Hypereimunoglobulin E syndrome (HIES), also known as Job’s syndrome or Buckley syndrome, is a primary immunological disorder of unknown etiology. HIES may debut with no genetic linkage, but autosomal-dominant and autosomal-recessive transmission patterns have been described.1-6 The autosomal-dominant form of hyperimmunoglobulin E syndrome (AD-HIES) is commonly characterized by:

1. elevated serum immunoglobulin E levels;
2. chronic eczematoid dermatitis;
3. recurrent skin abscesses that often lack the usual signs of inflammation such as warmth, erythema, and tenderness (“cold abscesses”);
4. lung staphylococcal infections with predisposition to formation of pneumatoceles;
5. characteristic facies with facial asymmetry;
6. prominent forehead;
7. deep-set eyes;
8. broad nasal bridge;
9. mild prognathism;10
10. scoliosis;
11. joint hyperextensibility;
12. decreased bone density leading to a high risk of bone fracture after minimal trauma.11

Retention of the primary teeth due to the lack of root resorption is a striking and unexplained feature which Grimbacher et al found in 72% of AD-HIES patients.1 The autosomal-recessive form of HIES (AR-HIES) differs from AD-HIES in that:

1. skeletal and dental abnormalities are absent;
2. there is increased susceptibility to severe fungal and viral infections;
3. there is a high incidence of vascular and infectious central nervous system complications.12

The pathophysiology of the HIES syndrome remains unclear. Immune studies have attributed infection susceptibility to:

1. defective neutrophil chemotaxis;
2. deficiency in humoral13,14 and cellular immune response15;
3. dysregulation of T-cell cytokine signals.16,17

The HIES diagnosis is based on the constellation of patients' clinical and laboratory features, as no specific diagnostic test is available. A HIES scoring system developed at the National Institutes of Health (NIH) to phenotype patients with AD-HIES is helpful (Table 1).1 HIES management is dependent on:

1. prophylactic antibiotics;
2. local debridement;
3. surgical incision and drainage of infectious lesions.9

Only a limited number of articles have described oral findings in HIES patients. These can include oral ulcerations,18 gingivitis,18 and prolonged oral and cervicofacial infections.19,20 O'Connell et al.18 found that 81% (13/16) of HIES-affected children 7 to 17 years old demonstrated a delay in permanent teeth eruption that amounted to more than standard deviation of the average eruption age. Twenty-eight percent (5/18) of HIES patients older than 20 years showed radiographic evidence of delayed exfoliation of primary teeth. Histological examination of retained deciduous teeth revealed an abnormal persistence of the Hertwig's epithelial root sheath, a finding that may partly be related to the primary teeth's delayed exfoliation.21

Since no previous report has described periodontitis in young HIES patients, the purpose of this report was to detail a 5-year-old girl with probable AR-HIES who exhibited advanced periodontitis in her entire primary dentition.

**Case report**

The 5-year-old female patient was the firstborn child of a Kurdish couple who are first cousins. She has 2 healthy younger brothers. None of her immediate family members have problems with infections or other HIES features. She was born at full-term by spontaneous vaginal delivery after an uncomplicated pregnancy. Shortly after birth, she developed severe eczema which has been difficult to manage because of frequent Staphylococcus aureus and Candida albicans supra-infections.

She had recurrent otitis media. By age 6, she had been hospitalized with pneumonia on 5 occasions and had 1 episode of S. aureus sepsis. At age 3, she developed severe HSV1-positive gingivostomatitis, for which she was admitted to the hospital and treated with intravenous acyclovir. She had an uneventful course of chickenpox at age 2 1/2, but developed shingles at age 6. She was almost exclusively breast-fed until age 15 months. After weaning, she fed poorly on a restricted diet, which resulted in severe failure to thrive. She had osteopenia and suffered 2 tibial fractures after minor trauma.

With dietary supplements and nasogastric feeding of an elemental formula, her growth velocity normalized, but her height and weight remain below the third percentiles. Other clinical and laboratory findings (Table 1) resulted in a HIES score of 64. Without including the finding of osteopenia and fractures, considered at this time to be related to dietary insufficiency, her HIES score is 60. Definite diagnosis, however, is controversial and remains to be confirmed by future development of reliable molecular diagnostic markers.

