Recurrent Fever Syndromes in Patients After Recovery From Kawasaki Syndrome

abstract

The recurrence of fever in a child with a history of Kawasaki syndrome (KS) poses a dilemma for clinicians who must consider the possibility of recurrent KS. In this report we present the cases of 4 patients who presented with classical symptoms of KS, were successfully treated with intravenous immunoglobulin, and later experienced a reappearance of inflammatory symptoms in a pattern consistent with a recurrent fever syndrome. The association of these syndromes within the same patient suggests that some patients may have a genetic propensity toward altered immune responses and autoinflammatory syndromes. We propose that these 2 syndromes exist within a family of febrile disorders related to innate immune dysregulation. Pediatrics 2011;127:e489–e493

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KEY WORDS
recurrent fever, Kawasaki syndrome, autoinflammatory syndromes

ABBREVIATIONS
KS—Kawasaki syndrome
IVIg—intravenous immunoglobulin
PFAPA—periodic fever, aphthous stomatitis, pharyngitis and adenitis

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1218
doi:10.1542/peds.2010-1218

Accepted for publication Oct 22, 2010

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PEDIATRICS (ISSN Numbers: Print, 0631-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).
The diagnosis of Kawasaki syndrome (KS) is based on clinical criteria with no specific laboratory diagnostic test. Early treatment with intravenous immunoglobulin (IVIg) is important for reducing the risk of cardiac sequelae.

With increasing awareness of KS cases with incomplete clinical signs, or IVIg resistance with persistent fever after treatment, the distinction between recurrent KS and other fevers of unknown origin, specifically the recurrent fever syndromes, becomes more difficult.

The term “recurrent fever syndrome” encompasses a number of genetically defined autoinflammatory disorders as well as clinically defined entities such as periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. The hereditary fever disorders consist of recurrent episodes of fever associated with specific constellations of rash, lymphadenopathy, oral ulcerations, ocular findings, abdominal complaints, and arthralgias, whereas patients with PFAPA syndrome have fever episodes at regular intervals with associated symptoms often limited to the head and neck. Many patients with hereditary fever disorders have evidence of chronic inflammation, whereas patients with PFAPA syndrome are completely healthy between episodes and demonstrate normal growth and development.

The presence of these 2 conditions within a single patient suggests a possible genetic predilection for inflammatory dysregulation. Indeed, recent reports have implicated mutations in immunoregulatory pathways in the pathogenesis of KS. Such defects may also result in an increased likelihood of developing other inflammatory syndromes such as the recurrent fever disorders. In this report, we highlight 1 representative case among 4 patients who were initially diagnosed with KS and successfully treated with IVIg and who subsequently developed recurrent fever syndromes.

**CASE REPORTS**

A 3-year-old white boy presented with a 7-day history of fever to 105°F, rash, injected conjunctivae, swollen lips, strawberry tongue, and edema of the hands and feet. Laboratory investigation revealed marked inflammation with an erythrocyte sedimentation rate of 94 mm/hour. He was diagnosed with KS on the seventh day of fever, successfully treated with 1 dose of IVIg (2 g/kg), and initiated on aspirin therapy. An echocardiogram showed no cardiovascular abnormalities (Table 1). Two years after his initial diagnosis of KS, he developed recurrent episodes of fever associated with oral ulcers, pharyngitis, lymphadenopathy, headache, nausea, and vomiting. These febrile episodes occurred every 3 weeks and lasted 4 to 5 days. The maximum temperatures reached during these episodes ranged from 102°F to 105°F. Results of multiple streptococcal throat cultures were negative. Febrile episodes were successfully terminated with prednisolone (1 mg/kg) administered at the onset of fever, but recurrent use of steroids shortened the periodicity of the fever cycle to 2-week intervals and thereafter were limited to only intermittent use. Between febrile episodes, he was well with normal growth and development and no recurrent infectious illnesses.

