Clinical manifestations in the oral cavity in patients with hyper-IgE syndrome

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Abstract

Introduction: Hyper-IgE syndrome is a rare autosomal recessive or dominant manner due to gene mutations. This syndrome, from mutations in the STAT3 gene, is characterized by elevated levels of IgE > 2000 IU/ml, eczema, skin abscesses, recurrent respiratory infections, skeletal abnormalities, oral mucosal lesions, impaired eruption of permanent teeth and root resorption of deciduous teeth.

Aim of the study: Determine phenotypic characteristics of hyper-IgE syndrome in the oral cavity with regard to a modifying impact of environmental factors.

Results: Examination of the oral mucosa revealed white lichenoid lesions, atrophy of the lingual papillae, median schistoglossia, palatine fibrosis, erosions, ulceration and scarring, angular cheilitis. Candida albicans was identified, despite antifungal treatment. Dental examination revealed caries, unerupted teeth, persistent deciduous teeth, and tooth wear. The phenotypic variability in the oral cavity might have been due to environmental factors.

Conclusions: Although the genetic causes of hyper-IgE have been identified, the pathogenesis of oral lesions in those patients remains to be clarified. The current knowledge allows associating the oral mucosal lesions, i.e., fungus infections, hyperkeratosis and fibrosis, with the STAT3 gene mutation. It also helps to consider its role in odontogenic disorders, particularly in inhibiting eruption of permanent teeth and root resorption in deciduous dentition.

Key words: hyper-IgE syndrome (HIES), oral mucosal lesions, candidosis, dental abnormalities, impaired eruption of teeth.

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Material and methods

The study included four patients with autosomal dominant hyper-IgE syndrome (13.5-29 years) followed up regularly in Immune Diseases Ward, Department of Gastroenterology, Hepatology and Immunology, and Department of Oral Pathology, The Children’s Memorial Health Institute, Warsaw, Poland. Three patients were diagnosed with the STAT 3 gene mutation, patient No 3 was undergoing genetic testing (at the time of the study).

Clinical assessment was focused on the patients’ general health status, documented in their medical records, dental examination, and radiology (pantomography). Physical examination included evaluation of the following:

- oral hygiene status: PI I [16];
- health status of paradental tissues: gingival pocket depth (> 4 mm), GI [16];
- health status of the oral mucosa (type and site of lesions) – examination focused on the presence, type and site of lesions in the oral mucosa based on the WHO Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases [17];
- dental status:
  - type of dentition (deciduous/permanent),
  - number of missing teeth,
  - number of teeth with active carious foci,
  - number of teeth with enamel defects: a modified DDE (limited enamel opacities, diffuse opacities, and enamel hypoplasia) [18],
  - number and type of permanent teeth with tooth wear: severity of tooth wear/TWI according to Smith and Knight (1984):
  0 – no signs of enamel loss/no contour change in paracervical surface area
  1 – visible loss of enamel surface/minimal change in enamel contour
  2 – enamel loss with dentine exposure < 1/3 dentine/dentine loss < 1 mm
  3 – enamel loss with dentine exposure > 1/2 dentine/dentine loss < 1-2 mm from pulp with no exposure of pulp or secondary dentine
  4 – total enamel loss with exposure of pulp or secondary dentine thickness > 2 mm [9, 20].

Clinical examination was completed, according to medical indications, based on accessory investigations, i.e., pantomography, and mycology. Sample material for mycology was obtained by a direct smear from the buccal and lingual mucosa. The clinical material was quantitatively cultured on the Sabouraud solid medium. The culture was incubated at a temperature of 37°C. The fungal species were identified using the ID 32°C test (bioMerieux) to assess their biochemical properties [21].

Results

Patients’ general health condition/status

Patients’ characteristics, including their age, gender, and medical history, based upon the latest HIES diagnostic guidelines, are presented in Table 1 [6]. All patients had developed general manifestations typical of the AD HIES; for which they had received several courses of a long-term antibiotic therapy. They also had iron deficiency anemia (n = 2), bronchial asthma (n = 1), digestive disorders: gastritis (n = 1). On the examination day, patient No 2 was noted to have aggravated skin problems (severe pruritus, scratched papules covered with eschar), patient No 4 had a submucosal abscess at area of teeth 04 and 05. All the subjects had been treated with antibacterial and antymycotic agents; three patients, with agents for their digestive disorders (abdominal complaints following a long-term bactrim therapy), and iron preparations, one subject used anti-asthmatic inhalants (Table 1).
Table 1. Patients with hyper IgE according to age, sex, general health status, and pharmacological treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>No 1</th>
<th>No 2</th>
<th>No 3</th>
<th>No 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.5</td>
<td>29</td>
<td>18.5</td>
<td>20</td>
</tr>
<tr>
<td>Sex/Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin lesions abscesses</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>chronic eczema</td>
<td>+</td>
<td>+ (severe)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>mucodermal candidiasis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>organ abscess</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>recurrent respiratory or/and urinary infections</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>sinusitis, otitis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>skeletal abnormalities</td>
<td>scoliosis, pathological fractures</td>
<td>scoliosis</td>
<td>pathological fractures</td>
<td>pathological fractures</td>
</tr>
<tr>
<td>facial dysmorphia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>other</td>
<td>iron deficiency anemia, bronchial asthma, gastritis</td>
<td>iron deficiency anemia</td>
<td>gastrointestinal disorders</td>
<td>gastrointestinal disorders (condition following hepatic abscess)</td>
</tr>
<tr>
<td>Pharmaceutical agents taken on examination day</td>
<td>bactrim, orungal</td>
<td>bactrim, ketokonazole, flixotide, helicid, sorbifer durules</td>
<td>bactrim, brungal, banigast</td>
<td>bisepol, augmentin, metronidazole diflukan, ketokonazole, ranitidine</td>
</tr>
</tbody>
</table>

