J Microbiol Immunol Infect
2002;35:57-60

Clinical features of atypical Kawasaki disease

Yu-Chia Hsieh, Mei-Hwan Wu, Jou-Kou Wang, Ping-Ing Lee, Chin-Yun Lee, Li-Min Huang

Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan, ROC

Received: December 13, 2000 Revised: July 17, 2001 Accepted: August 8, 2001

From 1989 through 1998, a total of 132 children admitted to the National Taiwan University Hospital were identified as having Kawasaki disease. Twenty (15%) of them did not meet the diagnostic criteria of Kawasaki disease, but were considered atypical Kawasaki based on the specific clinical signs and exclusion of other causes by serologic study and culture result. The patients' age ranged from 5 months to 11 years, with a mean of 22.2 months and a median of 15 months. The male to female ratio was 1.9:1. Twenty-five percent (5/20) of them had coronary arterial lesion. No difference was found in the age distribution, sex, and rate of coronary artery involvement between typical and atypical Kawasaki disease. All patients were treated with intravenous immunoglobulin and aspirin except for 2 patients. At follow-up, patients with coronary arterial lesions had a prognosis as good as those with typical Kawasaki disease. According to these observations, atypical Kawasaki disease may be part of Kawasaki disease occurring via the same pathogenesis, but has incomplete manifestation. Clinical practitioners should have a high index of suspicion to diagnose and initiate prompt treatment to reduce the comorbidity of coronary arterial disease in patients with atypical Kawasaki disease.

Key words: Atypical Kawasaki disease, coronary arterial lesion, intravenous immunoglobulin

The 6 classic features of Kawasaki disease, well known since Dr. Tomisaku Kawasaki [1] first described the disease in 1967, are prolonged fever, conjunctivitis, lymphadenopathy, polymorphous exanthem, mucosal change, and extremity change. This systemic vasculitis syndrome can involve coronary arteries in as many as 25% to 30% of patients [2]. However, the etiology remains elusive and a definitive laboratory diagnostic test is pending.

From past clinical observations and epidemiologic studies, Kawasaki disease is presumed to result from immunoregulatory abnormalities caused by infectious agents in certain immunologically susceptible individuals. Because Kawasaki disease has clinical manifestations similar to some bacterial superantigen-mediated diseases such as toxic shock syndrome and scarlet fever, its pathogenesis is presumed to embrace superantigen-activated T-cell proliferation with resulting large amounts of cytokine production [3-6]. The direct interaction between superantigen and Vβ region in the T-cell receptor may have an important role in the etiology of Kawasaki disease, but this needs to be further defined.

Corresponding author: Dr. Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, 100, Taiwan, ROC. E-mail: lmhuang@ha.mc.ntu.edu.tw

The diagnosis of Kawasaki disease is purely clinical, based on the 6 diagnostic criteria. Occasionally, some patients presenting with 3 or 4 manifestations of Kawasaki disease are seen, and are considered as cases of atypical Kawasaki disease [7,8]. Placement of a clinical diagnosis for these patients is sometimes difficult. Reports have suggested that atypical Kawasaki disease tends to attack infants and is more likely to affect the coronary artery [9-11]. It is thus important to clarify the clinical patterns of atypical Kawasaki disease. This study describes the clinical picture of atypical Kawasaki disease, and compares the age at onset, sex, season of onset, clinical features, and complications of the 2 diseases.

Materials and Methods

A total of 132 cases of Kawasaki disease admitted to the National Taiwan University Hospital between January 1989 and December 1998 were analyzed retrospectively. The diagnosis of Kawasaki disease was made when 5 or more of the following 6 criteria are present: (1) fever persisting for 5 days or more; (2) changes in the peripheral extremities, including reddening of the palms and soles, and indurative edema or membranous desquamation of the fingertips; (3) polymorphous exanthema; (4) bilateral conjunctival injection; (5) changes in the lips and oral cavity, including reddening of lips, strawberry tongue, and

