ARTICLE

Clinical Features of Patients With Kawasaki Disease Whose Parents Had the Same Disease

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Objective: To observe the clinical characteristics of patients with Kawasaki disease whose parent also had the same disorder.

Design: Cross-sectional study using the data from nationwide surveys of Kawasaki disease in Japan.

Setting: All hospitals with a bed capacity of 100 or more and pediatric departments in Japan.

Patients: All patients described on the 16th and 17th surveys covering the 4-year period from January 1, 1999, through December 31, 2002.

Main Outcome Measures: We compared clinical details, including sibling case, recurrence, diagnosis, administration of intravenous immunoglobulin, and coronary abnormalities, between patients whose parents had Kawasaki disease and patients with no parental history of Kawasaki disease. We also observed age at onset and sex of affected parent-offspring pairs with Kawasaki disease confirmed by using the data of previous nationwide surveys.

Results: The odds for having sibling cases were significantly increased among patients whose parents also had Kawasaki disease (odds ratio, 6.94; 95% confidence interval, 2.77-17.38). Patients with parental Kawasaki disease were more likely to experience recurrent Kawasaki disease, receive additional administration of intravenous immunoglobulin, and experience coronary abnormalities at 1 month after onset. Among confirmed parent-offspring pairs with Kawasaki disease, the mean age at onset of offspring was younger than that of their parents (25.6 vs 41.8 months), despite the lack of statistical significance.

Conclusions: Some cases of Kawasaki disease show familial susceptibility to the disorder. Family history, especially parental history of Kawasaki disease, may be an indicator of disease severity.

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MORE THAN 35 YEARS have passed since Kawasaki disease was first described.[1] The total number of patients who had Kawasaki disease in childhood and who were older than 20 years in 2001 was estimated to be approximately 50000.[2] These patients have reached reproductive ages; thus, familial cases of 2 generations occur in some hospitals.[3-7] The clinical characteristics of parent-offspring pairs with Kawasaki disease have been provided from these case reports. Since 1970, 17 nationwide epidemiologic surveys of Kawasaki disease have been performed in Japan. After the 16th nationwide survey, which covered the 2-year period from January 1, 1999, through December 31, 2000, we asked whether parents whose children were described as patients with Kawasaki disease had themselves experienced the same disease. Family history of Kawasaki disease may also be considered as a risk factor for disease severity and complications, including coronary abnormalities, because genetic predisposition is suspected as one of the risk factors for many other disorders, including coronary heart disease.[8] In addition, we previously demonstrated that the probability of a history of Kawasaki disease was significantly higher in those parents whose children had Kawasaki disease when compared with parents in the general population.[9] This observation suggests that a genetic susceptibility to Kawasaki disease may be involved in its occurrence. The relationship between the clinical features of Kawasaki disease affecting parents and their offspring provides an opportunity to understand the genetic contribution of this disease. Therefore, we compared the clinical details of patients with Kawasaki disease whose parents also had this disease with those of patients with no parental history of Kawasaki disease.

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Table 1. Clinical Characteristics of Patients With Kawasaki Disease Whose Parents Did and Did Not Have the Same Disease

Characteristic	Patients Whose Parents Had Kawasaki Disease (n = 65)*	Patients Whose Parents Did Not Have Kawasaki Disease (n = 32201)*	Odds Ratio (95% Confidence Interval)
Male sex	39 (60.0)	18565(57.7)	1.10 (0.67-1.81)
Aged <12 mo	21 (32.3)	8434 (26.2)	1.34 (0.80-2.26)
Sibling case	5 (7.7)	382 (1.2)	6.94 (2.77-17.38)
Recurrence	6 (9.2)	1100 (3.4)	2.88 (1.24-6.67)
Complete case	50 (76.9)	26738(83.0)	0.68 (0.38-1.21)
Administration of intravenous immunoglobulin			
Initial	49 (75.4)	27693(86.0)	0.50 (0.28-0.88)
Additional†	14 (28.6)	3432 (12.4)	2.83 (1.52-5.26)
Coronary abnormalities‡	8 (12.3)	1696 (5.3)	2.52 (1.20-5.30)
Dilatation	5 (7.7)	1047 (3.3)	2.48 (0.99-6.19)
Aneurysms	3 (4.6)	515 (1.6)	2.98 (0.93-9.51)

*Data are given as number (percentage) of patients.
†Among the patients who initially received intravenous immunoglobulin.
‡At 1 month after onset.

