Maternal Antibody against Toxic Shock Syndrome Toxin–1 May Protect Infants Younger than 6 Months of Age from Developing Kawasaki Syndrome

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The symptoms of Kawasaki syndrome (KS) suggest a possible relationship between KS and superantigen(s). The infrequent occurrence of KS among young infants may be due to a passive maternal antibody. We investigated the antibody titers for superantigens (toxic shock syndrome toxin [TSST]–1, staphylococcal exotoxin B, and streptococcal pyrogenic exotoxins C and A) in 15 patients with KS who were < 6 months of age prior to gamma globulin therapy and in 10 mothers of patients with KS < 6 months of age. Significant findings were observed for only TSST-1 among the 4 anti-superantigens. The proportion of patients with KS who had high anti–TSST-1 titers was significantly higher than that among infant control subjects (33% vs. 5%, respectively; \( P = .031 \)). The mean anti–TSST-1 titer for the mothers was significantly lower than that of adult control subjects \( (P = .021) \). Among infants < 6 months of age, TSST-1 may be related to KS, and a maternal antibody may protect infants from developing KS.

Kawasaki syndrome (KS) is an acute febrile illness of unknown etiology. The symptoms of KS (fever, skin rash, and mucosal inflammation) suggest a possible relationship between KS and superantigens [3–6], others have failed to find the same results [7–9]; thus, this hypothesis remains controversial. The fact that a single infectious agent could not be identified as the cause of KS may suggest the possibility of involvement of multiple agents, each of which leads to a common pathway for KS. The presence of multi etiologic agents may make it difficult to clarify the etiology of KS. Therefore, to elucidate the etiology, it is important to focus investigations on a group of patients who have the same specific characteristics.

KS occurs predominantly in children < 5 years of age; however, it rarely occurs in young infants [2]. This infrequent occurrence may be due to the presence of a passive maternal antibody. We, therefore, investigated the pathogenic involvement of superantigens in patients with KS who were < 6 months of age.

Patients and Methods

Patients and samples. Twenty patients with KS who were < 6 months of age were admitted to the Kagoshima University Hospital or the Kagoshima City Medical Association Hospital (Kagoshima, Japan) between January 1994 and December 2000, and 15 (9 boys and 6 girls) of these patients participated in this study. The average age of the participants was 0.34 ± 0.10 years (range, 0.2–0.4 years). All children met the entry criteria, which included fever for 5 days accompanied by the presence of at least 4 of the 5 following manifestations: bilateral conjunctival injection, changes in the lips and oral cavity, nonpurulent cervical lymphadenopathy, polymorphous exanthema, and changes in extremities [1]. Serum samples were obtained from these patients and stored at −30°C until the assay was performed. On average, samples were obtained 4.5 ± 4.6 days (range, 1–20 days) after the onset of fever. Of the 15 samples, 14 were obtained before intravenous gamma globulin (IVGG) therapy, and 1 sample was obtained, 20 days after onset of fever, from a patient treated without IVGG.

Twenty-two infants < 6 months of age who visited or were admitted to the hospitals for an infection of the respiratory tract, bowel, or urinary tract were included as control subjects (13 boys and 9 girls; average age, 0.32 ± 0.09 years [range, 0.2–0.4 years]).

Eight of the mothers of the 15 patients with KS volunteered to participate in this study. Two additional mothers of patients with KS < 6 months of age and from whom serum samples were not obtained for this study also participated. Thus, a total of 10 mothers of patients with KS participated in this study, and the average age of the mothers was 29.7 ± 3.9 years (range, 25–38 years). Blood samples were obtained from the mothers while their children were hospitalized. Forty healthy adult volunteers (16 men and 24 women) were included as control subjects for comparison with the mothers, and the average age of these control subjects was 30.7 ± 7.7 years (range, 20–47 years).
**Results**

Patients with KS had higher mean antibody titers against TSST-1 and SEB than did the infant control subjects; however, these differences were not statistically significant (table 1). The mean antibody titers against SPEC and SPEA for patients with KS did not differ from those for infant control subjects.

Five patients with KS and 1 infant control subject had high anti–TSST-1 titers (33% vs. 5%, respectively; \( P = .031 \)). Two patients and 2 infant control subjects had high anti-SEB titers, and 1 patient and 1 infant control subject each had high anti-SPEC titers. No patients with KS had high anti-SPEA titers, but 1 infant control subject did. No patients with KS showed multiple high anti-superantigen titers.

