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Kawasaki Disease in Monozygotic Twins

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Abstract

Multiple lines of evidence suggest that susceptibility to Kawasaki disease (KD) is influenced by host genetics. Subclinical coronary artery vasculitis may be present in monozygotic twins who are discordant for clinical signs of KD. Health care providers should consider laboratory testing and echocardiography in both monozygotic twins when only one twin presents with clinical KD.

Keywords

Kawasaki disease; monozygotic twins; subclinical; coronary artery dilatation; aortic root dilatation

INTRODUCTION

Studies of twins have provided valuable insight into the genetic basis of many different conditions. Although a role for genetics in susceptibility to Kawasaki disease (KD) has been widely accepted, data regarding concordance of KD in monozygotic twins has been conflicting (1, 2). The current hypothesis is that an infectious agent triggers immune activation in genetically susceptible hosts who then manifest the clinical syndrome that we recognize as KD. Environmental exposure to the unknown agent of KD is thought to be the inciting event. Because twins during childhood often share the same environmental exposures, one would expect a high rate of concordance for KD in twin pairs. To our knowledge, there is only one published series of monozygotic twins that found a concordance rate of 11/78 (14.1%)(2). We present here a series of monozygotic twins in whom concordance for vasculitis would have been missed without laboratory and echocardiographic examination.

PATIENTS & METHODS

Patients and clinical data

We reviewed the records of the 440 KD patients treated at Rady Children's Hospital San Diego from January 2003-July 2009 who met the American Heart Association case definition. (3) For the retrospective review of monozygotic twin pairs, we ascertained patient sex, age at KD onset, ethnicity, response to IVIG therapy, pre-treatment laboratory data, and echocardiographic data. IVIG non-responders were defined as KD patients treated within the first 10 days after fever onset who had persistent or recrudescent fever

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(T≥38.3°C) 36 hours to 7 days following the end of the IVIG infusion (2g/kg). Echocardiograms measured the internal diameters of the proximal right (RCA) and left anterior descending (LAD) coronary arteries, and the measurements were normalized for body surface area and expressed as standard deviation units from the mean (Z-score) (4). Patients were classified as normal (z-score <2.5), "dilated" (Z-score ≥2.5 and returns to <2.5 within at 2 month period) or "aneurysm" (focal dilatation of coronary artery segment 1.5 times the diameter of the adjacent segment). The variable Zworst was created using the Z-score for the largest dimension for each coronary artery segment on any echocardiogram during the acute and subacute period. Aortic root (AoR) dimensions (annulus and sinus) were also measured and expressed as Z-scores. Patients with a Z-score >2.0 were defined as having AoR dilatation.

For the prospective evaluation of monozygotic twin pairs, we established a protocol to perform echocardiography and to measure a complete blood count, erythrocyte sedimentation rate (ESR), and levels of C-reactive protein (CRP), alanine aminotransferase (ALT) and γ-glutamyl transferase. The UCSD Institutional Review Board approved our research protocol and informed consent was obtained from the parents of all subjects.

Literature review

All English and Japanese texts describing monozygotic KD twins were identified by searching PubMed for the keywords "Kawasaki disease and twins" and by cross-referencing published Japanese texts.

RESULTS

Of the 440 KD patients, 15 (3.4%) were twins: 11 dizygotic twins (2.5%) and 4 monozygotic twins (0.9%). According to the medical record, none of the dizygotic twins were concordant for clinical KD. For two of the monozygotic twin pairs (Twin A diagnosed with KD, Twin B clinically well, Table 1, Pairs 1 and 2), a physical examination and laboratory studies were available for the two B twins in each pair and both were normal. Echocardiograms on the well B twins were not performed during the acute illness of the A twins. Two twin pairs were evaluated prospectively (Table 1, Pairs 3 and 4) with a clinical history, physical examination, laboratory testing and echocardiography performed concomitantly on both twins.

