

MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

Hyper-IgE syndrome: dental implications

Luca Esposito, MD, DDS,^a Laura Poletti, DDS,^b Cinzia Maspero, MD, DDS,^a Alessandro Porro,^c Maria Cristina Pietrogrande, MD,^d Paola Pavesi, MD,^e Rosa Maria Dellepiane, MD,^e and Giampietro Farronato, MD, DDS,^f Milan, Italy
UNIVERSITY OF MILAN

Hyper-IgE syndrome (HIES) is a rare multisystem disorder with both immunologic and nonimmunologic features. It is characterized by extremely elevated IgE serum levels, eczema, and recurrent skin and pulmonary infections. Dental anomalies are often included, such as retention of deciduous teeth together with ectopic eruption or noneruption of permanent teeth. Severe susceptibility to caries and mycotic infections, insufficient transversal diameter of the palate, mucosal plaques, and fissures typically located on the tongue and on the palate are often present. The aim of this study was to review the literature and to report a 6-year observation of 6 patients with HIES (aged 8-39 years) with focus on their oral problems and the treatment provided. The importance of the role of the dentist both in early diagnosis of this syndrome and in monitoring oral conditions was stressed. The dentist can prevent infective complications and intercept the development of malocclusion with a reduction of the need for complex treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:147-153)

The hyper-IgE syndrome (HIES) is a rare form of immunodeficiency that was first observed by Davis et al.¹ in 1966. They reported 2 sisters showing serious eczema, sinopulmonary infections, and *Staphylococcus aureus*-related cold abscesses (characterized by slow development and little inflammation). They called it Job's syndrome, because the pain and the sores reminded them of that biblical character (Job 2:7). In 1972, Buckley et al.² described a similar case history in 2 boys with elevated immunoglobulin E (IgE) levels and called it Buckley's syndrome. The detection of high IgE level and neutrophil chemotaxis deficit in all 4 patients revealed the existence of a syndrome, renamed hyper-IgE syndrome.³ HIES is now recognized as a multisystemic disorder with both immunologic and

nonimmunologic features. It is characterized by the clinical triad of high serum levels of IgE (>2000 IU/mL), eczema, and recurrent staphylococcal skin and lung infections. Osteopenia, minimal trauma fractures, scoliosis, central nervous system abnormalities, arterial aneurysms, characteristic facial appearance, and dental anomalies, such as retention of primary dentition and alterations of oral mucosa and gingiva are common features.⁴ The dental clinical history of 6 patients with HIES is reported as they consulted the Paediatric and Orthodontic Departments at the IRCCS Cà Granda Policlinical Hospital (University of Milan) from January 2004 to December 2010.

ETIOLOGY AND PATHOGENESIS

HIES is a rare syndrome (incidence <10⁻⁶), with no difference for gender and race.^{5,6} Although it was first identified in 2 girls with red hair, this is not a common finding.⁷ HIES is a genetic disease, as recent studies have confirmed. Two autosomal forms have been described: a dominant one (AD-HIES) and a recessive one (AR-HIES).

The pathophysiology of the disease has not been completely understood; however, the clinical phenotype of HIES is one of both excessive and inadequate inflammation. Missense or in-frame deletions in the SH2 and DNA binding domains in the STAT3 gene (Signal Transducer and Activator of Transcription 3) were identified as the etiology for most AD-HIES. The STAT3 gene is a downstream effector of the T helper 17 (Th17)-inductive cytokines, including interleukin (IL)-6, IL-12, and IL-23, and is essential for differentiation of Th17 cells, which are important in eliminat-

^aAssistant Professor, Department of Orthodontics, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

^bPostgraduate Resident, Department of Orthodontics, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

^cUndergraduate Resident, Department of Orthodontics, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

^dProfessor, U.O.C. Pediatria II, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

^eAssistant Professor, U.O.C. Pediatria II, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

^fProfessor, Department of Orthodontics, IRCCS Cà Granda - Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

Received for publication Jul 28, 2011; returned for revision Mar 7, 2012; accepted for publication Apr 5, 2012.

© 2012 Mosby, Inc. All rights reserved.

2212-4403/\$ - see front matter

<http://dx.doi.org/10.1016/j.oooo.2012.04.005>

ing extracellular fungi and bacteria through the production of cytokines, such as IL-17 and IL-22. The mutation could trigger poor activation of the Th17 cells and subsequent defective inflammatory reaction against the pathogens.^{8,9} The AR-HIES form (which shows partly different clinical features) is probably ascribable to either a mutation of the TYK2 gene (Tyrosine Kinase 2), or the DOCK8 gene (Dedicator of Cytokinesis 8). Combined B- and T-cell immunodeficiency is reported in DOCK8 mutations, whereas impaired Th17 function, owing to the defective signal transduction for multiple cytokines, is associated with TYK2 deficiency.¹⁰ There are still several patients with the HIES phenotype in which the underlying defect is unknown, however.