The mean anti–TSST-1 titer for the mothers of patients with KS was significantly lower than that for the adult control subjects (table 1). The difference was still significant in a comparison between mothers of patients with KS and adult female control subjects. In contrast, the mean titers for SPEC, SPEA, and SEB were not significantly different.

The relationships between the anti-superantigen titers of 8 pairs of patients with KS and their mothers are shown in figure 1. Six patients showed a higher anti–TSST-1 titer than did their mothers, and 1 patient had an anti-SEB titer higher than that of her mother. For SPEC and SPEA, all the patients’ titers were lower than the titers of their mothers. Among the 8 patient-mother pairs, 7 patients showed a higher titer than their mothers for 1 of the superantigens.

Because a relationship between KS and staphylococcal toxin was suggested, results of a throat culture done at admission were reviewed. Cultures of oropharyngeal swab samples were done for 11 patients with KS, all of which showed normal flora. Five patients’ cultures contained a few colonies of *S. aureus*, whereas 6 did not. All of these colonies of *S. aureus* were methicillin sensitive, and analysis of the TSST-1 gene was not done. The mean anti–TSST-1 titer for the *Staphylococcus*-positive patients was higher than that for the *Staphylococcus*-negative patients (0.796 ± 0.579 vs. 0.164 ± 0.242, respectively), but this difference was not significant (\( P = .141 \)).

### Table 1. Anti-superantigen antibody titers for infants with Kawasaki syndrome (KS), their mothers, and adult and infant control subjects.

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>TSST-1</th>
<th>SEB</th>
<th>SPEC</th>
<th>SPEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt;6 months of age (37)</td>
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<td></td>
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<tr>
<td>Patients with KS (15)</td>
<td>0.482 ± 0.531^a</td>
<td>0.326 ± 0.525</td>
<td>0.040 ± 0.049</td>
<td>0.011 ± 0.010</td>
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<tr>
<td>Control subjects (22)</td>
<td>0.191 ± 0.244^b</td>
<td>0.252 ± 0.332</td>
<td>0.034 ± 0.059</td>
<td>0.014 ± 0.021</td>
</tr>
<tr>
<td>Mothers of patients with KS (10)</td>
<td>0.101 ± 0.165^c,d</td>
<td>0.420 ± 0.312</td>
<td>0.281 ± 0.242</td>
<td>0.099 ± 0.101^e</td>
</tr>
<tr>
<td>Adult control subjects (40)</td>
<td>0.447 ± 0.485^d</td>
<td>0.577 ± 0.458</td>
<td>0.147 ± 0.199</td>
<td>0.040 ± 0.052</td>
</tr>
<tr>
<td>Women (24)</td>
<td>0.434 ± 0.468^f</td>
<td>0.635 ± 0.457</td>
<td>0.159 ± 0.207</td>
<td>0.057 ± 0.061^f</td>
</tr>
<tr>
<td>Men (16)</td>
<td>0.467 ± 0.525^g</td>
<td>0.491 ± 0.459</td>
<td>0.129 ± 0.192</td>
<td>0.013 ± 0.011^ef</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean antibody titer ± SD. \( P \) values were estimated by use of the Mann-Whitney *U* test. SEB, staphylococcal exotoxin B; SPEA, streptococcal pyrogenic exotoxin A; SPEC, streptococcal pyrogenic exotoxin C; TSST-1, toxic shock syndrome toxin–1.

^a\( P = .078 \),
^b\( P = .021 \),
^c\( P = .034 \),
^d\( P = .040 \),
^e\( P = .003 \),
^f\( P = .007 \).
The present study focused on patients with KS who were <6 months of age and showed that the proportion of subjects with high anti–TSST-1 titers was significantly higher among patients with KS than among infant control subjects. This study also showed that the mean anti–TSST-1 titer for the mothers of patients with KS was significantly lower than that of the adult control subjects. These findings suggest an etiologic relationship between TSST-1 and KS in children <6 months of age. They also suggest that maternal antibody against TSST-1 may protect infants from developing KS.

The relationship between KS and superantigens has been discussed since Abe et al. [3] suggested that KS might be caused by superantigens. Abe et al. based this suggestion on their finding of the selective expansion of T cells expressing T cell receptor variable regions Vb2 and Vb8 in KS. Increased Vb2 T cells were reported subsequently by other researchers [5, 6]. In addition, Leung et al. [4] reported that KS might be caused by a new clone of TSST-producing staphylococci. Some investigators have failed to detect these abnormalities [7–9], whereas others have mentioned the relationship between KS and other superantigens [10, 11]; thus, this controversy is unresolved.

