Abstract

Kawasaki disease has been researched for 32 years but its aetiology is still unknown. Conventional therapy for the disease includes corticosteroids and aspirin (acetylsalicylic acid) as anti-inflammatory and/or antithrombotic agents but they have not been proven to prevent coronary artery aneurysms. Although a high incidence of liver dysfunction in Japanese patients with Kawasaki disease receiving high dose aspirin (≥80 mg/kg/day) suggests racial differences in salicylate sensitivity, the duration of fever in patients receiving high dose aspirin is shorter than that in patients receiving moderate dosages (30 to 50 mg/kg/day). Furthermore, most corticosteroid-resistant patients were found to develop coronary artery aneurysms, many of which were large. With the clarification of the pathogenesis and clinical features of Kawasaki disease, advances in its treatment have been achieved. The introduction of high-dose intravenous γ-globulin (IVGG) was an epoch in this field and IVGG is now a standard therapy with the incidence of persistent coronary aneurysms 1.9% in children with the disease receiving IVGG. Today, research is mainly directed toward the treatment of IVGG-resistant patients. One to 3 days of pulsed doses of methylprednisolone (30 mg/kg/day) or readministration of IVGG 1 g/kg (once to several times) has been recommended for patients with IVGG-resistant Kawasaki disease.
Kawasaki disease, generalised vasculitis and organopathies of unknown aetiology, was first described by Dr Tomisaku Kawasaki in 1967 in Japan as the acute febrile mucocutaneous lymph node syndrome\(^1\) with fever, rash, non-exudative conjunctivitis, inflammation of the oral mucosa, erythema and swelling of the hands and feet, and cervical adenitis. It was subsequently found to be the leading cause of acquired heart disease in children in both Japan and the US. It occurs more often in boys than in girls, with a ratio of about 1.5 : 1, and mostly in children younger than 5 years of age with a recurrence rate less than 2%. More than 140 000 cases were reported in Japan from 1967 through December 1996. Kawasaki disease has now been reported worldwide.

The occurrence of Kawasaki disease epidemics and the wave-like spread of such epidemics suggests that the disease is caused by a microbial agent. Onouchi et al.\(^2\) reported that there is a close correlation between the speed of the epidemic spread of Kawasaki disease among cities in metropolitan areas and the number of daily passengers on intercity mass transportation. However, secondary cases occurring in contacts of affected patients are extremely rare.

Although an aetiological agent has not been identified, recent attention has focused on a family of enterotoxins produced by a variety of different strains of bacteria. These bind to specific variable beta regions of the T-cell receptor in conjunction with major histocompatibility complex class 2 antigens and act as superantigens to induce T-cell proliferation and cytokine release.\(^3\) Immunological findings in Kawasaki disease are similar to those induced by the enterotoxin family.

There is no specific diagnostic test for Kawasaki disease, but clinical diagnostic guidelines proposed by the Kawasaki Disease Research Committee, supported by the Ministry of Health and Welfare of Japan, assist in the diagnosis of typical Kawasaki disease (table I).\(^4\)

The clinical features of Kawasaki disease are those of acute self-limiting febrile illness. However, the major pathological features are carditis and a vasculitis affecting small and medium sized blood vessels throughout the body. The coronary circulation is particularly affected, with coronary artery aneurysm (the major life-threatening complication) developing in 15 to 25% of children with the disease. The main causes of death in the acute phase of Kawasaki disease are congestive heart failure due to carditis, and rupture or thrombotic occlusion of coronary artery aneurysm.\(^5-7\) Therefore, treatment is initially aimed at reducing inflammation (particularly in the coronary arterial wall and myocardium) as well as preventing coronary thrombosis by inhibiting platelet aggregation.

Conventional therapy for Kawasaki disease includes corticosteroids\(^8\) and aspirin\(^9\) as anti-inflammatory and/or antithrombotic agents, but they have not been proved to prevent coronary artery aneurysms. High dose intravenous \(\gamma\)-globulin (IVGG), reported in 1984,\(^10\) has been a standard therapeutic regimen.

1. **Aspirin**

In the pre-\(\gamma\)-globulin era, aspirin and corticosteroids were used for the treatment of Kawasaki disease because of their anti-inflammatory effects. Although the therapeutic effects of aspirin in Kawasaki disease are controversial, it remains the drug of choice to be used either as monotherapy or in combination with IVGG therapy.

Both high dose (80 mg/kg or more daily) and moderate dose (30 to 50 mg/kg daily) regimens of aspirin have been used in the acute phase of Kawasaki disease. These regimens, either on their own or in conjunction with IVGG, are associated with a 15 to 25% incidence of coronary artery aneurysm or ectasia\(^11,12\) which is similar to the incidence reported during the natural course of the disease.\(^13,14\) This finding is consistent with prospective studies performed in the \(\gamma\)-globulin era, which showed that aspirin alone was ineffective in reducing the prevalence of coronary artery disease. Aspirin has never been documented in a prospective study to reduce the prevalence of coronary artery abnormalities.