diffuse injection of the oral mucosa; and (6) cervical lymphadenopathy. The diagnosis of atypical Kawasaki disease was defined as the presence of 4 criteria, or the presence of coronary arterial lesions plus 2 to 3 criteria. Two-dimensional echocardiography was used to define coronary arterial lesion. A coronary artery with an internal diameter of more than 2 mm in patients aged less than 2 years, or more than 2.5 mm in patients older than 2 years, was classified as coronary dilatation. If the internal lumen of a segment was more than 8 mm, it was classified as giant aneurysm; those between 2 or 2.5 mm and 8 mm were classified as small to large aneurysms. Intravenous immunoglobulin (IVIG) and aspirin were initiated once the diagnosis was made, except for 4 patients with typical and 2 with atypical Kawasaki disease, in whom no coronary arterial lesions were found; these patients were given only aspirin. Some differential diagnoses including Epstein-Barr virus infection, mycoplasma infection, scarlet fever, and toxic shock syndrome were ruled out by serologic data, viral and bacterial cultures, and clinical course.

The frequency at which each criterion occurred in both the typical and atypical Kawasaki disease groups was calculated and compared.

All patients were followed up at clinics after discharge. Patients with coronary arterial lesions received a 2-dimensional echocardiograph every 2 months. Age, sex, age at onset, and clinical symptoms and signs were recorded.

Statistical analysis

Chi-square tests were used to measure the association between typical and atypical Kawasaki diseases and their clinical criteria, and a p value less than 0.01 was considered significant. Regression rates of coronary arteritis were calculated using the Kaplan-Meier method.

Results

Among the 132 patients with Kawasaki disease, 20 (15%) belonged to the category of atypical Kawasaki disease according to their incomplete presentations. Of them, 13 were boys and 7 were girls. The male to female ratio of 1.9:1 was similar to the 1.6:1 ratio found in the typical Kawasaki disease group (69 boys and 43 girls). The atypical Kawasaki disease group had a mean age of 22.2 months, a median age of 15 months, and a range from 5 months to 11 years. As to the age distribution, 45% of patients with atypical and 40.4% with typical Kawasaki disease were infants (p=0.97) (Table 1). The frequency of infants contracting atypical Kawasaki disease was not significantly higher compared with that of typical Kawasaki disease. No significant difference was noted in other age subgroups.

The frequency at which each criterion of Kawasaki disease occurred in atypical cases were as follows: fever persisted for more than 5 days was noted in 19 (95%) of 20 patients, changes of extremities in 17 (85%), changes of oral mucosa in 15 (75%), conjunctivitis in 15 (75%), and skin rash in 9 (45%); significant lymphadenopathy did not occur. The proportion of conjunctivitis, skin rash, and lymphadenopathy were significantly lower in patients with atypical Kawasaki disease (Table 2). Table 3 listed each principle criterion that these 20 atypical patients have matched.

Coronary arterial involvement was observed in 5 (25%) of 20 patients with atypical and in 40 (35.7%) of 112 patients with typical Kawasaki disease (p=0.352) (Table 2). These coronary arterial lesions were either coronary artery dilatations or small-to-large aneurysms, and no giant aneurysm was detected in either group. The rates of coronary vasculitis in atypical and typical Kawasaki disease groups did not differ significantly. These patients were followed up using 2-dimensional echocardiography at regular intervals of 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after the onset of fever. Children who had either atypical or typical Kawasaki disease with coronary vasculitis had similar regression rates on follow-up visits.

Within the 10-year period studied, 3 patients experienced recurrent Kawasaki disease. All of them were typical cases associated with coronary arteritis. One patient had the first episode at the age of 5 months

Table 1. Age distribution of typical and atypical Kawasaki disease

Age, years	No. of cases	
	Typical disease	Atypical disease
<1	45	9
1-≤2	34	7
2-≤3	15	2
3-≤4	9	1
4-≤5	1	0
>5	8	1
Total	112	20

Table 2. Frequency of coronary artery involvement and of each principal diagnostic criterion met by typical and atypical Kawasaki disease patients

