months[27]; and Lehmann et al. measured the concentrations of IgG, IgM and IgA antibodies against HCoV NL63 and OC43 in the blood of children showing the signs and symptoms of KS for 3–10 days and healthy controls, but did not find any difference between the two groups.[28] The data regarding bocavirus (a virus that has recently emerged as a possible cause of respiratory infection) are also unconvincing[29]: although it was identified in the serum, stool and cerebrospinal fluid of some children with KS, no definitive conclusion could be drawn concerning its etiological role.

The limited etiological importance of the pathogens so far identified seems to be supported by the studies of Benseler et al.[30] and Jordan-Villegas et al.,[31] who found that that concomitant infections in children with KS did not alter the response to treatment with intravenous immunoglobulins, and did not influence the risk of coronary artery involvement or affect overall cardiovascular outcomes. However, the lack of any clear relationship between one or more pathogens and the development of KS does not exclude the possibility that a real infectious disease may be involved, and other factors support this hypothesis. On the other hand, the unsuccessful identification of a specific pathogen to which KS could be ascribed has led some authors to postulate that variants of normal flora in the gut, oral cavity or skin of young children with a genetic defect of proper immune maturation do not induce immune tolerance as self commensals, but rather induce an imbalance of the immune system, leading to a hyperimmune reaction and the manifesting KS.[32]