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Commentary

The Adult After Kawasaki Disease

The Risks for Late Coronary Events

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Under what circumstances should a transient childhood illness be considered a lifelong potential cardiac risk factor? Do all patients who have had Kawasaki disease (KD) require special follow-up, intermittent cardiac testing, and preventive measures beyond the American Heart Association (AHA) recommendations for all Americans? If not, which patients are at significant risk for late coronary events to justify being placed in a high-risk category? These are the questions that must be answered to recommend a careful follow-up régime for those who are at risk and to reassure the others. The impact of carrying a lifetime diagnosis of high potential coronary involvement cannot be underestimated.

It has been 42 years since Tomisaku Kawasaki described the disease that carries his name (1). Although most of the reported cases and follow-up studies of children who have had KD (1) have been described in Japan, the disease is now recognized to be commonplace throughout the world. It is estimated that there are 10,000 new cases per year in Japan alone (2) and 4,000 in the U.S. (3). Considering the rest of the world, it is not unreasonable to estimate that there may be as many as 1,000,000 patients worldwide, (diagnosed and undiagnosed) who have had the disease since it was first described in 1967. In addition, it is reasonable to assume that many undiagnosed patients were affected before that time.

Among the vast cohort of KD survivors, it is important to determine which patients have residual coronary abnormalities that are known to be associated with late cardiovascular events. To make this determination, the level of initial coronary involvement must be considered, that is, in descending order of significance, patients who had giant aneurysms (>8 mm), large aneurysms (6 to 8 mm), smaller aneurysms (persistent or regressed), transient coronary dilation, and, finally, those who had no discernable coronary involvement at the time of diagnosis.

Persistent giant aneurysms are associated with a high risk for late complications, including thrombosis, stenosis, and calcification, potentially leading to myocardial infarction and significant late mortality. Although at apparent less risk, patients with *large aneurysms* initially, also have been reported to have angiographic coronary findings later in life. There is no controversy that these patients will require follow-up, testing, and management. Fortunately, individuals with residual giant or large aneurysms represent <1% of patients who have had KD (4,5). In a recent multicenter study by the Pediatric Heart Network in the U.S. (5), among 195 carefully observed patients with acute KD, 4 (2%) patients had echocardiography evidence of aneurysms, only one of whom had an aneurysm with a maximal diameter exceeding 6 mm. None had giant aneurisms (>8 mm).

Patients with well-defined but *small aneurysms* during KD represent the vast majority of those who had coronary aneurysms during the acute illness but are still a small minority of the total KD population. In recent years, since early intravenous immunoglobulin (IVIG) therapy has been standard, there have been fewer such patients (5,6) Approximately one-half of small aneurysms will regress with time. To determine the risk level for late coronary events for these patients, an attempt must be made to extract these cases from large follow-up KD studies documenting late deaths or complications that are almost always associated with giant aneurysms. Unfortunately, in many of these reports, the early status of the coronary arteries may not be emphasized or even specified. Thus, when a study indicates that the risk level for late mortality or morbidity is significant for patients who had aneurysms during the acute phase of KD, it is often not known whether this would be true if the obvious high-risk patients with giant/large aneurysms were not included.

Nakamura et al. (7) reported up to 17 years' follow-up of 6,576 patients who had KD from 52 collaborating hospitals in Japan. Beyond the acute phase, the rate of mortality was not increased compared with the expected number of deaths calculated from Japanese vital statistical data. There were 18 fatal cases. Of these, 2 died with "coronary insufficiency," one at 11 months of age and the other at 6 years. In 2 cases, KD was suspected, but not proven to be a factor. The remaining deaths were not related to KD. The authors of this study did not include morbidity, and there are no data regarding the status of the coronary arteries in this population during their acute illnesses.

From 1977 to 2005, Tsuda et al. (8) described 19 deaths among 580 patients followed after KD, 12 having died

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suddenly (defined as within 24 h of a precipitating event). The ages ranged from 16 months to 27 years with a median of 16 years. Two of the 19 died of noncardiac causes. The others had severe multivessel coronary disease previously demonstrated on angiography; 6 had a history of myocardial infarction. Three young adults who were known to have severe coronary disease since infancy were the only deaths since 1999. The patients described in this study had KD before the IVIG era and clearly represent the most severe cases. There were no deaths in patients who did not have known severe coronary disease. Late mortality or morbidity from coronary disease in patients who had small persistent or regressed aneurysms was not reported.

In the present era, 94% to 98% of patients who had KD during the last 25 years did not have aneurysms, including 80% to 85% before the advent of IVIG treatment (4,6). A review of the large follow-up studies of KD indicates that patients who had *transient coronary dilation or normal coronaries* during the acute illness have not been shown to have late coronary artery complications (6,9). Dilation usually regresses during the first weeks after the acute illness, and the authors of follow-up studies have indicated that the coronaries remain normal by echocardiographic and angiographic criteria. Japanese investigators (6,9) have agreed to classify these patients as having normal coronary arteries. There are no follow-up studies that describe late cardiac events associated with the original KD.