We found that there might be a relationship between TSST-1 and KS. The results of investigations of anti–TSST-1 antibody in patients with KS have been reported elsewhere: Terai et al. [9] and Nishiyori et al. [12] investigated anti–TSST-1 antibody in patients with KS and found no significant difference between the patients with KS and infant control subjects. Because KS may be caused by many types of agents, selection of subjects on the basis of their young age may have made the results of our study simpler and easier to interpret. Since our findings showed a relationship between KS and TSST-1 in children <6 months of age, the other studies that showed a relationship between KS and TSST-1 might be expected to have included many patients with KS who were <6 months of age [3, 5, 6]; however, they included few patients <6 months of age. This difference might be explained by differences in the patients' race or geographic location.

TSST-1 is known to cause toxic shock syndrome [13]. As shown by Takahashi et al. [14], TSST-1 relates to the neonatal disease characterized by systemic exanthema and thrombocytopenia in the first week of life. In their study, all the patients with toxic shock syndrome–like exanthematous disease (NTED) were carriers of methicillin-resistant S. aureus and were neonates who did not have anti–TSST-1 antibodies. Of the carrier neonates who possessed anti–TSST-1 antibodies, none showed symptoms of NTED [14]. These findings suggest that maternal anti–TSST-1 antibody protects neonates from developing NTED. A similar phenomenon was observed in the present study: low anti–TSST-1 antibody titers were observed for the mothers of patients with KS <6 months of age.

Although patients with NTED had low anti–TSST-1 titers, patients with KS in the present study had high anti–TSST-1 titers. The time from TSST-1 exposure to development of the disease among patients with NTED is within 1 week [14], but the time may be longer for patients with KS.

Although the mean anti–TSST-1 titer for the mothers of patients with KS differed from that for the adult control subjects, low anti–TSST-1 titers were observed for both groups. If anti–TSST-1 titers <0.101 (the mean titer for the mothers of patients with KS) are considered to be low, then 33% of the adult control subjects had low anti–TSST-1 titers (figure 1). We therefore suspect that infants with low maternal anti–TSST-1 antibody are not rare. This suspicion, however, cannot explain the infrequent occurrence of KS among young infants. To explain this discrepancy, an additional factor(s) must be important for the development of KS disease after exposure to TSST-1. In fact, 1 infant in the control group in the present study showed a high anti–TSST-1 titer without developing KS.

**Figure 1.** Relationships between the anti-superantigen titers of 8 pairs of patients with Kawasaki syndrome (KS) who were <6 months of age and their mothers. Among the 8 pairs, 6 infants with KS had higher anti–toxic shock syndrome toxin (TSST)-1 titers than did their mothers. One patient had an anti–staphylococcal exotoxin B (SEB) titer higher than that of her mother. The titers for streptococcal pyrogenic exotoxin C (SPEC) and streptococcal pyrogenic exotoxin A (SPEA) for all patients were lower than those for the mothers. A, adult control subjects; C, control subjects <6 months of age; KS, patients with KS; M, mothers of patients with KS; OD, optical density.
In this study, samples were obtained for culture as part of routine examinations; therefore, we could not detect organisms that might grow after 48 h of culture. In 45% of patients with KS who were <6 months of age, *S. aureus* was found in throat swab samples obtained at admission, and it was not rare to find a few colonies of *S. aureus* in throat swab samples considered to be normal. Asahi et al. [15] investigated normal nasopharyngeal flora and reported that *S. aureus* was isolated in 32% of 4–5-month-old infants [15]. However, the possibility remains that small amounts of *S. aureus* can be related to KS, because small amounts of superantigen can cause huge immunologic effects. In addition, the patients with KS who were found to be carriers of *S. aureus* had a higher mean anti–TSST-1 titer. This finding might support an etiologic relationship between TSST-1 and KS.

There may be multiple etiologic agents for KS. In the present study, we examined 1 possible agent, TSST-1, in patients with KS who were <6 months of age. Since the present study examined only 1 possible agent, further investigation is necessary to clarify other etiologies for KS. A relationship between the infrequent occurrence of KS among young infants and passive maternal antibody has been suggested in the past. We believe that this speculation is proven by the results of the present study.

**References**


