Oral Diseases (2008) 14, 73–81. doi:10.1111/j.1601-0825.2007.01363.x

http://www.blackwellmunksgaard.com

ORIGINAL ARTICLE

Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome

DL Domingo[1], AF Freeman[2], J Davis[3], JM Puck[3], W Tianxia[1], SM Holland[2], TC Hart[1]

[1]*National Institute of Dental and Craniofacial Research, Bethesda, MD, USA;* [2]*National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA;* [3]*National Human Genome Research Institute, Bethesda, MD, USA*

AIM: Hyperimmunoglobulin-E syndrome (HIES) is a primary immunodeficiency characterized by eczema, recurrent skin and lung infections with pneumatocoele formation, and extremely elevated serum immunoglobulin-E. The precise immunologic defect and genetic etiology remain unknown. Non-immunologic findings include characteristic facial features (prominent forehead, fleshy nasal tip, and increased interalar distance); skeletal involvement (pathological fractures, scoliosis, and craniosynostosis); and retention of primary teeth. This study aims to characterize intraoral soft tissue findings in HIES patients.

METHODS: Sixty HIES patients (4–54 years, 27 males, 33 females) received intraoral and radiographic evaluations. Chronological dental development was also assessed.

RESULTS: Lesions of the hard palate and dorsal tongue were found in 55% and 60% of patients, respectively. Palatal lesions ranged from a generalized surface keratosis to a midline sagittal fibrotic bridge. Tongue lesions consisted of multiple fissures and a midline cleft. On the lip and buccal mucosa, keratotic plaques and/or surface fissures were found in 8% and 23% of patients, respectively. Manifested in 76.7% of patients, the intraoral lesions were significantly more prevalent than the characteristic facial traits ($P = 0.0013$).

CONCLUSIONS: Alterations in oral mucosa and gingiva were present in the majority of HIES patients. These novel intraoral findings may facilitate the diagnosis of HIES.

Oral Diseases (2008) **14**, 73–81

Keywords: hyper-IgE; immunodeficiency; mucosa; gingiva; dentition

Correspondence: Demetrio L Domingo, DDS, MS, Clinical Research Core, National Institute of Dental and Craniofacial Research, National Institutes of Health, 10 Center Drive, Building 10, Room 1N-117 MSC 1191, Bethesda, MD 20892, USA. Tel: (301) 594 9726/ (301) 402 9877, Fax: (301) 402 9885, E-mail: ddomingo@mail.nih.gov
Received 20 October 2006; accepted 8 December 2006

Introduction

Hyperimmunoglobulin-E syndrome (HIES) is a rare primary immunodeficiency (incidence $< 1/10^6$) characterized by eczema, recurrent skin and lung infections with pneumatocoele formation, and extremely elevated serum immunoglobulin-E (usually > 2000 IU ml^{-1}) (Grimbacher *et al*, 2005). Both the precise immunologic defect and genetic etiology of HIES remain unknown, although most cases are sporadic or inherited in an autosomal dominant manner (AD-HIES) (Grimbacher *et al*, 1999a). Autosomal recessive inheritance has also been described (AR-HIES) (Grimbacher *et al*, 2005). Management of HIES is primarily directed at prevention and treatment of infections with long-term systemic antibiotics and antifungals, as well as topical therapy for eczema and drainage of abscesses. Although not generally indicated, case reports and series have described therapeutic benefits from intravenous immunoglobulins, cyclosporine, and other immunomodulators (Grimbacher *et al*, 2005).

Also known as Job's syndrome (Online Mendelian Inheritance in Man No. 147060 and No. 243700), HIES is now recognized as a multi-system disorder with both immunologic and non-immunologic features (Grimbacher *et al*, 1999b). With variations in frequency and severity, the clinical manifestations of HIES involve the immune system, skeletal tissue, connective tissue, and dentition. Characteristic facial features in HIES patients include prominent forehead, deep-set eyes, broad nasal bridge, fleshy nasal tip, and increased interalar distance (Grimbacher *et al*, 1999a). The facial skin appears coarse and exhibits prominent pores. Reported bone anomalies include recurrent pathologic fractures, scoliosis, craniosynostosis, and hyperextensibility of joints (Grimbacher *et al*, 2005). The AR-HIES variant, in addition to the classical immunologic findings, is characterized by severe recurrent viral infections (e.g., molluscum contagiosum, herpes zoster), autoimmunity, central nervous system involvement (e.g., hemiplegia, ischemic infarction, subarachnoid hemorrhages), the absence of pneumatoceles, the lack of scoliosis and

pathologic fractures, and high mortality (Renner *et al*, 2004).

Intraorally, aberrations of tooth eruption have been described. Prolonged retention of the primary teeth and delayed eruption of the underlying permanent teeth, due to mechanisms that remain undefined, have been reported (O'Connell *et al*, 2000). Oral candidiasis (pseudomembranous, erythematous, median rhomboid glossitis, and angular cheilitis) is a common finding. One study reported the presence of asymptomatic midline tongue defects in two affected siblings (O'Connell *et al*, 2000), indicating a possible developmental etiology. In addition, a high-arched and wide palate had been noted in some patients. Based on these earlier findings, a more comprehensive and systematic characterization of the oral cavity was warranted. This study aimed to further characterize the spectrum of intraoral phenotypes in HIES, which may aid in distinguishing the syndrome from similar, often confused conditions (e.g., severe atopic dermatitis, Wiskott-Aldrich syndrome, and Ommen syndrome) (Leung and Geha, 1988; Grimbacher *et al*, 2002).