Pathophysiology of the Coronary Arteries After KD

In this issue of the *Journal,* Gordon et al. (10) review the literature concerning the histopathology of the coronary arteries after KD. The hallmark of the coronary findings is that of intimal thickening, which may progress to localized stenosis in coronary segments adjoining giant aneurysms. Thrombi within the aneurysms also may partially or totally occlude the coronary vessel. In some cases, the obstructed aneurysm may recanalize, leaving various degrees of obstruction. Severely injured coronary arteries may calcify, further increasing the risk of chronic coronary disease. Thus, patients with giant coronary aneurysms secondary to KD are major candidates for coronary events beyond childhood.

Intimal thickening also has been described in coronary arteries with regressed aneurysms and in a few patients with what were considered to be normal coronary arteries based on echocardiography. The authors of some studies have described abnormal responses to vasodilatory agents in coronary segments where aneurysms had regressed, but other investigators have failed to confirm this finding. It is important to note that there have been no studies that indicate that these observations could be correlated with or predictive of clinical events in former KD patients at any age. Although concerns have been raised, there also is no direct evidence that premature artherosclerosis is especially prone to become superimposed on the typical Kawasaki micopathology of the coronary arteries.

Management of the Adult With KD

In their comprehensive review of the myocardial and cardiovascular findings associated with KD, the authors conclude that "on the basis of the accumulating evidence, it is likely that patients with known aneurysms during the acute phase of KD will have some cardiovascular morbidity as young adults." This statement is true for patients with giant aneurysms, possibly true for some patients with large aneurysms, but is not evidence based for those with small aneurysms, given the absence of late data showing that they are in increased danger of clinical events in adult life. A rare suspicious anecdote is not sufficient. The authors also state that "there is clearly a growing population of young adults with potentially important coronary artery disease after KD during childhood, and cardiologists specializing in adult patients must be prepared to care for them." The small group of patients who have residual giant aneurysms, virtually all of whom having been recognized during childhood, will require care as adults, but there is evidence to indicate that their numbers are decreasing rather than increasing. The patients who had small coronary aneurysms or no aneurysms, who have not been shown to be in jeopardy for late complications, represent 99% of the KD population.

The identification of KD survivors with large or giant aneurysms must be vigorously pursued, with appropriate follow-up visits and diagnostic studies as recommended by the AHA guidelines (risk level IV and V) (11). Medical or surgical management may be required. The group of patients who had small aneurysms that may or may not have resolved represent 80% of the patients who had developed aneurysms after KD in the modern era, but only 4% of all patients who had the disease. It is recommended by the AHA guidelines that these patients (risk level III) should be treated with low-dose aspirin until aneurysms are documented to have regressed. It is also recommended that they have annual cardiology follow-up with noninvasive testing (with echocardiograms and electrocardiograms, as well as biannual stress test/evaluation of myocardial perfusion scan). It could be argued that this degree of follow-up and testing may be somewhat stringent when applied to all patients in this category.

Patients with no coronary changes at any stage, and those with transient coronary ectasia that disappears within the first 6 to 8 weeks represent 95% of all individuals who had KD during childhood. The guidelines (risk levels I and II) for these patients advocate cardiovascular risk assessment counseling at 5-year intervals. These patients have not been

shown to be at increased risk for cardiovascular events in adulthood, and cardiologists must be aware that even such a minimal follow-up recommendation may have a significant effect on men and women who have been looking at themselves as having had a benign childhood disease with no significant concerns for late heart disease beyond what all Americans face.

Psychiatrists tell us that being identified as a potential "chronic or high-risk heart patient" can affect patients' sense of their own vitality or longevity. Chronic background anxiety will often lead to inappropriate and unnecessary changes in self-image and life style. Fear and emotion are likely to transcend the understanding of probabilities. The published guidelines should never stand alone. They should be reviewed individually and interpreted on a one-to-one basis so that each post-KD individual will have a clear perspective as to what is actually known about late risk in his/her particular circumstance. The guidelines are simply "guidelines," and as new information becomes available, they will undoubtedly be subject to future revisions. It is possible that the nature of this enigmatic disease may change over time, but at the present state of our knowledge, it is important to avoid creating "patients" among individuals who have not been shown to be at increased late risk for a cardiac event.

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REFERENCES

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974;54:271–6.
2. Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, Yanagawa H. Increasing incidence of Kawasaki disease in Japan: nationwide survey. Pediatr Int 2008;50:287–90.
3. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB, Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 2003;112:495–501.
4. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. J Epidemiol 2008;18:167–72.
5. Newburger J, Sleeper L, McCrindle B, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki Disease. N Eng J Med 2007;356:663–75.
6. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. Circulation 1996;94:1379–85.
7. Nakamura Y, Yanagawa H, Harada K, Kato H, Kawasaki T. Mortality among persons with a history of Kawasaki disease in Japan. Arch Pediatr Adolesc Med 2002;156:162–5.
8. Tsuda E, Arakaki Y, Shimizu T, et al. Changes in causes of sudden deaths by decade in patients with coronary arterial lesions due to Kawasaki disease. Cardiol Young 2005;15:481–8.
9. Senzaki H. Long-term outcome of Kawasaki disease. Circulation 2008;118:2763–72.
10. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: myocardial and vascular complications in adulthood. J Am Coll Cardiol 2009;54:1911–20.
11. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747–71.

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