By the age of 11, the patient’s febrile episodes spontaneously resolved without apparent sequelae. We have observed this pattern in 3 additional patients to date (summarized in Table 1). Each of these patients presented at younger than 5 years and met the classical criteria for KS. Each was treated successfully with 2 g/kg IVIg for the initial presentation of KS but developed recurrent fevers in the months after resolution of KS symptoms. Despite the variation in time to develop a recurrence of fevers, each of the patients developed a defined pattern of symptoms that fit a recurrent fever syndrome (Table 2). In 2 of the 3 cases, fevers were similarly responsive to prednisolone, and recurrent episodes resolved after tonsillectomy in the other case.

**DISCUSSION**

We report a series of 4 patients who each met clinical criteria for KS and had an appropriate response to standard IVIg therapy but subsequently developed recurrent febrile episodes within weeks to months after the initial KS diagnosis. We propose that this as-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis, mo</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Duration of fever, d</th>
<th>Pharyngitis</th>
<th>Lymphadenopathy</th>
<th>Conjunctival injection</th>
<th>Strawberry tongue</th>
<th>Exanthem</th>
<th>Edema/peeling</th>
<th>C-reactive protein, mg/dL</th>
<th>Erythrocyte sedimentation rate, mm/h</th>
<th>Urinalysis</th>
<th>Echocardiogram</th>
<th>C-reactive protein, mg/dL</th>
<th>Erythrocyte sedimentation rate, mm/h</th>
<th>Urinalysis</th>
<th>Echocardiogram</th>
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<tbody>
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<td>36</td>
<td>Male</td>
<td>White</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7.4</td>
<td>94</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>6</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>Female</td>
<td>Hispanic</td>
<td>35</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7.4</td>
<td>94</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>6</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
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<td>Male</td>
<td>White</td>
<td>10</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>3.8</td>
<td>49</td>
<td>NA</td>
<td>Normal</td>
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<td>49</td>
<td>NA</td>
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</tr>
<tr>
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<td>10</td>
<td>Male</td>
<td>Hispanic</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3.8</td>
<td>3.8</td>
<td>NA</td>
<td>Normal</td>
<td>NA</td>
<td>3.8</td>
<td>NA</td>
<td>Normal</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
TABLE 2  Summary of Recurrent Febrile Episodes in 4 Patients With a History of KS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time to fever recurrence, mo</th>
<th>Duration of episodes, d</th>
<th>Periodicity of fevers, wk</th>
<th>Pharyngitis</th>
<th>Aphthous stomatitis</th>
<th>Lymphadenitis</th>
<th>Eye symptoms</th>
<th>Abdominal pain</th>
<th>Nausea/vomiting</th>
<th>Rash</th>
<th>Erythrocyte sedimentation rate, mm/h</th>
<th>C-reactive protein, mg/dL</th>
<th>Prednisone responsive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>4 to 5</td>
<td>3</td>
<td>+</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>&lt;0.5 to 7.4</td>
<td>&lt;0.3 to 8.5</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>4 to 5</td>
<td>4</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>1 to 6</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4 to 5</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>3 to 94</td>
<td>0.3 to 8.5</td>
<td>Not used</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1 to 10</td>
<td>2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>10 to 82</td>
<td>NA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

a Lost to follow-up.
b Tonsillectomy.

tation may be attributable to shared genetic links influenced by environmental factors, and we encourage primary care pediatricians to consider recurrent fever syndromes in the differential diagnosis of patients with a history of KS.

Recurrence of prolonged fevers in a patient with a history of KS presented a clinical challenge of distinguishing between recurrent KS versus a recurrent fever syndrome. Recurrent KS occurs in up to 10% of Japanese children with a history of KS and an unknown, although much lower, percentage of children of other genetic backgrounds. Further complicating the differential diagnosis is the frequent occurrence of incomplete KS in infants and younger children. Pattern recognition of symptoms subsequently led to the diagnosis of a recurrent fever syndrome. The differential diagnosis of recurrent fevers included the hereditary recurrent fever syndromes as well as PFAPA syndrome. In 3 of 4 cases, the febrile episodes were responsive to single, low-dose prednisone, which is consistent with a diagnosis of PFAPA syndrome. For patient 4, the symptomatology and prednisone responsiveness were consistent with PFAPA syndrome, although the length of the febrile episodes was atypical. In each case, the patients were well between episodes and had normalized C-reactive protein levels. The clinical presentations, lack of chronic inflammation, ethnicity, and the ultimate disappearance of recurrent fever episodes made a hereditary fever syndrome unlikely. Although genetic testing is available for the known hereditary fever syndromes, it was not performed for these patients. As the pathogenesis of PFAPA syndrome is currently unknown, no specific gene test is available, and the mechanism behind the development of recurrent fevers in these patients remains an enigma.