Symptom/sign	Typical disease n = 112 (%)	Atypical disease n = 20 (%)	*p*
Coronary arteritis	40 (35.7)	5 (25)	0.352
Fever ≥5 days	107 (95.5)	19 (95)	0.916
Rash	105 (93.75)	9 (45)	<0.001
Conjunctivitis	109 (97.3)	15 (75)	<0.001
Mucosal change	100 (89.3)	15 (75)	0.079
Extremity change	106 (94.6)	17 (85)	0.115
Lymphadenopathy	41 (36.6)	0	0.001

and a second attack 2 months later. Another patient developed the disease at 11 months old, and experienced a second attack 5 months later. The third patient was first attacked at the age of 2 years 9 months, and at 13 months later. The frequency of recurrent Kawasaki disease was 2.3% (3/132). Four patients had persistent fever or progressive coronary arteritis despite the administration of IVIG, and their illness was defined as prolonged Kawasaki disease. All of them had typical Kawasaki disease with coronary arterial change, and the disease responded to the second regimen of IVIG. The frequency of prolonged Kawasaki disease was 3.8% (5/132).

Discussion

The pathognomic coronary vasculitis associated with Kawasaki disease may lead to a major cardiac catastrophe and even sudden death in affected children. Fortunately, IVIG has been proven to be effective in decreasing the occurence of coronary artery aneurysm [12]. Since 1981, cases with incomplete criteria of Kawasaki disease but unique features such as unexplained fever, coronary change, or peripheral desquamation have been gradually revealed [8,9,13-15]. Strict adherence to the diagnostic criteria for Kawasaki disease may result in missed atypical cases and deprive patients of immunoglobulin treatment. This may be clinically significant, as some researchers believe that these atypical cases are more likely to be infants and to develop coronary arteritis [9-11]. However, studies with large numbers of patients with atypical Kawasaki disease are lacking. This study included 20 patients with atypical Kawasaki disease during a 10-year period in one teaching hospital in Taiwan and gathered data on the demographics, frequency, clinical manifestations, and complications of this disease.

In this series of patients, the prevalence rate of atypical Kawasaki disease in the whole population of Kawasaki disease was 15%. This rate was close to the estimated 10% and 18.5% in 2 studies [8,16]. A remarkable finding in this study was that atypical cases were not restricted to infants as previously suggested [9-11]. In addition, patients with atypical and typical Kawasaki disease had similar rates of coronary artery involvement (25% vs 35.7%, p=0.352). The etiologies of atypical and typical Kawasaki disease may differ, or they may have the same etiology but with different degrees of clinical penetration. Results in this study indicated that patients of these 2 types of disease cannot be differentiated by their age, sex, or clinical outcome. This finding is more supportive of the speculation that typical and atypical Kawasaki disease have the same etiology but different penetration. However, it should be noted that the diagnosis of atypical Kawasaki disease has not been standardized. Previous investigators made the diagnosis basing mainly on the presence of coronary

Table 3. Atypical Kawasaki disease patients exhibiting different criteria combinations (n = 20)

Symptom/sign	No. of cases							
	8	3	3	1	2	1	1	1
Coronary artery lesion	-	-	-	-	+	+	+	+
Fever ≥5 days	+	+	+	-	+	+	+	+
Skin rash	-	+	+	+	-	-	-	+
Lymphadenopathy	-	-	-	-	-	-	-	-
Oral mucosa lesion	+	+	-	+	+	+	-	-
Extremity involvement	+	+	+	+	-	-	+	+
Conjunctivitis	+	-	+	+	+	-	+	-

Note: + = present; - = absent

artery involvement; in this study, diagnosis was based on the number of criteria met. The National Taiwan University Hospital is also more experienced with diagnosing and treating Kawasaki disease, and has been on the alert for its possible occurrence. Early recognition and treatment may also have some impact on results of this study. Not all investigators agree that atypical Kawasaki disease has poorer outcome; one report from Japan concluded that coronary involvement in incomplete Kawasaki disease was less frequent, and that severe or even fatal results in these patients were overemphasized [16].

Some important figures were revealed in this study. Recurrent Kawasaki disease was noted in 2.3% of the patients, close to the 3% rate reported in Japan during 1991 to 1992 [17]. According to one case-control study, the risk of recurrence of Kawasaki disease was positively correlated with IVIG use. The presence of coronary artery lesions *per se* did not affect recurrence [17]. In Taiwan, IVIG is often administered when the diagnosis is established, but no increase in recurrence rate was observed.