Methods

Sixty patients with a diagnosis of an HIES (4–54 years, mean 44.25 years, 27 males, 33 females) were enrolled in an IRB-approved natural history protocol at the National Institute of Allergy and Infectious Disease, Bethesda, MD. A scoring system based on 19 clinical and laboratory criteria was developed to aid in the diagnosis of HIES (Grimbacher *et al*, 1999b). Findings such as IgE and eosinophil levels, respiratory infections and pneumatocele formation, eczema, candidiasis, scoliosis and fractures, primary teeth retention, and characteristic facies, were assigned a point value on the basis of their incidence in and specificity for HIES (Grimbacher *et al*, 1999b). Two HIES medical research team members assessed the presence of HIES facial features (i.e., prominent forehead with deep-set eyes, increased width of the nose, a full lower lip, and thickening of the nose and ears) and scored alar widths based on standard deviations from normal anthropometric measurements (Farkas *et al*, 2005). A cumulative score of 40 points or greater on HIES evaluation system was considered diagnostic of HIES. Most patients were from multiplex kindreds consistent with autosomal-dominant inheritance (AD-HIES). Patients who scored between 20 and 39 trait points but had relatives who scored over 40 points were considered to be highly suspicious of having HIES and were included in the study. Also evaluated were patients with pedigrees and clinical features consistent with the AR-HIES variant (Renner *et al*, 2004).

All patients received comprehensive intraoral and craniofacial examinations at the National Institute of Dental and Craniofacial Research Clinical Research Core dental clinic. Radiographic evaluations of teeth, gnathic bones and surrounding structures were conducted, using digital panoramic and lateral cephalometric radiographs (Planmeca PM 2002 CC Proline with Dimax2; Planmeca Oy, Helsinki, Finland). Additional intraoral radiographs including periapical, bitewing and occlusal views were taken as clinically indicated. Oral mucosal and gingival tissues were evaluated for irregularities and presence of lesions. Surface diameters and depth of lesions were measured, and significant findings were photographed. Symptomatic complaints involving oral structures were addressed. All patients had a positive history of intraoral candidiasis with the majority receiving systemic antifungals for prophylaxis (e.g., fluconazole, itraconazole).

Findings from dental charts and radiographic records of individual patients were compared to standardized age ranges for the exfoliation of primary teeth and eruption of permanent teeth (Woelfel, 1990). Patients older than 7 years, the age of onset for the transition phase between primary and permanent dentition (i.e., mixed dentition), were assessed for retention of primary teeth, as evidenced by delayed root resorption of primary teeth, retention of underlying permanent teeth, or creation of double rows of teeth where succedaneous teeth erupted adjacent to the primaries. In addition, chairside interviews were conducted to assess the timing of primary and permanent teeth eruption, exfoliation of primary teeth, and history of extractions of primary teeth. The presence of other dental anomalities (e.g., hypodontia, hyperdontia, taurodontism), based on clinical and radiographic findings, was also noted.

Results

Scores for HIES diagnosis ranged from 23 to 100 points (mean 67.62). Caucasians comprised the large majority of the group ($n = 38$), along with five African-Americans, six Hispanics and one Asian (Table 2). Forty-six patients (4–54 years, 21 males, 25 females) received trait scores of 40 points or greater (range 41–100, mean 72.91). Six patients (5–34 years, 2 males, 4 females) received less than 40 points (range 23–36, mean 29.83) but were members of HIES kindreds with relatives who scored above 40. Eight patients (three sets of siblings and one non-related patient, age 10–20 years, four males, four females) were diagnosed with AR-HIES based on pedigree analysis and clinical findings (i.e., atypical dermatitis, absence of pneumatoceles, and lack of scoliosis and pathologic fractures) (Renner *et al*, 2004).

As assessed by the HIES medical research team, characteristic facial features were found in 28 of the 60 patients (46.7%) (Figure 1). Among those aged 7 years or older ($n = 56$), 36 (64.3%) had clinical or radiographic findings of retained primary teeth (Figures 2 and 3) or otherwise reported a history of primary teeth retention. The number of retained teeth ranged from 2 to 20.

Irregularities of oral mucosal and gingival tissues were found in the hard palate, dorsal tongue, buccal mucosae and upper and lower lip mucosae. The following classification system was used for these intraoral lesions:

Hard palate

Anomalies of the hard palate either covered the entire palatal surface or were confined to the midline. The