We have identified a population of pediatric patients in San Diego, California, with recurrent fever syndromes (unpublished data), and systematic review of our patients’ histories revealed the cases discussed above and also 4 additional patients with recurrent fever syndrome with first-degree relatives with a history of KS. At this time, it is unclear whether the association between KS and PFAPA syndrome in these patients represents a genetic predisposition to autoinflammatory responses, susceptibility to environmental exposures, or a combination of the two. The low prevalence of these 2 syndromes poses a challenge to answering this question.

The general prevalence of recurrent fever disorders, other than the hereditary syndromes reported in specific geographic regions, is not well established. Over the last 3 years, we have identified 84 cases of recurrent fever syndromes of various etiologies in children in San Diego County (unpublished data), which yields an annual incidence of 9 to 34 in 100 000 children younger than 18 years, whereas the annual incidence of KS in San Diego County is 21.7 in 100 000 children younger than 5 years. We estimate that the probability of a child having both of these rare conditions to be \( <5 \times 10^{-6} \) or 1 in 19 million, on the basis of available data from San Diego County. Thus, 4 cases of KS among 84 patients with known recurrent fever syndrome (4.7%) is higher than would be expected by chance alone.

The association of KS and other immune-mediated conditions has been recognized, as has been recognized between KS and atopy and KS and psoriasis in children, which suggests that patients with KS may have a general propensity toward immunodysregulation. The similarities between the presentation of KS and recurrent fever syndromes may suggest activation of similar pathways that trigger innate immune responses. In addition, similarities in cytokine profiles are apparent in acute KS and in recurrent fever syndromes, including elevations in the levels of tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), interleukin 1\( \beta \) (IL-1\( \beta \)), and IL-6, and several recent studies found that IVIg increases the level of IL-1Ra, an inhibitor of the cytokine IL-1\( \beta \) that has been shown to be important in the pathogenesis of several autoinflammatory syndromes. As such, we hypothesize that KS and
Classical Kawasaki syndrome is possible that additional patients with a recurrent fever syndrome because of the diagnosis frequently seen with recur- tors for larger studies. Given the delay in mulatethediagnosisarethelimitingfac- pattern recognition of symptoms to for- as individual disorders and the need for both KS and recurrent fever syndromes ver syndrome. However, the rarity of consequently presented with a recurrentfeversyndromes.Althoughmucosalin- dromes. Similarly, the strawberry tongue observed in patients with KS is absent in patients with recurrent fever. These mutually exclusive findings should be noted during a febrile epi- sode and may lead the clinician toward a specific diagnosis. From a laboratory perspective, both KS and recurrent fever syndromes demonstrate elevated C-reactive protein level and erythrocyte sedimentation rate during the acute pe- riod, and they normalize between febrile episodes. The identification of a pattern of recurrent fevers with additional clinical signs (Table 3) becomes the most important diagnostic feature.

CONCLUSIONS
In this report we have described a subset of patients with KS who went on to develop recurrent fever syndromes, which indicates that these disorders may have a common immunologic thread, specifically related to immunodysregulation of innate immune effec- tor mechanisms. For community pedi-
atriacians treating patients with a history of KS, the recurrence of febrile episodes should lead to the consideration of alternative diagnoses, including recurrent fever syndromes.

ACKNOWLEDGMENTS

This work was supported in part by grants from the University of California San Diego Department of Pediatrics and a resident research grant from the American Academy of Pediatrics (awarded to Dr Broderick) and National Institutes of Health, National Heart, Lung, and Blood Institute grant K24 HL074864 (awarded to Dr Burns).

REFERENCES