At age 5, the patient was referred to the dental clinic at the British Columbia's Children's Hospital, Vancouver, British Columbia, Canada, with the chief complaint of painful gingival enlargements over the past 2 months. The mother reported significant gingival bleeding during brushing. The

---

**Table 1. Scoring System for Clinical and Laboratory Findings in HIES Patients**

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin abscesses</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
<td>5-6</td>
<td>&gt;6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia (episodes over lifetime)</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal lung abnormalities</td>
<td>Absent</td>
<td>Bronchiectasis</td>
<td>Pneumatocele</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained primary teeth</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis; maximum curvature</td>
<td>&lt;10°</td>
<td>10°-14°</td>
<td>15°-20°</td>
<td>&gt;20°</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures with minor trauma</td>
<td>None</td>
<td>1-2</td>
<td>3</td>
<td>&gt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest eosinophil count (cells/ml)</td>
<td>&lt;700</td>
<td>700-800</td>
<td>&gt;800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>AbSENT</td>
<td>Mildly present</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn rash</td>
<td>AbSENT</td>
<td>Moderate</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema (wet stage)</td>
<td>AbSENT</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections per year</td>
<td>1-2</td>
<td>3</td>
<td>4-6</td>
<td>&gt;6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidias</td>
<td>None</td>
<td>Oral</td>
<td>Fingernail</td>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other serious infections</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal infection</td>
<td>AbSENT</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperextensibility</td>
<td>AbSENT</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>AbSENT</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased nasal width</td>
<td>&lt;1 SD</td>
<td>1-2 SD</td>
<td>&gt;2SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High palate</td>
<td>AbSENT</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young-age correction</td>
<td>15 years</td>
<td>2-5 yrs</td>
<td>1-2 yrs</td>
<td>&lt;1 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Grimbacher et al.*
†Points are assigned to each finding on the basis of its incidence and specificity for HIES. Based on the frequency and severity of HIES characteristics exhibited, HIES is considered highly likely, with an HIES score >40 points, and possible with a HIES score >20 points. At 10 to 15 points, the presence of HIES genotype is undetermined. At <10 points, the patient is unlikely to have HIES. Shaded area denotes the scores for the patient in this case, totaling 64 points.
‡Normal=<130 IU/ml.
mother recalled no recent changes in medications or oral care. The extraoral examination revealed very dry, crusted lips and bilaterally erythematous cheeks. Her neck and extremities showed eczematous, excoriated scaling lesions. The intraoral findings are summarized in Table 2. Also, the tongue surface was smooth but deeply fissured. Gingiva appeared fiercely red and edematous with spontaneous bleeding (Figure 1). The child was in the primary dentition stage, and all teeth except nos. E, F, and G showed probing pocket depths of 5 mm or more and Class III mobility. Radiographic examination revealed advanced horizontal alveolar bone loss around all primary teeth (Figure 2). Minor interproximal dental caries lesions were detected.

For bacteriological examination, paper-point samples were collected from 4 advanced periodontitis lesions and processed separately. A polymerase chain reaction methodology was used to identify suspected periodontopathic species. The study lesions yielded Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Eikenella corrodens, Campylobacter rectus and Prevotella nigrescens. No sample revealed Actinobacillus actinomycetemcomitans.

The patient’s advanced periodontitis prevented a conservative therapy. All primary teeth were extracted under general anaesthesia. Healing proceeded uneventfully and resulted in the elimination of soft tissue inflammation. The treatment aimed at:

1. minimizing the risk of infection by periodontopathic bacteria in the gingival crevice of erupting permanent teeth;
2. preventing a systemic dissemination of pathogens having the potential to cause pneumonia.

Histopathological analysis performed on 4 representative gingival lesions and associated teeth revealed heavily inflamed gingiva with elongated rete ridges and a predominance of plasma cells and intraepithelial polymorphonuclear leukocytes (Figures 3A to 3C). The root cementum appeared necrotic with no periodontal ligament attachment (not shown). The teeth showed no evidence of pulpal pathosis.
The patient was re-evaluated at 1 and 6 weeks after the extractions. Her mother noticed a marked reduction in the child’s oral discomfort and significant improvement in her appetite. Gingival healing was satisfactory, but regeneration of alveolar bone was not observed. Whether a period of edentulousness may prevent the recurrence of periodontitis in the permanent dentition remains to be determined with future monitoring. Prosthetic replacement of primary teeth and interceptive orthodontic treatment due to early loss of primary teeth are pending upon improvement of the patient’s periodontal health.