METHODS

The 16th and 17th nationwide surveys of Kawasaki disease in Japan covered each 2-year period of January 1, 1999, through December 31, 2000, and January 1, 2001, through December 31, 2002, respectively. All hospitals with a bed capacity of 100 or more and pediatric departments were requested to report cases. In the 16th survey, questionnaire forms were sent to 2619 hospitals, of which 1741 (66.5%) responded. In the 17th survey, there were 1642 reports from 2413 hospitals (68.0% response rate). We were able to observe the number of patients whose parents had Kawasaki disease on the 16th survey because that questionnaire included parental history of Kawasaki disease for the first time. Then, we sent an additional questionnaire form to each hospital that had described parents with a history of Kawasaki disease on the 17th nationwide survey to confirm the parental history of Kawasaki disease. The following details about the parents were requested: name (initials), sex, date of birth, date at onset, age at onset, and the name of the hospital where the patient received treatment. These parental data were verified using previous information reported on all the previous nationwide surveys of Kawasaki disease. We identified patient lists from these previous surveys based on the calendar year in which the parent was diagnosed as having Kawasaki disease, and then searched the patient lists of the applicable survey for their initials, sex, and date of birth as reported on the additional questionnaire. When a parent's initials, sex, and date of birth reported on the additional questionnaire matched those reported on previous nationwide surveys, this parent was considered as having had Kawasaki disease.

We observed the characteristics of Kawasaki disease patients with parental Kawasaki disease when notified in the current 2 surveys. We compared features, including sex, age, whether a sibling case, recurrence, complete cases, intravenous immunoglobulin treatment, and coronary abnormalities, at 1 month after onset in patients with a parental history of Kawasaki disease vs those without such a parental history. We defined complete cases as those who featured 5 or all 6 of the principal symptoms.[10] We defined coronary abnormalities as coronary dilatation, aneurysms, giant aneurysms, and stenosis. We listed the clinical pictures of confirmed cases of parent-offspring pairs with Kawasaki disease based on the data of the nationwide surveys. We could only compare sex and age at onset of parents with those of offspring because the clinical details collected on the previous nationwide surveys on which the parents had been described as patients with Kawasaki disease were only items of sex and age at onset.

The odds ratios and their 95% confidence intervals for the clinical items were calculated to compare patients with a parental history of Kawasaki disease with patients who had no parental history of Kawasaki disease. We analyzed age at onset of confirmed parents and their children with Kawasaki disease by using the Wilcoxon signed rank test. This study was approved by the Institutional Review Board of Jichi Medical School.

RESULTS

CLINICAL FEATURES OF PATIENTS WITH PARENTAL KAWASAKI DISEASE

Sixty-five patients were identified, representing 0.2% of all cases. Five cases were sibling cases (**Table 1**). When compared with patients with no parental Kawasaki disease, the odds ratio for having sibling cases was 6.94. The odds ratio for experiencing recurrent Kawasaki disease was also significantly high. Although 75.4% of patients with parental Kawasaki disease had received initial intravenous immunoglobulin treatments, the odds ratio was significantly low. Similarly, the proportion of patients diagnosed as being complete cases among patients with parental Kawasaki disease was smaller than among the patients with no parental history, but the odds ratio was not statistically significant. Of the patients with parental Kawasaki disease, 28.6% of those who had received initial intravenous immunoglobulin treatment were subsequently given a further course of intravenous immunoglobulin and 12.3% had coronary abnormalities at 1 month after onset. The odds ratios for receiving additional intravenous immunoglobulin treatment and experiencing complicating coronary abnormalities were significantly greater in those patients with a parental history of Kawasaki disease than in those without such a history. The odds ratios for patients with dilatation or aneurysms of coronary arteries were also high, but not statistically significant.

Table 2. Characteristics of 10 Confirmed Cases of Parent-Offspring Pairs With Kawasaki Disease*

Case No.	Data for Children: Sex/Age at Onset, mo	Diagnosis	IVIG Therapy	Coronary Abnormalities†	Parental Sex/Age at Onset, mo
1	M/7	Complete	–	–	M/8
2	M/10	Complete	–	–	M/53
3	M/17	Incomplete	–	–	M/55
4	M/23	Complete	+	+	M/87
5	M/27	Complete	+	–	F/31
6	M/32	Complete	+	–	F/5
7	M/65	Complete	–	+	F/49
8	F/12	Complete	+	–	F/47
9	F/23	Complete	+	–	M/44
10	F/40	Complete	+	–	F/39

Abbreviations: IVIG, intravenous immunoglobulin; +, present; –, absent.
*There were no sibling cases.
†At 1 month after onset.

THE RELATIONSHIP BETWEEN PARENTS AND THEIR OFFSPRING WITH KAWASAKI DISEASE

In the 17th nationwide survey, 31 hospitals described a total of 32 patients whose parents had a history of Kawasaki disease. Of these 32 patients, 1 was referred to another hospital from which we could obtain no further information; thus, additional questionnaires were sent to the remaining 30 hospitals. We received additional data from a total of 29 parents who had had Kawasaki disease. From these parents, 9 cases were confirmed by the data of the previous nationwide surveys of Kawasaki disease. These parents were diagnosed as having Kawasaki disease from May 29, 1972, through July 25, 1979, and had been confirmed as patients with Kawasaki disease using the patient lists from the second to the sixth surveys. Although one parent was not described on any previous surveys, he was included as a confirmed case because he remembered that he had seen a physician to follow up his Kawasaki disease until he was aged 13 years. Therefore, 10 parents were confirmed as cases with Kawasaki disease in this study.