CLINICAL AND IMMUNOLOGIC FEATURES OF THE DISEASE

HIES is characterized by a triad of eczema, recurrent skin and lung infections, and excessively elevated serum IgE levels. The HIES carriers show a very pruriginous eczematous dermatitis from birth, frequently associated with skin lichenification. *Staphylococcus aureus* often superinfects the lesions. It may reach subcutis and the nearby lymph nodes and develop cold abscesses, which may require surgical drainage and parenteral antibiotic treatment. Recurrent infections of the upper and lower respiratory tract may be manifest from a very early age. *Staphylococcus aureus* and *Haemophilus influenzae* are the most common pathogens of acute pneumonia. If a proper therapy is not promptly administered, it may worsen to pneumatocele and develop chronic bronchopathy with bronchiectasis. Patients with HIES are especially prone to chronic mycological infections. The classic targets are the mucous membrane of the oral cavity and the nails, but deep-seated infections could also occur. Autoimmune disorders and tumors seem more frequent than usual. High levels of serum IgE (as high as 100,000 IU/mL) are a standard feature. Neutrophilic chemotaxis deficit may account for recurrent infections. Immunologic research is focused on the balance between Th1/Th2, because a prevalent Th2 response or a weak Th1 response could be responsible for increased production of IL-4, IL-10, and IL-13, which induce a greater production of IgEs. A minor interferon- γ presence could pave the way for *Staphylococcus aureus* and *Candida albicans* infections.^{5,6}

The AD- and AR-HIES forms share these common features, but they differ in many others. AD-HIES is now recognized as a multisystem disorder with various connective tissue, skeletal, and vascular abnormalities. The clinical phenotype of HIES is overall similar between DNA binding and SH2 domain mutations in STAT3.¹¹ Patients with AD-HIES have a typical facies,

with bulging forehead, deep-set eyes, prominent and broad nose, swollen lower lip, and thick nasal and auricular skin. Osteoarticular damage may be present in the form of osteoporosis, with spontaneous fractures, scoliosis, articular hyperextensions, and cranial synostosis. Oral anomalies with failure of deciduous teeth exfoliation are common. Dilatation of the coronary artery, aneurysms, and convolutions are common in adults with AD-HIES, but are usually asymptomatic. Many of these characteristic findings accumulate with age. As compared with the AD-HIES form, the AR form (first reported by Renner et al. in 2004¹²) lacks the somatic features, such as the typical facies, scoliosis, and dental alterations. Patients with AD-HIES often have a much higher rate of cutaneous viral infections such as *Molluscum contagiosum*, *Herpes simplex*, and *Varicella*, and although pneumonias occur, pneumatoceles do not form. Moreover, they have frequent neurological complications, ranging from facial paralysis to hemiplegia, which are often fatal in childhood.^{6,13,14}

DENTAL IMPLICATIONS

In 1999, an extensive survey by Grimbacher et al.¹⁵ revealed that 72% of patients with HIES who were older than 8 years showed retention of the deciduous teeth, noneruption of the permanent teeth, or double dentition (i.e., 1 row of deciduous teeth, 1 row of permanent teeth). The permanent teeth are usually radiographically visible and their development is age consistent. The HIES induces a delayed eruption, but it does not affect the development of the permanent dentition. The delayed eruption appears to be a result of nonexfoliation of the deciduous teeth and not because of delayed eruption of the permanent teeth. This may be because of a lack of stimulation of the resorption process of the deciduous roots. If the deciduous teeth are removed before the teenage years, however, the permanent teeth grow properly.¹⁶ Retention of deciduous teeth can be seen only among the patients with AD-HIES. Among patients with AR-HIES, the tooth-eruption pattern and timing occur normally; their only oral anomaly is an unusual rate of severe cavities. As a result, they often need premature extractions. A double row of teeth prevents proper oral hygiene and favors gingivitis and dental decay. Patients with HIES show alteration in facial growth. They have a peculiar facies, easily spotted at 16 years. Grimbacher et al.'s research revealed a high, arched palate in 71% of the subjects, a cleft lip and palate in 1 patient, and midline sagittal clefts in the middle third of the tongue in 2 patients.¹⁵ Oral superinfections of the mucous membrane (usually mycotic) result in lesions, erythema, and atrophy.⁴

Table 1. The scoring system by Grimbacher et al.¹⁷ used to screen HIES in our 6 patients

<i>Clinical findings</i>	<i>Points</i>									
	<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>10</i>
Highest serum immunoglobulin E level (IU/mL)	<200	200–500			501–1000				1001–2000	>2000
Skin abscesses	None		1–2		3–4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10°		10–14°		15–20°				>20°	
Fractures with minor trauma	None				1–2				>2	
Highest eosinophil count (cells/ μ L)	<700			>700–800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1–2	3	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width	<1 SD	1–2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 y			2–5 y		1–2 y		$\leq$ 1y		

<15 points: patient not affected; 15 to 39 points: possible diagnosis; 40 to 59 points: probable diagnosis; $\geq$ 60 points definitive diagnosis.