The frequency of each diagnostic criterion being met was compared between the 2 groups of patients. Unexplained fever, mucosal change, and extremity change including initial indurative edema followed by erythema or desquamation were highly associated with both typical and atypical Kawasaki disease. On the other hand, rash, conjunctivitis, and lymphadenopathy were seen less often in patients with atypical presentation. Some literature [9,10] proposed that the only pathognomic laboratory test for all Kawasaki disease is thrombocytosis, but almost 10 days after the onset of illness is needed before thrombocytosis is detectable, and treatment may be delayed during this period. Results suggest that when children develop prolonged fever combined with mucosal change, extremity change, or both, either typical or atypical Kawasaki diseases should be suspected. Standard treatment including IVIG should be given as early as possible to achieve good outcome.

References

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi-Japanese J Allerg 1967; 16:178-222.
2. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Ezo G, Yamakawa R. Long-term consequences of Kawasaki disease: a 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.
3. Abe J, Kotzin BL, Jujo K, Melish ME, Glode MP, Kohsaka T, Leung DY. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. Proc Natl Acad Sci USA 1992;89:4066-70.
4. Abe J, Kotzin BL, Meissner C, Melish ME, Takahashi M, Fulton D, Romagne F, Malissen B, Leung DY. Characterization of T cell repertoire changes in acute Kawasaki disease. J Exp Med 1993;177:791-6.
5. Pietra BA, de Inocencio J, Giannini EH, Hirsch R. T cell receptor V beta family repertoire and T cell activation markers in Kawasaki disease. J Immunol 1994;153:1881-8.
6. Barron KS, Shulman ST, Rowley A, Taubert K, Myones BL, Meissner HC, Peters J, Duffy CE, Silverman E. Report of the National Institute of Health on Kawasaki disease. J Rheum 1999;26:170-90.
7. Japan Kawasaki Disease Research Committee. Diagnostic Guidelines of Kawasaki Disease. 4th Revision. Tokyo: Kawasaki Disease Research Committee;1984.
8. Burns JC, Wiggins JW, Toews WH, Newburger JW, Leung DY, Wilson H, Glode MP. Clinical spectrum of Kawasaki disease in infants younger than 6 months of age. J Pediatr 1986;109: 759-63.
9. Rowley AH, Gonzalez-Crussi F, Gidding SS, Duffy CE, Shulman ST. Incomplete Kawasaki disease with coronary artery involvement. J Pediatr 1987;110:409-13.
10. Levy M, Koren G. Atypical Kawasaki disease: analysis of clinical presentation and diagnostic clues. Pediatr Infect Dis J 1990;9:122-6.
11. Huang YC, Huang FY, Lee HC. Atypical Kawasaki disease: report of two cases. Acta Paediatr Sin 1992;33:206-11.
12. Bolz D, Arbenz U, Fanconi S, Bauersfeld U. Myocarditis and coronary dilatation in the 1st week of life: neonatal incomplete Kawasaki disease? Eur J Pediatr 1998;157:589-91.
13. Wu MH, Lue HC, Cheng SJ, Sung TC. Echocardiographic visualization of coronary arterial lesions in Kawasaki disease. Acta Pediatr Sin 1986;27:1-9.
14. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, Glode MP, Mason WH, Reddy V, Sanders SP. The treatment of Kawasaki syndrome with intravenous gammaglobulin. N Engl J Med 1986;315:341-7.
15. Fukushige J, Nihill MR, McNamara DG. Spectrum of cardiovascular lesions in mucocutaneous lymph node syndrome: analysis of eight cases. Am J Cardiol 1980;45:98-107.
16. Canter CE, Bower RJ, Strauss AW. Atypical Kawasaki disease with aortic aneurysm. Pediatrics 1981;68:885-8.
17. McCowen C, Henderson DC. Sudden death in incomplete Kawasaki disease. Arch Dis Child 1988;63:1254-6.
18. Fukushige J, Takahashi N, Ueda T, Ueda K. Incidence and clinical features of incomplete Kawasaki disease. Acta Paediatr 1994;83:1057-60.
19. Nakamura Y, Yanagawa H. A case-control study of recurrent Kawasaki disease using the database of the nationwide surveys in Japan. Eur J Pediatr 1996;155:303-7.