Oral health status

Oral mucosal lesions and dental abnormalities in patients with AD HIES are summarized in Table 2.

The oral hygiene and health status of the gingiva and mucous membrane

All the subjects had dental plaque deposits (PLI: 1.66-2.58), mild or moderate gingivitis (GI: 0.83-2.00). Three patients had inflammatory erythema on the marginal gingiva. In one patient, it also involved the attached gingiva and the mucosa of the remaining oral regions. There were no gingival pockets ≥ 4 mm.

All the patients were found to have white hyperkeratotic lesions in the mucosa of the cheeks, alveolar processes, palate, tongue, and retromolar regions. In both women, the oral mucosa was pale, particularly in the palate (iron deficiency anemia). Circumoral vitiligo was noted in one patient. Three patients had angular chelitis and candidiosis (Fig. 1). Mycology showed a high titre of *Candida albicans* (> 10^3 CFU/ml) in all our patients, despite administration of antymycotic treatment. Two subjects had fibrosis in the hard palate. One person had ulceration on the lateral lingual margin, and one had a post-ulcerative scar. In two patients were observed changes on the tongue: deep median sulcus or grooves on dorsal surface with papillary atrophy. There were favourable environmental factors contributing to mucosal lesions in all the subjects (Table 1). A significant effect might have been exerted by iron deficiency anemia, digestive disorders and pharmacological agents.

Dental health status

All patients presented with dental caries and pathological attrition (max. values TW1 – 2), two – enamel hypoplasia of permanent dentition. Persistent deciduous teeth were found in two patients; in three subjects, permanent teeth were absent (a radiogram showed retained teeth, an absent bud of tooth 24) (Fig. 2). In one patient, teeth 83 and 43 were found to be in two rows.

Radiology

Radiology revealed absence of the dental bud of tooth 24 (patient No 1), retained teeth with well formed roots (patients No 1, 2, 4), an abnormal bone structure, including an irregular border of alveolar processes (all subjects), osteosclerotic lesions (patient No 1) (Fig. 2), osteolytic foci in a root area (patient No 4). It is worth noting that reduced bone density foci were also present in the root region of non-carious teeth with preserved vital pulp.
Discussion

Hyper IgE syndrome is a multisystem condition associated with a dysfunction of the immune system, in which clinical manifestations affect the connective tissue and the skeletal system [8, 22]. Oral lesions in patients with HIES involve both the mucous membrane and dentition, and represent one of the features characteristic of the HIES inherited in an autosomal dominant pattern. The etiology of the changes in oral mucosal in patients with AD HIES has not been fully explained. The role of the STAT3 gene mutation in the etiology of palatine fibrous lesions also appears to be of significance. The gene plays its role in regulating the key cytokines (IL-6, IL-10, IL-17, IL-21, IL-22, IL-23) and Th17 deficit.

Table 2. Lesions in the oral mucosa and dental abnormalities in patients with AD HIES