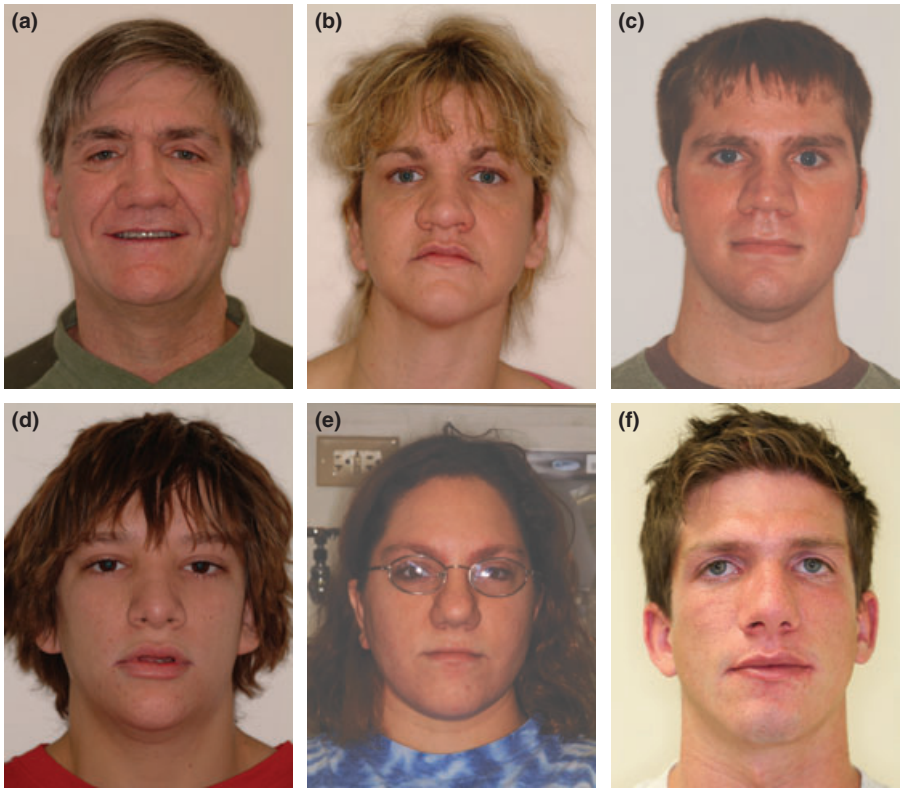

Figure 1 Characteristic facial features found in six unrelated HIES patients: prominent forehead, deep-set eyes, broad nasal bridge, and fleshy nasal tip. All six patients received the maximum scores for HIES facial features and alar widths

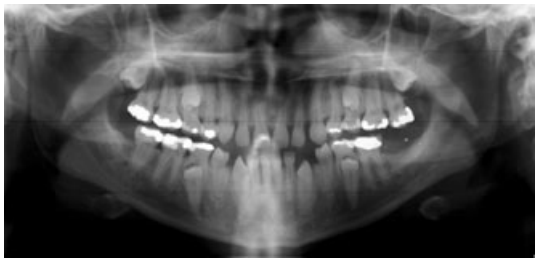

Figure 2 Twenty-five-year-old HIES patient with prolonged retention of the primary dentition and delayed eruption of permanent teeth

midline lesions consisted of a sagittal, linear, fibrotic bridge with varying surface morphologies. As no prior descriptions of these findings were found in the literature, the following classification system was formulated for these new palatal findings (Figure 4):

P1 The mildest palatal manifestation characterized by a generalized surface keratosis intersected by superficial fissures forming nonspecific patterns or a cobblestone configuration.
P2 A thin midline sagittal fibrotic thickening covering less than the entire length of the hard palate.
P3 A thicker linear fibrotic bridge, some surrounded by small papules, covering the entire length of the hard palate.
P4 The most severe palatal presentation consisting of a thick multilobular cylinder, sagittal and midline, with multiple surface papules and nodules, some surrounded by deep grooves and cavernous clefts around the junction of the hard palate and soft palate.

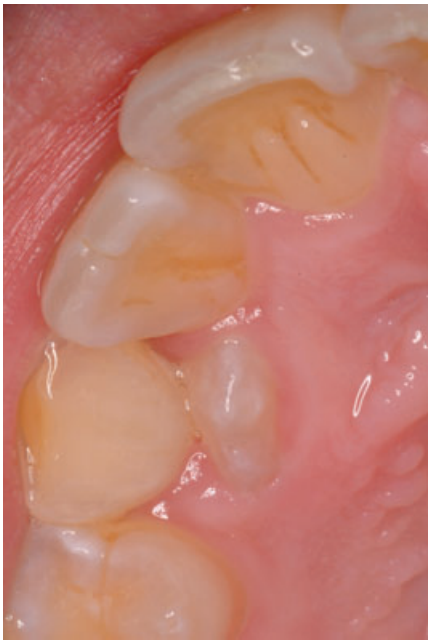

Figure 3 Twenty-three-year-old HIES patient with double rows of upper anterior teeth due to lack of root resorption in primary teeth and lingual eruption of permanent teeth

