Response to cimetidine in a 1-year-old child with PFAPA syndrome

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by periodic febrile attacks recurring regularly every 2 to 8 weeks. Although tonsillectomy is offered as an effective treatment, the effectiveness of cimetidine treatment is still controversial. In this article, we describe two cases. A 1-year-old girl with PFAPA syndrome received cimetidine treatment and febrile attacks were reduced. Tonsillectomy was successfully performed on a 6-year-old boy with PFAPA syndrome. We suggest that the use of cimetidine may reduce febrile attacks of PFAPA syndrome until an age that is safer for tonsillectomy.

Key words: cimetidine, tonsillectomy, PFAPA syndrome, febrile attacks.

Case Reports

Case 1

A 1-year-old girl with an unremarkable medical history suffered from periodic febrile attacks accompanied by aphthous stomatitis and pharyngitis every 4 to 8 weeks. She was diagnosed with PFAPA syndrome after 1 year from the first febrile attack in accordance with the diagnostic criteria advocated by Thomas et al. Blood tests showed that leukocytes ranged from 10,930 to 18,800 /mm³ without neutropenia. This suggested that febrile attacks were not due to cyclic neutropenia, a major differential diagnosis. In febrile attacks, prednisolone (0.5 mg/kg, a single dose) was effective in reducing the fever. She was started on cimetidine treatment (20 mg/kg, twice daily). She has not suffered from a febrile attack for more than 8 months. No side effect was detected due to cimetidine treatment.

Case 2

A 6-year-old boy with an unremarkable medical history suffered from periodic febrile attacks accompanied by aphthous stomatitis, pharyngitis, and cough every 2 to 8 weeks (Table I). He was diagnosed with PFAPA syndrome in accordance with the same criteria described above at the age of 3 years, although onset was at the age of 1 year. Blood tests showed that leukocytes ranged from 11,130 to 19,730 /mm³ without neutropenia. In febrile attacks, prednisolone (0.5 mg/kg, a single dose or 1 mg/kg, twice a day) was effective in reducing the fever. He underwent tonsillectomy at the age of 6 years to avoid frequent absences from school. He has not suffered from a febrile attack for more than 7 months since having tonsillectomy.

Discussion

We observed two important clinical issues
from our cases. Cimetidine treatment reduced febrile attacks of PFAPA syndrome. Additionally, tonsillectomy was effective against PFAPA syndrome, as we expected.

Vanoni et al. referred to more than 80% effectiveness of orally given prednisolone or betamethasone as treatment for febrile attacks\textsuperscript{13}. Although they also referred to possibility of colchicine, cimetidine and anakinra as prophylactic treatment, the effectiveness of these drugs is still controversial\textsuperscript{13}.

Cimetidine treatment can reduce febrile attacks of PFAPA syndrome. Cimetidine is a common H2 antagonist that inhibits suppressor CD8+ T-lymphocyte activation and chemotaxis\textsuperscript{11,12}. Thomas et al.\textsuperscript{3}, Feder et al.\textsuperscript{4}, and Wurster et al.\textsuperscript{12} reported 43%, 27%, and 24% effectiveness, respectively, of cimetidine for PFAPA syndrome. Because the effectiveness described above are not sufficiently high, some pediatricians hesitate to prescribe cimetidine for PFAPA syndrome. Our patient showed a reduction of febrile attacks of PFAPA syndrome.

Tonsillectomy is effective against PFAPA syndrome. Previous reports have shown 63–100% effectiveness of tonsillectomy for PFAPA syndrome\textsuperscript{3,4,6-8,12}. Our case 2 also showed effectiveness of tonsillectomy for PFAPA syndrome.

Febrile attacks of PFAPA syndrome can begin, at the earliest, at the age of 1 month\textsuperscript{1,3,8,14}. Complications following tonsillectomy are more common in children younger than 3 years\textsuperscript{15}. Although prednisolone treatment is highly effective for the treatment of febrile attacks of PFAPA syndrome, it shortens the interval of febrile attacks\textsuperscript{12,16}. Cimetidine treatment may be useful for reducing febrile attacks of PFAPA syndrome until the age of 3 years.

In conclusion, cimetidine treatment can reduce febrile attacks and tonsillectomy is effective against PFAPA syndrome in our cases. We propose to use cimetidine to reduce febrile attacks of PFAPA syndrome until the age of 3 years. Cimetidine treatment could be recommended to reduce the attacks of PFAPA syndrome. Further studies are needed to determine whether cimetidine treatment can become a main therapeutic strategy prior to tonsillectomy.

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REFERENCES


Table I. Characteristics of Two Patients with PFAPA Syndrome.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Interval of febrile attacks</th>
<th>Symptoms</th>
<th>Leukocytes count (/mm$^3$)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>4–8 weeks</td>
<td>High fever, pharyngitis, aphthous stomatitis</td>
<td>10,930 - 18,800</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2–8 weeks</td>
<td>High fever, cough pharyngitis, aphthous stomatitis</td>
<td>11,130 - 19,730</td>
<td>PSL Tonsillectomy</td>
</tr>
</tbody>
</table>

F: female, M: male, PSL: prednisolone