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Can Kawasaki Disease Be Managed?

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COMMENTARY

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Abstract

Kawasaki Disease (KD) is the leading cause of acquired cardiovascular disease among children, but management of KD has received relatively little attention. In the US alone, about 5500 cases were estimated in 2009. KD is most common among Asian and Pacific Islander children but can affect all ethnicities and races. Timely and accurate diagnosis remains critical, but difficult: the etiology of KD is unknown, and no accurate diagnostic laboratory test has been developed. Continuing medical education can help physicians, clinicians, and nurse practitioners accurately diagnose and treat KD. A registry specific to KD or a surveillance system may be necessary to increase awareness among health care professionals and to decrease complications related to misdiagnosis.

What is Kawasaki Disease?

Kawasaki Disease (KD) is an acute febrile illness that can potentially affect the heart and its larger arteries. It often affects children younger than five years.[1] KD is also called mucocutaneous lymph node syndrome, because it involves lymph nodes, skin, and mucous membranes inside the mouth, nose, and throat.[1,2] According to the American Heart Association[3] and the Centers for Disease Control and Prevention,[1] KD diagnostic criteria include high fever lasting four or five days, along with four or more of the following seven symptoms: 1) rash, 2) red eyes, 3) red, swollen, and cracked lips, 4) "strawberry" tongue, 5) swollen hands and feet, 6) swollen lymph nodes, and 7) redness of the palms and soles of the feet.

Statistics and Recent Trends

In the US alone, about 5500 cases of KD were estimated in 2009.[1] In Japan, a 2008 nationwide study conducted by Nakamura et al[4] found that 19,138 patients were suffering from KD during the 2-year period 2003–2004, revealing the continuation of an upward trend that started in Japan in the mid-1990s. A survey in 2009 suggested that the incidence is also rising in India.[5] This may be explained by greater awareness or by rapid industrialization.[6]

The latest incidence statistics available for the US are from a 2010 retrospective national study by Holman et al[7]: the rate of hospitalization related to KD in 2006 was 20.8 per 100,000 children younger than age 5 years. It is more frequent in children older than 1 year and toddlers ages 1 to 4 years. KD affects all ethnicities and races, but it is most common among children of Asian and Pacific Islander descent, with 30.3 cases per 100,000 hospitalizations. The incidence for non-Hispanic Blacks, non-Hispanic Whites, and Hispanics is 17.5, 12, and 15.7 cases per 100,000 hospitalizations, respectively.[7]

KD is the leading cause of acquired cardiovascular disease in children in the US.[8] The etiology of KD remains unknown after 40 years of intense research,[9] and no laboratory test can accurately diagnose KD and atypical cases that are approximate KD but do not meet all diagnostic criteria for KD.[1] Delayed diagnosis and treatment remain prevalent and unavoidable.[10] Diagnosis is further complicated in that KD shares symptoms and signs with other illnesses.[2] Therefore, the real number of undertreated and misdiagnosed cases is unknown.[11]

Diagnosis and Etiology

Virtually all deaths in patients who have experienced KD result from cardiac sequelae, or secondary cardiac conditions such as arrhythmia, chest pain, myocardial infarction (MI), and sudden death.[12,13] Mortality peaks 15 to 45 days after the initial onset of fever. However, sudden death from MI may occur many years later in individuals who had coronary artery aneurysms (CAA) and stenoses as children. The potential for death years later because of KD complications suggests that it is important to follow KD patients throughout childhood. Many cases of fatal and nonfatal MIs in young adults have been attributed to "missed" KD in childhood.[12]

A recent study by Coustasse and associates[10] revealed that fewer than half of the patients in their Texas sample (n = 303) were correctly diagnosed with KD upon hospital admission. The majority of KD cases were misdiagnosed. In their cross-sectional analysis, there were 41 admitting diagnoses other than KD. Although misdiagnosis appears to be common, the overwhelming majority (> 96%) of children with KD are hospitalized.[14,15] The remaining 4% are treated on an outpatient basis.