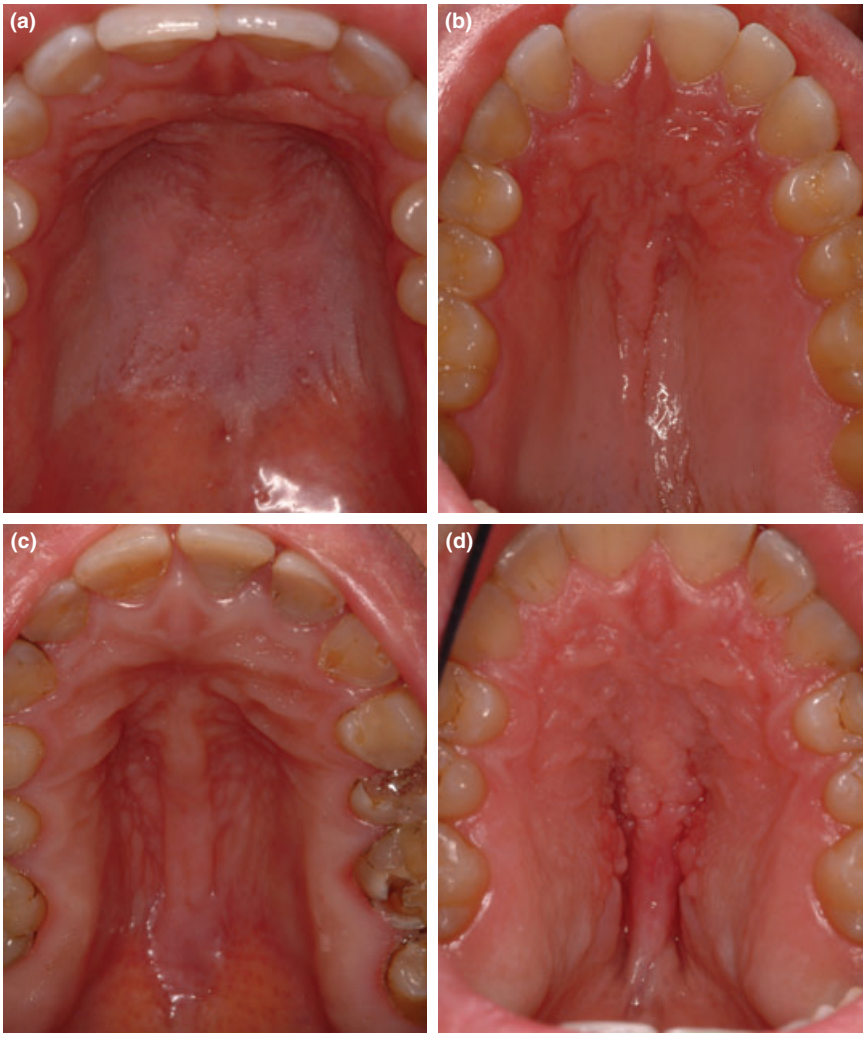

Figure 4 Significant findings in the hard palate. P1. Surface keratosis intersected by superficial fissures. P2. Midline sagittal fibrotic thickening covering less than the entire of the hard palate. P3. Midline sagittal linear fibrotic bridge covering entire length of the hard palate. P4. Midline sagittal irregular cylinder with surrounding papules, nodules and clefts

Tongue

Categories of tongue lesions were based on modified Farman's parameters of fissured tongue (Farman, 1976) and were sub-classified as follows (Figure 5):

T1 Superficial grooves (< 1 mm) distributed over less than one-third of the dorsal tongue surface.
T2 Deep grooves (> 1 mm) distributed over less than one-third of the dorsal tongue.
T3 Deep grooves (> 1 mm) distributed over more than one-third of the dorsal tongue.
T4 Very deep (> 2 mm) solitary midline pyramidal or ovoid cleft, with or without overlying tissue flap or fissures, located in the median raphe anterior to the circumvallate papillae.

Buccal mucosa (Figure 6)

BM1 Multiple, non-rubbable with a gauze pad, keratotic mucosal lesions; striated, patchy or plaque-like; with or without surrounding erythema or fissures; unilateral or bilateral.
BM2 Multiple mucosal fissures; shallow or deep; unilateral or bilateral.

Lip mucosa (Figure 7)

LM1 Multiple, non-rubbable with a gauze pad, keratotic mucosal lesions; striated, patchy or plaque-like; with or without surrounding erythema or fissures; on the upper and/or lower lip.
LM2 Multiple mucosal fissures; shallow or deep; on the upper and/or lower lip.

The majority of patients ($n = 46$, 76.7%) exhibited at least one lesion of the oral mucosa or gingiva (Table 1). All intraoral soft tissue lesions were asymptomatic, with the majority of patients being unaware of their presence.

Table 2 summarizes the distribution of oral lesions found in this patient group. Lesions of the hard palate and dorsal tongue – prevalences of 55% and 60%, respectively – were observed in over half of the patients. Lesions of the buccal mucosae were found in 23% of patients, with keratotic lesions occurring slightly more