Discussion

This child has clinical and laboratory features consistent with HIES. Having unaffected, consanguineous parents suggests the autosomal-recessive form of HIES. Her NIH-HIES score of 64 is in the 36 to 53 range that Renner et al determined in AR-HIES patients greater than age 1. Moreover, she has experienced problems with viral infections (herpes gingivostomatitis, shingles) that are common in this condition. Although other reports of oral complications in HIES mention oral ulcers and gingivitis, the authors believe this is the first known report of generalized advanced periodontitis. Aggressive periodontitis around every tooth in a dentition is a very rare occurrence in prepubertal children. Considering the predisposition of HIES patients to recurrent infections, it is not surprising that such individuals are at risk of developing aggressive periodontal disease. The periodontitis lesions studied yielded mixtures of P gingivalis, T forsythia, T denticola, E corrodens, C rectus, and P nigrescens. These bacteria are typically found in adults and children with severe periodontitis and gingivitis, but are usually not prominent in young children. HIES-associated immunodeficiencies could permit periodontopathic bacteria to colonize young individuals. A actinomycetemcomitans was not detected in the periodontitis lesions studied, even though the organism is a major pathogen in various types of destructive periodontal disease in children and adolescents. In contrast to the present patient’s periodontal condition, however, A actinomycetemcomitans is typically associated with a localized pattern of periodontal destruction and relatively little gingivitis.

HIES patients may experience an aggravated course of periodontitis because of defective polymorphonuclear leukocytes, deficient antibody responses, and changes in the T-helper (Th)1/Th2 balance towards a Th2 response. The Th2 predominance may accelerate periodontal breakdown through an overproduction of IgE. The Th2-related interleukin (IL)-4 and IL-13 cytokines enhance IgE production, whereas the Th1-related interferon-γ and IL-12 suppress IgE production. The elevated IgE level, resulting from the Th2 predominance and reduced interferon-γ level may cause a release of bone-resorbing prostaglandin-E, L-1β, and tumor necrosis factor-α from monocyctic cells. At the same time, interferon-γ and transforming growth factor-β, which are major anti-inflammatory and bone resorption-inhibitory mediators, are reduced in HIES patients. All together, rapid periodontal tissue destruction in HIES patients could be due to the combined effect of highly virulent periodontopathic bacteria, deficient polymorphonuclear leukocytes responses, increases in potent bone-resorbing cytokines, and decreases in bone resorption-inhibitory cytokines.

The ideal management of HIES-associated periodontitis would be to correct the underlying defects. HIES patients have been treated with histamine receptor 2 antagonist, cromoglycate, levamisole, cyclosporine A, interferon-γ/α, and intravenous γ-globulin—all with limited effectiveness. Bone marrow transplantation to correct the underlying immunodeficiency has failed to yield clinical improvement. The main management strategies continue to be: (1) prophylactic antibiotics; (2) timely treatment of infections; and (3) surgical intervention as necessary.

In terms of periodontal care, no study is available to delineate the extent to which HIES patients respond to conventional anti-infective treatment. Even though Papillon-Lefèvre syndrome has different pathogenic mechanisms, the management approaches for periodontitis in Papillon-Lefèvre syndrome patients may also be applicable to the severe periodontitis in this case. Treatment studies of Papillon-Lefèvre syndrome periodontitis show that extraction of hopeless teeth or the entire primary dentition decreases the risk of infection around later erupting teeth. All primary teeth were extracted in this patient. Whether or not a period of edentulousness improves the prognosis of the permanent teeth is unknown.

Conclusions

It should be realized that valuable diagnostic clues of a serious medical disorder might be obtained by identifying severe periodontal destruction along with salient systemic disease.
The cooperation between pediatricians and pediatric dentists is necessary for providing comprehensive treatment of children with systemic diseases.

Hyperimmunoglobulin E syndrome's clinicopathologic features are not uniformly expressed in individuals with the different genetic variants. The classic features include: (1) recurrent skin and lung staphylococcal infection; (2) chronic eczematoid dermatitis; and (3) elevated serum IgE level. Aggressive periodontitis may also be an associated phenotype. Efficacious periodontal therapy of HIES-related periodontitis remains to be determined.

References
The purpose of this retrospective longitudinal study was to examine the spontaneous mandibular arch dimension changes in patients with class I malocclusions following rapid palatal expansion. Serial models of 30 patients with transverse discrepancies treated only with rapid palatal expansion in the early or mid-mixed dentition were measured for changes in: (1) mandibular arch width; (2) arch length; and (3) arch perimeter. Measurements were obtained at 4 assessment stages: (1) pre-expansion; (2) short-term follow-up; (3) progress; and (4) long-term follow-up. The authors reported a statistically significant increase in intermolar arch width following RPE, but reported no changes in: (1) intercanine width; (2) arch length; or (3) arch perimeter attributable to RPE.

**Comments:** This is one of those classic reports where the results are shown to be statistically significant, but the clinical significance is questionable. From pre-expansion to long-term follow-up (approximately 10 years), a mean increase in intermolar arch width of slightly less than 1 mm was observed ($P<0.05$).

**Address correspondence to Dr. Anna Carolina Lima, Avenida Alberto Andaló, 4025, São José do Rio Preto, SP 15015-000, Brazil.**


18 references