Twin Pair 3

Twin A presented on the 11th day of fever with a diffuse maculopapular rash, erythematous lips and oropharynx, bilateral conjunctival injection, and erythema of the palms and soles. Laboratory studies revealed acute inflammation consistent with KD and an echocardiogram revealed dilated right and left coronary arteries (Table 1). Twin B had a history of fever lasting 48h beginning 2 days after the onset of fever in Twin A. The parents reported transient conjunctival injection lasting 48h and swelling of the hands and feet lasting 72h. At the time of presentation to the hospital, Twin B was clinically well. Because of the history and shared genetic potential for KD, laboratory investigation and an echocardiogram were performed on Twin B (Table 1). Laboratory results revealed anemia for age, thrombocytosis, an elevated ESR, and elevated concentrations of CRP and ALT. Although the coronary artery dimensions were normal, the aortic root was dilated with a Z-score of 3.2. Both Twin A and B were treated with IVIG with resolution of fever and clinical signs (Twin A). Twin A also received infliximab (5 mg/kg) as additional anti-inflammatory therapy because of concerns about coronary artery dilatation and the development of thrombocytopenia with evidence of diffuse intravascular coagulation. He responded well to treatment with resolution of the acute inflammatory state and normalization of the internal diameter of the

coronary arteries. Re-examination by echocardiography one year later revealed normal Z-scores for Twin A (RCA Z 1.0, LAD Z 0.9) and a borderline dilated LAD for Twin B (RCA Z 1.1, LAD Z 2.0, aortic sinus Z 1.4).

Twin Pair 4

Twin A presented on the 6th day of fever with a fine papular rash, erythematous lips and oropharynx, bilateral conjunctival injection, and swollen dorsa of the feet. Laboratory studies revealed acute inflammation consistent with KD and an echocardiogram was normal (Table 1). The patient received standard therapy with IVIG and aspirin but had recrudescent fever 36h following the end of the first IVIG infusion requiring a second dose of IVIG and ultimately oral cyclosporine before the inflammation and fever subsided. Serial echocardiograms revealed normal internal diameters of the coronary arteries and aortic root. Twin B had a negative review of systems, normal physical examination, and normal laboratory values (Table 1). The echocardiogram was delayed due to scheduling problems and was normal when performed 7 mos. after the acute illness in Twin A.

Because of our experience with Pair 3, we recalled the 2 monozygotic twin pairs ascertained by retrospective review for whom Twin B had only been evaluated with laboratory investigations during the acute illness in Twin A (Table 1). Both B twins had a normal echocardiogram when studied 2 to 6 years later.

A search of bibliographic databases in English and Japanese for monozygotic twins with KD revealed three English language and six Japanese language reports (Supplemental Digital Content 1 and 2, tables). Of the nine twin pairs, five pairs were concordant and were diagnosed with KD within 10 days of each other. These five B Twins, three manifested at least 4/5 clincal criteria while the remaining two manisfested only 2/5 or 3/5 clinical criteria, respectively. Of the 4 discordant pairs, the B Twins never had laboratory investigation and only one underwent echocardiography to detect subclinical evidence of KD vasculitis. Thus, the presence of incomplete KD in these B Twins could have evaded detection. Of the 4 twin pairs who were concordant for KD and had echocardiographic results reported, two pairs were discordant for coronary artery abnormalities (SDC 1 [table], Pair 4 and SDC 2 [table], Pair 3).

DISCUSSION

Increasing evidence supports the hypothesis that KD susceptibility is genetically determined and that siblings of an index case have a higher risk of KD as compared with population controls. We found one of four twin pairs to have evidence for incomplete KD including elevated acute phase reactants and aortic root dilatation. Without specific testing for subclinical KD, this twin would not otherwise have come to medical attention. This example raises the question of whether all identical twins of an index KD case should undergo investigation for subclinical vasculitis. It also raises the disturbing, and currently unanswerable, question of how much clinically unrecognized KD may exist that, despite mild clinical disease, is capable of causing vascular injury.

A genetic influence on KD susceptibility is suspected due to the following observations. Although KD has been reported in most ethnic groups, the disease is overrepresented among Asian/American populations (5, 6). In Hawaii, the annual incidence for Japanese-Americans approaches 200/100,000 children less than 5 yrs. of age, which is similar to the incidence for Japanese living in Japan (7, 8). Asians in San Diego County have a 2.7-fold increased risk as compared with all other ethnic groups, even after controlling for socioeconomic status as a potential confounding factor (9). In Japan, siblings have a 10-fold increased relative risk of KD (10). The incidence of KD was two-fold higher in parents of children with KD and the

incidence of recurrent KD and KD in siblings was 5–6 times higher in these multi-generation KD families (11). Finally, there is an emerging recognition of KD pedigrees (12, 13).