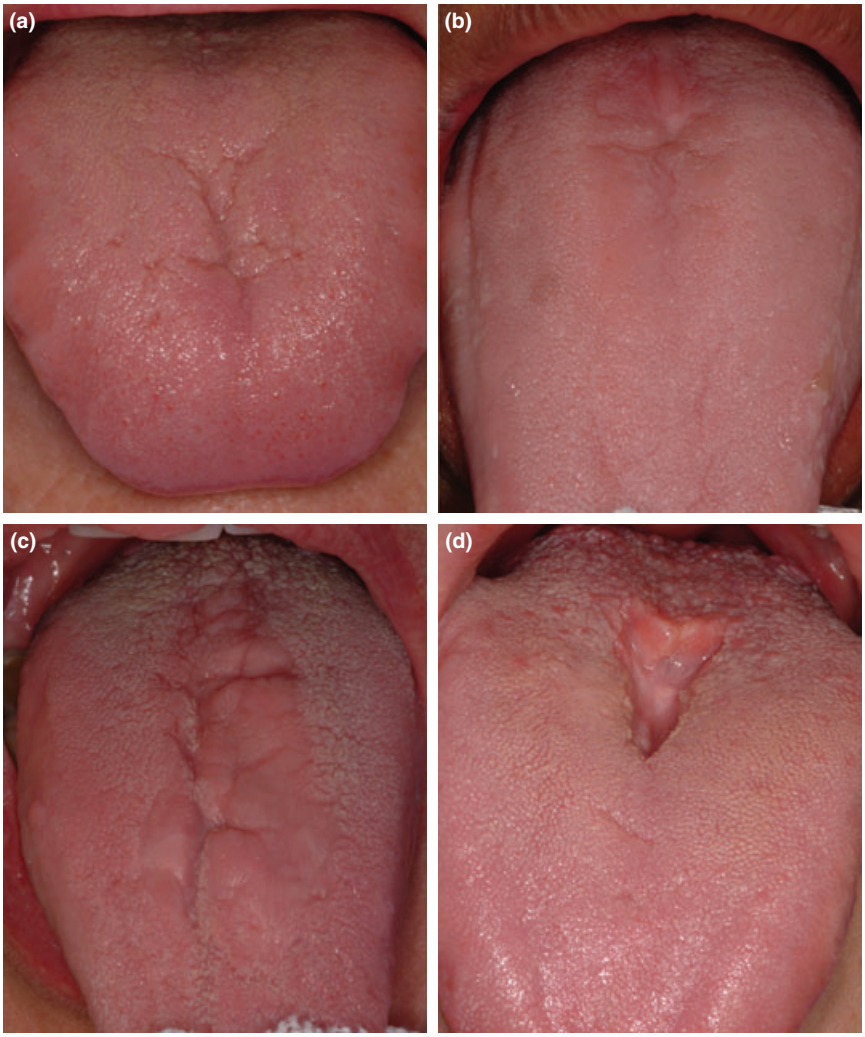

Figure 5 Significant findings on the tongue. T1. Superficial fissures (< 1 mm) distributed over less than one-third of the dorsal tongue. T2. Deep grooves (> 1 mm) distributed over less than one-third of the dorsal tongue. T3. Deep grooves (> 1 mm) distributed over more than one-third of dorsal tongue. T4. Very deep (> 2 mm) midline pyramidal or ovoid cleft with or without surrounding tissue flap or fissures

frequently than mucosal fissures. Involvement of the lip mucosae was found in 8% of patients. Of all the subcategories, localized superficial grooves of the dorsal tongue (T1) and a midline sagittal fibrotic thickening covering less than the entire length of the hard palate (P2) were the most common lesions (prevalence of 30% and 23%, respectively).

Fisher's exact test for the association between gender and the 12 subcategories of oral lesions showed no significant association (p values ranged from 0.223 to 1.00). Additional statistical calculations showed no significant association to age (two-sample t-test $p = 0.299$–0.973).

Among the individuals with AR-HIES ($n = 8$), six (75%) exhibited intraoral lesions and none exhibited the characteristic facial traits.

Comparisons between intraoral soft tissue lesions and other known HIES characteristics

The association of intraoral lesions with the following previously described features of HIES was assessed: (1) the characteristic facial features and (2) retention of primary teeth (Table 1).

A very high incidence of intraoral lesions was found in patients with characteristic HIES facial features ($n = 28$). Nearly all patients with HIES facies ($n = 26$, 93%) exhibited at least one oral lesion. Only two (a black male aged 24 years and a Caucasian male aged 35 years) were free of lesions in the mouth.

In the entire patient cohort ($n = 60$), intraoral lesions ($n = 46$) were found to be significantly more common than the characteristic HIES facies ($n = 28$) (Fisher's exact $p = 0.0013$). Similarly, in the AR-HIES group ($n = 8$), the distribution of oral lesions ($n = 6$) was significantly higher than that of characteristic facies ($n = 0$) (Fisher's exact $p = 0.0070$).

In patients presenting with retained primary teeth or a reported history of retained primary teeth ($n = 36$), 29 (80.6%) exhibited intraoral lesions. Statistical comparison of oral lesions (46 of 60) and retained primary teeth (36 of 56) found no significant difference in their distributions (Fisher's exact $p = 0.0767$).

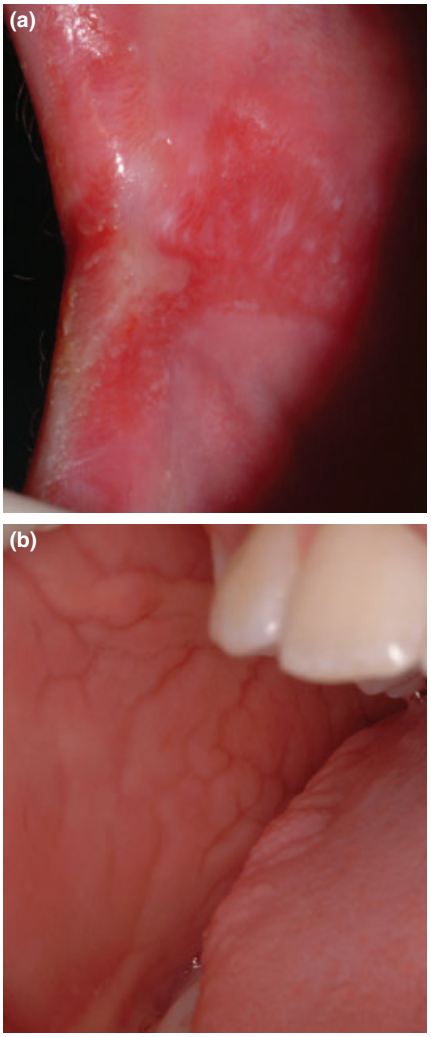

Figure 6 Lesions on the buccal mucosa. BM1. Multiple non-rubbable keratotic striations and/or plaques, with or without surrounding erythema and fissures. BM2. Multiple mucosal fissures

