Kawasaki Disease

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KEYWORDS

- Kawasaki disease • Coronary artery • Aneurysm
- Intravenous immunoglobulin • Vasculitis
- Mucocutaneous lymph node syndrome

HISTORICAL PERSPECTIVES

Kawasaki disease (KD) is a systemic vasculitis of unknown cause and the leading cause of acquired heart disease in North American and Japanese children.[1,2] This disease was first reported in 1967 by Dr Tomisaku Kawasaki.[3] His original case series of pediatric acute mucocutaneous lymph node syndrome described 50 Japanese patients with the clinical signs and symptoms that we now refer to as KD.[3] In 1965, Dr Noboru Tanaka was the first pathologist to recognize the potentially serious and fatal complications of this disease when he discovered coronary artery thrombosis in a child who died unexpectedly.[4] Dr Takajiro Yamamoto was the first physician to note cardiac complications in nonfatal cases.[4,5] He described electrocardiogram abnormalities in these patients and published this finding in a report in 1968.[4,5]

In 1970, the first Japanese nationwide epidemiologic survey of KD was undertaken.[6] This study clearly established the link between KD and coronary vasculitis.[4,6] Although KD was first described in Japan, similar cases were being seen around the world in the 1960s and 1970s.[4] The first North American description was published in 1976 from Hawaii.[7]

EPIDEMIOLOGY

There have been 20 nationwide epidemiologic surveys of KD in Japan. The average annual incidence in 2005 and 2006 was 184.6 per 100 000 children less than 5 years of age.[8] In 2008, in the latest survey, the incidence increased to 218.6 per 100 000 children less than 5 years of age.[9] The latest incidence is even higher than the rates seen in the epidemic years of 1979, 1982, and 1986.[9] As in previous surveys, the incidence was highest in children aged 6 to 11 months.[9] Patients with affected siblings were seen in 1.4%; and 0.7% of patients had at least 1 parent with a previous history of KD.[9] Recurrence of the disease was seen in 3.5% of patients.[9]

KD has been described in more than 60 countries.[10] The annual incidence of KD is highest in Asian countries.[11] After Japan, Korea (105/100 000)[12] and Taiwan

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Pediatr Clin N Am 59 (2012) 425–445
doi:10.1016/j.pcl.2012.03.009 **pediatric.theclinics.com**
0031-3955/12/$ – see front matter

(68/100 000)[13] have the next highest incidences. It is presumed that the incidence is high in other Asian countries but cases may not be as well documented as in Japan.[11]

In the United States, the incidence in the year 2006 was estimated to be 20.8/100,000 in children less than 5 years of age.[14] Race-specific incidence rates showed that the disease was most common among Americans of Asian and Pacific Island descent.[14] In Ontario, the most populous province in Canada, the incidence increased over time from 14.4/100 000 in children less than 5 years of age in 1995 to 1997 to 26.2/100 000 in 2004 to 2006.[11] This is most likely because of better disease recognition over the years, particularly for incomplete cases.[11] In this study, a seasonal pattern was observed, with an increase in cases in the late fall and winter, similar to Japan.[11] The male/female ratio was 1.62:1.[11] Children less than 5 years of age made up 73% of cases seen.[11] Although race was not evaluated, Ontario has a large Asian population and it was suggested that the incidence of KD in Ontario, and possibly of Canada, may be one of the highest outside Asia.[11] Other reported incidences include Ireland (15.2/100 000),[15] England (8.1/100 000),[16] New Zealand (8.0/100 000),[17] and Australia (3.7/100 000).[18]

CAUSE

The cause of KD remains unknown. It is suspected that there is activation of the immune system by an infectious trigger in a genetically susceptible host.[19] An infectious cause is suspected for several reasons. First, the clinical characteristics of KD resemble an infection and the illness is self-limited.[20] Second, the epidemiologic features, such as age of affected children, seasonality of cases, and occurrence of community outbreaks and epidemics, are all consistent with an infectious trigger.[20] However, no known infectious agent has been consistently found. Genetics may explain why certain ethnicities are at increased risk.[20] This risk persists despite a move from 1 country to another.[21] As well, the risk of disease in a child born to a parent with a history of KD, or in siblings of affected children, is higher than in the general population.[22]

There is still significant controversy about the mechanism of immune system activation in patients with KD. Some investigators believe that a bacterial superantigen leads to massive stimulation of T lymphocytes.[23] Others suggest that an oligoclonal IgA immune response is occurring rather than a polyclonal one.[24] This theory is supported by the discovery of IgA plasma cells infiltrating the coronary artery aneurysms in patients who died in the acute phase of KD,[24,25] as well as the detection of virallike cytoplasmic inclusion bodies in ciliated bronchial epithelial cells of patients with KD.[24,26]

Recent data have suggested that T-cell activation is important in determining the susceptibility and severity of KD.[19] A genetic association study identified a polymorphism in the inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene on chromosome 19q13.2, which acts as a negative regulator of T-cell activation and may contribute to immune hyperreactivity in KD.[27] This polymorphism was significantly associated with KD susceptibility, and with an increased risk of coronary artery abnormalities (CAA), in both Japanese and American children.[27] An animal mouse model of KD has also identified regulation of T-cell activation as a critical determinant of coronary disease.[19]

Multiple studies are under way to identify genetic markers that influence disease susceptibility, disease severity, and treatment resistance in KD. Genetic studies to date have made significant contributions to this field,[27–31] and it is hoped that with further studies, the cause of KD will also be elucidated.