The proportion of males among confirmed parents with Kawasaki disease was the same as that of females (**Table 2**), but 7 (70.0%) of the 10 affected offspring were male. The mean ± SD age at onset of Kawasaki disease was 25.6 ± 17.2 months in the offspring vs 41.8 ± 23.7 months in the parents ($P = .10$). Among the 10 affected offspring, 9 (90.0%) were diagnosed as being complete cases, but intravenous immunoglobulin treatment was administered to only 6 (60.0%). Two children of confirmed pairs with Kawasaki disease had coronary abnormalities at 1 month after onset. None of the confirmed pairs with Kawasaki disease had sibling cases.

COMMENT

Siblings of patients with Kawasaki disease have a significantly greater chance of acquiring Kawasaki disease than do children of the same age in the general population.[11] This study showed that the risk of sibling cases was significantly increased for patients with parental Kawasaki disease. In addition, sibling cases have been reported with recurrent Kawasaki disease and coronary abnormalities.[12] The observation that patients with Kawasaki disease whose parents experienced the same disease were also likely to have sibling cases indicates the familial aggregation of the disorder. Patients with parental Kawasaki disease had a greater chance of experiencing recurrent Kawasaki disease, receiving additional intravenous immunoglobulin treatment, and having a coronary abnormality at 1 month after onset compared with those whose parents did not have Kawasaki disease. These results indicate that a family history of Kawasaki disease may be a significant risk factor for increased severity of the disease. Not all familial cases had severe manifestations of the disease, as shown by the low odds ratios for receiving intravenous immunoglobulin treatment and having complete case features. Among hospitals in Japan where patients with Kawasaki disease were treated, approximately 30% had their own regimen of intravenous immunoglobulin therapy, which was administered to patients with Kawasaki disease according to the severity of illness.[13,14] In these hospitals, pediatricians did not administer intravenous immunoglobulin for patients with low scores on severity indexes. This suggests that most patients who did not receive intravenous immunoglobulin therapy may have experienced less severe Kawasaki disease. These clinical characteristics were also demonstrated among confirmed cases of parent-offspring pairs with Kawasaki disease. We have to consider the selection bias introduced by sibling history of Kawasaki disease; also, parents who experienced Kawasaki disease may have been more likely to take their febrile child to the hospital to exclude Kawasaki disease. In this study, the proportion of complete cases among patients with parental Kawasaki disease was smaller than that among patients with no parental Kawasaki disease, although the odds ratio for complete cases was not statistically significant. We verified whether the parents described on the additional questionnaire had Kawasaki disease by using data on previous nationwide surveys. We searched patient lists of previous nationwide surveys for the identical information about parents who had a history of Kawasaki disease, such as name (initials), sex, and date of birth, because it was difficult for us to review the medical records of the parents.[9] However, there were some limitations in this method. Calendar years at onset of the confirmed parents were in the 1970s, and they were described from the second to the sixth nationwide surveys. Kawasaki disease was not recognized well among Japanese pediatricians in the 1970s. One of the reasons for less recognition of Kawasaki disease may have been the relatively low incidence of Kawasaki disease noted at that time.[15] If patients with Kawasaki disease were misdiagnosed as having other diseases, such as scarlet fever or Stevens-Johnson syndrome, they would not have been described on the nationwide surveys as having had Kawasaki disease. In addition, there was a relatively low response rate to surveys of Kawasaki disease that were conducted in Japan in that earlier era.[16] We also empha-

What This Study Adds

We have shown that the probability of a history of Kawasaki disease is significantly higher in parents with children who have Kawasaki disease than in parents within the general population. The clinical characteristics of patients and their parents with Kawasaki disease were important to reveal the genetic background of this disease. Patients with parental Kawasaki disease were more likely to have siblings who had the same disease, to have recurrent disease, and to experience coronary artery abnormalities. A parental history of Kawasaki disease may be an indicator of disease severity.

sized the relationship with age at onset between the confirmed parents and their children with Kawasaki disease. Although statistical significance was not reached, there was a trend for the age at onset of offspring to be younger than that of parents. The statistical power was small in this study because of the small sample size of confirmed pairs. The proportion of patients with Kawasaki disease whose parents experienced the same disease was only 0.2% in our study. Asking about a family history of Kawasaki disease, in particular about parental history, may be useful for considering the potential disease severity of affected patients. In addition, the genetic contribution to Kawasaki disease may be explored in these familial cases.

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