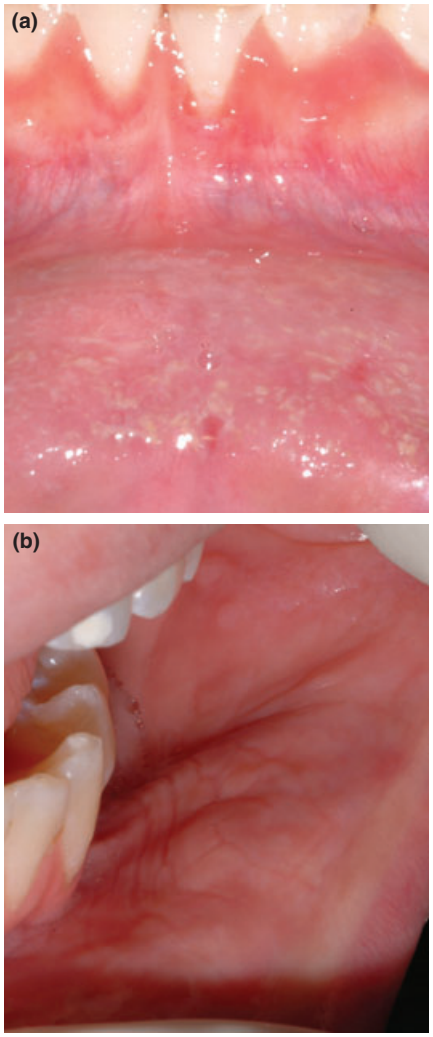

Figure 7 Lesions on the lip mucosa. LM1. Multiple non-rubbable keratotic striations and/or plaques, with or without surrounding erythema and fissures. LM2. Multiple mucosal fissures

One 19-year-old black female, in addition to having multiple unerupted succedaneous teeth and multiple retained primary teeth, exhibited supernumerary teeth (numbered 16s, 21s, 28s).

Discussion

Our findings demonstrate that intraoral soft tissue irregularities are prevalent in HIES and occur in greater frequencies than the characteristic HIES facial features. The distribution of these oral lesions was independent of age or gender. All intraoral lesions were asymptomatic and therefore required no palliative intervention. These lesions potentially represent (1) developmental abnormalities or (2) reactive lesions secondary to chronic infections associated with the syndrome. As extraoral soft tissue features are common in HIES, it seems plausible that these oral lesions are a manifestation of the effects of HIES on epithelial development. The high correlation (92%) of intraoral lesions and characteristic facial features suggests that these new oral findings are part of the clinical spectrum of HIES. That these oral lesions occur in significantly greater frequencies than the facial traits demonstrates their potential utility in the diagnosis of HIES, both in the AD-HIES and AR-HIES variants.

Prior studies have reported the difficulty of reliably determining HIES facial characteristics in patients younger than 7 years, with the features usually becoming evident by adolescence (O'Connell *et al*, 2000). In our study, all patients with observable facial features ($n = 28$) were older than 7 years (range 8–54 years), and of these 93% exhibited oral lesions. Intraoral lesions were also observed in 62.5% of patients without characteristic facies ($n = 32$, age 4–46 years). These findings suggest that these oral lesions may aid in the diagnosis of HIES, particularly in atypical patients and, in some cases, at an earlier age.

A lower correlation (80.6%) was calculated between oral lesions and retained primary teeth. However, we have observed that many parents were unaware of the

Table 1 Distribution of lesions on the oral mucosa and gingiva, retained primary teeth, and characteristic facies in HIES patients