For the four KD twin pairs from our center, three B twins had laboratory investigation in a timely manner and showed no evidence of systemic inflammation, but their echocardiograms were not performed until 7 mos.–6 yrs following the onset of KD in Twin A. Thus, transient coronary artery abnormalities could have been missed. For the nine cases reviewed from the literature, no distinct pattern emerges. Five of the nine twin pairs were concordant for clinically apparent KD and two of four pairs with data provided were discordant for the presence of coronary artery abnormalities. Based on our experience with twin pair 3, subclinical vasculitis cannot be excluded in the four discordant twin pairs. The apparent discordance in these twins could be due simply to inadequate, timely clinical investigation of each twin in the pair. True discordance between twins could result from differential exposure to the KD trigger or epigenetic mechanisms modifying KD susceptibility. Pre- or post-natal modification of genomic DNA including X-chromosome inactivation, hypermethylation of CpG islands, or histone post-translational modification could all play a role in altering KD susceptibility(14, 15).

We recognize several limitations to our study. In the San Diego series, the echocardiograms for the B twin in Pairs 1, 2, and 4 were performed months to years after the clinical illness in Twin A and thus transient dilatation of the coronary arteries and aortic root could have been missed. The limited number of twins studied precluded any meaningful statistical analysis of results.

Our small series supports the concept that when KD is diagnosed in a patient who has a monozygotic twin, the apparently well twin should be thoroughly screened for a history of clinical signs or symptoms suggestive of KD preceding or during the period of illness in the twin with KD. Any evidence of illness should precipitate an evaluation for subclinical coronary artery vasculitis including laboratory and echocardiographic investigation. Complete evaluation of the B twin could also be considered even in the absence of a history of clinical illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of monozygotic KD twins. Laboratory testing was performed in Twin B within 24 hours of laboratory testing in Twin A and before IVIG treatment in all cases.

	Pair 1		**Pair 2**		**Pair 3**		**Pair 4**	
Age (mo.)	58.6		12.5		18.1		25.5	
Sex	M		F		M		F	
Ethnicity	Caucasian		Japanese/Hispanic		Hispanic		Hispanic	
Twin designation[a]	A	B	A	B	A	B	A	B
Illness day at diagnosis[b]	5	NA	5	NA	11	9	6	NA
IVIG response	R	NA	R	NA	R	R	NR	NA
WBC ($\times 10^9$/L)	10.5	ND	8.2	3.6	11.3	8.5	14.4	8.7
% polymorphonuclear leukocytes	71	ND	66	32	42	34	41	21
% bands	4	ND	10	9	33	1	6	0
Age-adjusted Hgb (S.D. units)	−2.8	ND	−2.2	−0.6	−3.9	−2.8	−3.4	−2.5
Platelet count ($\times 10^9$/L)	565	ND	275	207	196	469	442	386
ESR (mm/h)	111	ND	52	17	54	54	45	10
C-reactive protein (mg/dL)	8	ND	13.5	0.7	22.7	3.6	8.3	<0.5
ALT (IU/L)	22	ND	35	ND	58	48	74	13
GGT (IU/L)	26	ND	110	ND	14	13	94	19
Internal vessel diameter normalized for body surface area	Nl	Nl (6 y)[c]	LAD Z_{worst} 2.8	Nl (2 y)	LAD Z_{worst} 2.8 RCA Z_{worst} 2.5	AoR Z_{worst} 3.2 (12 d)	Nl	Nl (7 mos.)

Abbr. IVIG, intravenous immunoglobulin; WBC, white blood cell count; Hgb, hemoglobin concentration; ESR, erythrocyte sedimentation rate nl range <15 mm/hr; C-reactive protein nl <0.7mg/dl; ALT, alanine aminotransferase, nl range 5–45 IU/L; GGT, γ-glutamyl transferase, nl range 6–19 IU/L; NA, not applicable; Z_{worst},Z-score of maximal dimension of coronary artery segment or aorta on any echocardiogram; R, IVIG responder; NR, IVIG non-responder; ND, no data; Nl, normal echo results.

[a] Twin A=clinically diagnosed as KD.

[b] Illness day 1 = first day of fever.

[c] Time interval between echo on Twin B and onset of KD in Twin A.