<table>
<thead>
<tr>
<th>Patient</th>
<th>No 1</th>
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<tbody>
<tr>
<td>PI 1</td>
<td>2.33</td>
<td>2.58</td>
<td>2.50</td>
<td>1.66</td>
</tr>
<tr>
<td>GI</td>
<td>0.83</td>
<td>1.66</td>
<td>1.50</td>
<td>2.00</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>pallor atrophic candidiasis; angular cheilitis; erosions and white lichenoid lesions on the buccal mucosa; black tongue; high palate</td>
<td>pallor pseudomembranous candidiasis; left angular cheilitis; white lichenoid lesions on the buccal and alveolar processes mucosa; post-ulcerative scar on the tongue; high palate</td>
<td>right angular eschar, circumoral vitiligo on the lips; erosions and white lichenoid lesions on the buccal and alveolar processes mucosa; ulceration, hyperkeratotic with lesions, deep median sulcus, with a papillary atrophy in anterior part of tongue; high palate with irregular fibromatoses</td>
<td>pseudomembranous candidiasis, angular cheilitis, angular hyperkeratosis, mucosal erythema and white lichenoid lesions (lips, cheeks), grooves on dorsal surface papillary atrophy in anterior part of tongue; high palate with erythema and fibromatoses surrounded by grooves</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Teeth</th>
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<tbody>
<tr>
<td>Dental caries</td>
</tr>
<tr>
<td>Tooth wear (TWI: min. – max.)</td>
</tr>
<tr>
<td>Enamel defects</td>
</tr>
<tr>
<td>Persistent deciduous teeth</td>
</tr>
<tr>
<td>Retained permanent teeth</td>
</tr>
<tr>
<td>Hypodontia</td>
</tr>
<tr>
<td>Radiogram</td>
</tr>
</tbody>
</table>
Dysfunction of the STAT3 gene can lead to candidosis and epidermal hyperplasia and keratosis [23]. Frequent infections with *Candida* spp. in persons with HIES have been confirmed in reports by other authors. They found that 83% of their patients had concomitant chronic mycoses of the skin and mucous membranes caused by infection with *Candida albicans* and other fungal strains [2, 8, 15]. The high risk of candidiosis is correlated with downstream of the Th17 and probably with reduced expression of certain AMPs with antifungal activity, namely β-defensins and histatins [24].

The palatine fibrous lesions, as reported in patients with HIES, may be caused by disorders associated with IL-6 (induced fibroblast proliferation and collagen production).

In contrast to other authors, we did not find rhomboid tongue in any of our patients [15]. There were, however, other lesions, i.e., tongue fissures, atrophied foliate papillae, ulceration, scars and a black tongue. In the etiology of these abnormalities, researchers should also consider the impact of environmental factors, e.g., iron deficiency anemia, a long-term antibiotic therapy, administration of anti-asthmatic inhalants, digestive diseases and disorders. Patients with hyper IgE syndrome may develop abnormal absorption from the digestive tract. The diagnosis also included eosinophilic gastroenteritis, hypersensitivity to food allergens and gastrointestinal infections, i.e., chronic candidiasis. Other authors also reported episodes of chronic diarrhea [25], gastrointestinal bleeding [26], and dysphagia caused by diverticula and esophageal stenosis [27]. A harmful effect is also due to a long-term antibiotic treatment, which, by acting on the intestinal bacterial flora, may inhibit vitamin synthesis. All those factors contribute to persistent fungal infections and induce manifestations typical of iron or vitamin deficiencies, e.g., paleness of the oral mucosa, atrophy of the lingual papillae, tongue fissures and slits, and angular cheilitis [28-30]. An unfavourable effect on the oral mucosa and dental tissue is also produced by a steroid anti-asthmatic agent used by a patient with bronchial asthma. Administration of steroid inhalants may be accompanied by e.g., irritation, hyperemia and thinning of the oral mucosa, submucosal petechiae, pruritus and oral pain, dysphagia. Those agents also contribute to fungal proliferation, and mechanical injuries [31].

It is considered that the phenotypic feature of AD HIES includes disorders in the eruption of permanent teeth and resorption of the deciduous teeth [2, 6, 8]. The STAT3 gene may also play a role in odontogenesis. As it is generally known, the process depends on a normal mutual relationship between the ectodermal oral epithelium and the mesenchymal tissue, controlled, at the molecular level, by a range of regulators coded by a multiplicity of genes. Odontogenic dental defects are usually caused by mutations in the genes coding the above regulators, i.e. signalling particles and transcription factors. They may occur as single defects, or in combination with defects in other tissues or organs, as one of the features of the genetic syndrome. Impaired epithelial development resulting from the STAT3 gene mutation may also play a role in the etiology of developmental dental defects. In our reported cases we noted enamel hypoplasia, an absent bud of a permanent tooth, abnormal eruption of permanent dentition, and delayed root resorption of deciduous teeth.

Results of our observation of the presence of persistent deciduous teeth and retained teeth are consistent with those reported by other authors. It has been found that, in 75% of patients over seven years of age, root resorption of deciduous teeth is abnormal [13, 14]. The researchers emphasize the fact that eruption of the permanent first and second molar teeth occurred at the appropriate age, which is indicative rather of a root resorption defect in the deciduous teeth, than of the tooth eruption process itself [13, 14].

Nevertheless, our assessment of a thirteen and a half-year old girl showed an inhibited eruption process of permanent second molar teeth and a premolar tooth despite an
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The manuscript has not been and will not be submitted to any other journal while it is under consideration by The Journal of Pediatrics.
There are any potential conflict of interest, real or perceived; this includes a description of the role of the study sponsor(s), if any, in: (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication because there are any sponsor(s).

The first draft of the manuscript wrote authors together and any honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

References