Gender	*Age*	*Race*	*P1*	*P2*	*P3*	*P4*	*BM1*	*BM2*	*T1*	*T2*	*T3*	*T4*	*L1*	*L2*	*R P T*	*J F*
F	45	Afr				Y										Y
M	12	Hisp		Y			Y				Y		Y			Y
M	54	Cauc				Y								Y	Y (20)	Y
F	22	Cauc		Y					Y						Y	Y
F	38 years 3 months	Cauc		Y			Y						Y		Y	Y
M	21	Cauc				Y		Y		Y					Y	Y
M	19	Cauc	Y					Y							Y(>10)	Y
F	21 years 9 months	Cauc										Y			Y (2)	Y
M	46	Afr														
M	28 years 11 months	Cauc													Y	
F	35 years 11 months	Cauc		Y						Y					Y	Y
M[b]	20 years 2 months	Hisp							Y						Y	
M[b]	12 years 6 months	Hisp	Y					Y			Y				Y	
F[b]	15	Hisp							Y						Y	
M	15	Hisp				Y									Y (4–5)	Y
F	26 years 3 months	Cauc							Y						Y	Y
M	24 years 10 months	Afr													Y	Y
M[c]	13	Cauc							Y							
F	7 years 7 months	Cauc	Y							Y					Y (4)	
M[a]	7 years 7 months	Cauc														
M	8 years 11 months	Cauc														
F[a]	33 years 4 months	Cauc		Y					Y							
F[b]	10 years 2 months	Cauc		Y				Y			Y			Y		
F[b]	16 years 11 months	Cauc		Y				Y			Y			Y		
M	46 years 11 months	Asn		Y					Y	Y						Y
F	27 years 4 months	Cauc								Y						Y
F	25 years 8 months	Hisp	Y				Y					Y			Y (4)	
M	42	Cauc			Y		Y			Y						Y
F	19	Cauc		Y												
F	51	Cauc				Y	Y				Y					Y
F	26	Cauc			Y					Y						
F[a]	12 years 3 months	Cauc	Y												Y (2)	Y
F	8 years 7 months	Cauc			Y										Y (2)	Y
M	14 years	Cauc			Y							Y			Y (9)	Y
M	35 years 9 months	Cauc													Y (2)	Y
M	8 years 6 months	Cauc		Y						Y						
F	36	Cauc		Y											Y	Y
F[a]	34	Cauc														
F	37 years 8 months	Cauc					Y				Y				Y(>4)	Y
M	22	Cauc	Y												Y (2)	Y
F	6 years 11 months	Cauc														
F	30 years 6 months	Cauc					Y	Y	Y						Y	
F[a]	11 years 4 months	Cauc													Y	
M	50	Cauc				Y			Y						Y (20)	Y
M[a]	5	Cauc														
F[b]	10 years 7 months	Cauc													Y	
M[b]	12	Cauc													Y (4)	
M	46	Cauc							Y							
M	8 years 6 months	Cauc							Y						Y (4)	
F	21	Cauc	Y				Y		Y						Y(>10)	Y
F	35 years 10 months	Cauc			Y				Y						Y (20)	
F	5 years 1 month	Cauc							Y							
M	4 years 5 months	Cauc														
M	13 years 7 months	Cauc		Y											Y(>10)	Y
F	7 years 6 months	Cauc		Y					Y						Y (3)	
F	19 years 7 months	Cauc		Y					Y						Y	Y
F	10 years 8 months	Cauc							Y							
M	11	Cauc							Y							
F	30 years 7 months	Cauc			Y							Y			Y (20)	Y
F	7 years 10 months	Cauc													Y	

F, female; M, male; Afr, African-American; Hisp, Hispanic; Cauc, Caucasian; Asn, Asian; Y, positive finding; P, palate; BM, buccal mucosa; T, tongue; LM, lip mucosa; RPT, retained primary teeth (numbers in parentheses indicate known quantities); JF, characteristic Job's facies.
[a]Patients with less than 40 HIES points but had a relative who scored over 40.
[b]Sibling groups with AR-HIES.
[c]Sporadic case with atypical features and possible AR-HIES.

Table 2 Summary of findings in the oral mucosa and gingiva

Intraoral soft tissue findings ($n = 60$)	*n*	*%*
Hard palate	33	55
P1	07	11.7
P2	14	23
P3	06	10
P4	06	10
Dorsal tongue	36	60
T1	18	30
T2	08	13
T3	06	10
T4	04	6.7
Buccal mucosae	14	23.3
BM1	08	13
BM2	06	10
Lip mucosae	05	8.3
LM1	02	3.3
LM2	03	5

chronology of primary teeth eruption and timely onset of mixed dentition, and it was not uncommon for patients or parents to have had no awareness of delayed dental development. Therefore, the finding of 65% of patients older than 7 years with retained primary teeth and/or prior extractions to allow eruption of underlying permanent teeth may be an underestimation. If true, the association between intraoral lesions and primary teeth retention may indeed be greater. One causative factor for delayed eruption – the abnormal persistence of Hertwig's epithelial root sheath in primary teeth – has been suggested (O'Connell *et al*, 2000); however, the actual mechanisms need to be confirmed in future studies. The difficulty in accurately ascertaining retention of primary teeth further demonstrates the potential utility of oral lesions in characterizing the syndrome.

Midline developmental defects such as vertebral body malformation, thymus gland pathology and increased nasal width have been reported as parts of the HIES phenotype spectrum (O'Connell *et al*, 2000; Grimbacher *et al*, 2005). Skeletal abnormalities with osteopenia and fractures from minimal trauma, especially of the ribs and long bones, are also known features of the disease. The midline sagittal linear thickenings of the hard palate (P2, P3, P4) found in the majority of our study group may be part of the spectrum of these HIES midline anomalies. In the most dramatic manifestation (P4), involvement of the underlying palatal bone is possible and may suggest abnormal palatal bone formation. In addition, these palatal lesions may be part of a reactive spectrum to recurrent oral infections experienced in HIES.

In the tongue, the most significant soft tissue lesion was the deep midline cleft anterior to the circumvallate papillae. These lesions were found in four unrelated patients (Table 1). These clefts were located in the segment of the tongue with poor vascular supply and low resistance to infection, an area predisposed to the development of median rhomboid glossitis (O'Connell *et al*, 2000). Hence, it is feasible that these midline tongue clefts resulted from recurrent surface alterations and deep secondary scarring due to compromised inflammatory responses. However, none of the patients reported a history of pain, sensitivity or bleeding in the area, features often expected of lesions of this magnitude. In addition, all four patients reported having had these tongue clefts their entire lives. It is therefore possible that these represent a developmental defect that resulted from failure of fusion of the lateral segments of the tongue.