Untreated, KD can lead to serious complications that involve the heart and cardiovascular system.[2] Because CAA occurs more frequently in untreated patients,[16] effective interventions are required to enhance clinicians' ability to accurately identify KD in children younger than age 5 years presenting with high fever and rash.[17] Treatment within 10 days after onset of fever is essential to decrease the risk of heart problems. With appropriate detection and treatment, the prevalence of CAA is reduced to as few as 1% and no more than 5% of cases.[18]

The Lloyd et al study[19] investigated clinical and epidemiologic features of KD and emphasized the likelihood of an infectious cause. Consequently, several microbial agents have been studied in connection with KD: *Rickettsiae, Propioni-*

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bacterium acnes, Klebsiella pneumoniae, Ehrlichia, parainfluenza virus types 2 and 3, Epstein-Barr virus, and rotavirus, among others.[20,21] Additional possible causes for the disease are prior respiratory disease; exposure to carpet cleaning chemicals; use of humidifiers; and living in close proximity to lakes, rivers, bays, or oceans.[8,22] Although multiple infectious agents and toxins have been implicated, none have been conclusively identified as a causative or contributing agent.[15]

Treatment

First-line treatment consists of intravenous immunoglobulin for 8 hours to 12 hours within 10 days of the first onset of fever. High doses of aspirin must be administered until the fever subsides. Aspirin should be continued and gradually tapered for at least 2 months to reduce the risk of spontaneous coronary thrombosis.[2,18] A substantial number of patients have an incomplete response to intravenous immunoglobulin and require additional treatment. Unresponsive patients are at high risk of coronary abnormalities and adverse events resulting from multiple therapies.[23] In 13% to 30% of KD patients, fever persists or recurs. Fever may recur several days after hospital discharge. Doctors must bear the responsibility of warning parents to return to the hospital if fever or other signs of KD recur; inadequate discharge instructions put patients at risk for developing coronary artery abnormalities.[24] Untreated recurrences can lead to aneurism of the coronary arteries, myocarditis,[25] toxic shock,[26] and sudden death.[27] Sudden death from MI can occur many years later in individuals who developed CAA and stenoses in childhood.[28]

Ongoing Surveillance

Developing and maintaining a KD-specific national registry or a KD surveillance system may help reduce the nationwide incidence of KD. National and state incidence is difficult to estimate, because reporting of KD cases to the Centers for Disease Control and Prevention remains sporadic,[9] and all tracking and reporting is left to state agencies to enforce.[29] As with any large passive surveillance system, only a fraction of cases is reported.[22] Researchers are forced to rely on hospital discharge data.[15] The central public health policy problems related to KD are the need to educate clinicians, and the need for a government policy ensuring the timely acquisition of accurate data for all suspected KD cases for purposes of early diagnosis, patient tracking, and determining the cause of the disease.[10]

Continuing Medical Education

Although KD is now the leading cause of acquired heart disease among children in developed countries,[30] its etiology remains unknown. To diagnose KD early and accurately, clinicians must be educated to recognize the signs and symptoms of KD and make differential diagnoses. This training should begin in medical schools and continue through continuing medical education courses. Pediatricians, emergency medicine physicians, and primary care physicians must stay abreast of the latest developments in pediatric medicine and infectious diseases. Continuing medical education has become increasingly important to the management of KD because of the serious and sometimes fatal consequences of delayed treatment caused by erroneous diagnoses. If professional associations and state licensure boards were to require KD-specific education, perhaps the national rate of misdiagnosis could be significantly reduced.

Conclusion

Because KD is the leading cause of acquired heart disease among children in the US, and considering the sudden deaths that result from coronary aneurysm and thrombosis, effective management of KD would substantially benefit public health.[8] It is imperative to educate physicians and other clinicians, including nurses, to recognize the signs and symptoms of KD, because delayed or erroneous diagnoses delay treatment and sometimes lead to death. This also hinders cost containment efforts at the national level. Active surveillance could potentially yield long-term benefits for clinicians, patients, and society as a whole by facilitating the identification, prevention, and treatment of KD. The financial costs and benefits of accurate diagnosis and treatment may be further quantifiable when more accurate data are available. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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The Principle of Life

Since all living things are warm, all dying things cold,
there must be a … seat and fountain,
a kind of home and hearth, where the cherisher of nature,
the original of the native fire, is stored and preserved;
from which heat and life are dispensed to all parts as from a fountain head;
from which sustenance may be derived; and upon which concoction and nutrition,
and all vegetative energy may depend. Now that the heart is this place,
that the heart is the principle of life … I trust no one will deny.

— *On Circulation of the Blood,* William Harvey, 1578 – 1657, English physician and first person to describe completely and in detail the systemic circulation and properties of blood being pumped through the body by the heart