Epidemiological studies have shown considerable variations in the prevalence of dorsal tongue fissures between ethnic populations, with reported incidences ranging from 0.6% to 30.6% (Yarom *et al*, 2004; Rioboo-Crespo *et al*, 2005). A review of the literature also indicated an absence of standard protocols and variations in the methodologies used to assess tongue fissures, possibly contributing to the wide variations in the prevalences reported among studies (Rioboo-Crespo *et al*, 2005). Our study utilized the modified Farman's parameters of fissured tongue and statistically investigated the data. Forty-eight percent (27 of 56) exhibited dorsal tongue fissures of varying severities (T1, T2, and T3). Of these, the superficial grooves distributed over less than one-third of the dorsal tongue (T1) were the most common finding (18 of 31; 30%). Prior studies have indicated a genetic basis for fissured tongue (Rioboo-Crespo *et al*, 2005); one cross-sectional study of Brazilian children reported a threefold increase in the prevalence in children with a history of allergy and a higher frequency in children with extra-oral anomalies (e.g., encephalopathy, cardiac deformities, and urologic defects), suggesting that genetic anomalies could increase a child's susceptibility to fissured tongue (Bessa *et al*, 2004).

In the mucosa of the lips and cheeks, keratotic lesions with radiating striations resembling lichenoid formations were observed. The inability to rub off both the striated and plaque-like keratotic lesions ruled out pseudomembranous candidiasis. In fact, their clinical presentation is suggestive of a proliferative healing process from recurrent mucosal infections. Future histopathological evaluations are warranted to define the microscopic features, and subsequent biopsies may be indicated for lesions exhibiting clinical transformation.

Summary

The intraoral findings of this study expand the clinical characteristics of HIES. Combined with the soft tissue features noted extraorally, these oral findings further demonstrate the effects of this multi-system disorder on normal epithelial development. Variances in the prevalence and severity of these oral findings may reflect the underlying heterogenous genetic basis of HIES. Therefore, until the underlying genes responsible for the condition are identified, genotype–phenotype correlations remain to be elucidated. Although their histologic properties have yet to be defined, these intraoral lesions represent novel findings that further elucidate the clinical spectrum of HIES. The presence of one or more intraoral lesions in

76.7% of cases, and their significantly higher prevalence than the facial traits in both AD-HIES and AR-HIES, highlight their potential utility in the diagnosis of HIES. Future studies will include histologic and immunohistochemical examinations of representative tissues. Since panoramic and lateral cephalometric radiographs were insufficient in characterizing the palatal abnormalities, advanced imaging modalities such as cone-bean computed tomography and magnetic resonance imaging, by allowing visualization of underlying bone, muscle, and connective tissue, may provide greater detail on the extent of the palatal and tongue lesions. In addition to other known features of the syndrome, clinicians may utilize these new oral entities in the recognition of HIES.

Acknowledgement

This work was supported by the intramural program of NIDCR, NIH.

References

Bessa CFN, Santos PJB, Aguiar CF *et al* (2004). Prevalence of oral mucosal alterations in children from 0 to 12 years old. *J Oral Pathol Med* **33:** 17–22.

Farkas LG, Katic MJ, Forrest CR (2005). International anthropometric study of facial morphology in various ethnic groups/races. *J Craniofac Surg* **16:** 615–646.

Farman AG (1976). Tongue fissures: a classification and comparative prevalence study among 825 European Caucasian and 605 Xhosa Negro school children. *J Biol Buccale* **4:** 349–364.

Grimbacher B, Holland SM, Gallin JI *et al* (1999a). Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. *N Engl J Med* **340:** 692–702.

Grimbacher B, Schaffer AA, Holland SM *et al* (1999b). Genetic linkage of hyper-IgE syndrome to chromosome 4. *Am J Hum Genet* **65:** 735–744.

Grimbacher B, Belohradsky BH, Holland SM (2002). Immunoglobulin E in primary immunodeficiency diseases. *Allergy* **57:** 995–1007.

Grimbacher B, Holland SM, Puck JM (2005). Hyper-IgE syndromes. *Immunol Rev* **203:** 244–250.

Leung DYM, Geha RS (1988). Clinical and immunologic aspects of the hyperimmunoglobulin E syndrome. *Hematol Oncol Clin North Am* **2:** 81–100.

O'Connell AC, Puck JM, Grimbacher B *et al* (2000). Delayed eruption of permanent teeth in hyperimmunoglobulinemia E recurrent infection syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **89:** 177–185.

Renner ED, Puck JM, Holland SM *et al* (2004). Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* **144:** 93–99.

Rioboo-Crespo MR, Planells-del Pozo P, Rioboo-Garcia R (2005). Epidemiology of the most common oral mucosal diseases in children. *Med Oral Patol Oral Cir Bucal* **10:** 376–387.

Woelfel JB (1990). Terminology. *Dental Anatomy: Its Relevance to Dentistry*, 4th edn. Lea & Febiger: Philadelphia, PA, pp. 18–32.

Yarom N, Cantony U, Gorsky M (2004). Prevalence of fissured tongue, geographic tongue and median rhomboid glossitis among Israeli adults of different ethnic origins. *Dermatology* **209:** 88–94.