DIAGNOSIS

The diagnosis of HIES is difficult because there are no simple laboratory tests that confirm the disease. In 1999, Grimbacher et al.^{15,17} examined 30 patients with HIES and 70 of their relatives from all over the world. From this analysis, he developed a useful scoring system and a point scale to spot the suspect sufferers based on clinical and laboratory findings (NIH-HIES). Inversely age-dependent points were assigned to individuals younger than 5 years to avoid false-negative scores in children. In fact, some of the clinical findings, such as scoliosis, the characteristic facies, and retained primary teeth, cannot be ascertained in children younger than 8 years and may first appear during adolescence (Table I). In 2010, the analysis of 100 unrelated patients with suspected HIES led to the development of a new scoring system based on 17 of the features used in the original scoring method, the recently reported laboratory feature of a very low Th17 CD4⁺ cell count, and the genetic diagnosis.⁸

TREATMENT

Treatment is based on prophylactic antimicrobials (antibiotics to prevent pneumonia and cutaneous abscesses, antifungals to prevent mucocutaneous candidiasis) and topical therapies (e.g., bleach baths) for eczema. Immunomodulatory agents have been used with varying success. Intravenous immunoglobulin has led to anecdotal improvement in some individuals. Bone marrow transplantation has been performed but it is likely not to be fully corrective.¹³

In our survey, we report on 6 patients affected by HIES who were diagnosed at the Paediatric Department at the IRCCS Cà Granda Policlinical Hospital (University of Milan). We describe the clinical features of these patients with emphasis on the oral implications and the treatment provided.

SURVEY DESCRIPTION

We followed 6 patients (3 males and 3 females). The average age at the first examination was 9.3 years (range 1-25 years). The age at which HIES was diagnosed was 2 to 12 years. The follow-up was on the average of 15 years (range 4-22 years). At the last examination, the average age was 23.3 years (range 9-39 years). Every patient was thoroughly and repeatedly examined and has undergone immunologic and genetic tests (the latter at the Royal Free Hospital's Department of Immunology in London). The oral evaluation was carried out in the orthodontic department of the Dental Clinic at the University of Milan from January 2004 to December 2010. The preliminary research included

1. intraoral examination

Table II. Main features of the 6 cases

<i>Patients</i>	<i>Case 1</i>	<i>Case 2</i>	<i>Case 3</i>	<i>Case 4</i>	<i>Case 5</i>	<i>Case 6</i>
IgE >2000 UI/mL	+	+	+	+	+	+
Eosinophilia	+	+	+	+	+	+
Skin abscesses	+	+	+	+	+	–
Recurrent respiratory infections	+	+	+	+	+	+
Pneumatoceles	+	+	–	+	+	–
Eczema	+	+	+	+	+	+
Mucocutaneous candidiasis	+	+	+	+	+	–
Retained primary teeth	+	+	+	+	+	+
Typical facies	+	+	+	+	+	+
STAT3 mutation	+	+	+	+	+	ND
Age, y	39	12	8	25	16	9
NIH-HIES score	68	58	63	76	65	32

HIES, Hyper-IgE Syndrome; *Ig*, immunoglobulin; *ND*, not determined; *STAT3*, Signal Transducer and Activator of Transcription 3; *NIH*, National Institutes of Health; +, presence of the feature; –, absence of the feature.

2. panoramic film, lateral and frontal cephalometric tracings
3. periodontal examination (plaque index, bleeding index, decayed/missing/filled teeth)
4. photographic recording

The orthodontic department provided the patients with HIES with long-term medical care to monitor their dentofacial growth and development and to provide early treatment of their complications. Therefore, we established the following:

1. follow-up of oral hygiene and gum conditions
2. monitoring and treatment of the cavities
3. extraction of the deciduous teeth at the correct time of exfoliation
4. treatment of oral mucous membrane superinfections with antimycotic-antibiotic drugs
5. orthodontic/orthopedic treatment (if necessary)

RESULTS AND DISCUSSION

The main clinical, immunologic, and genetic features of the 6 patients are reported in Table II. Peripheral eosinophilia was always evident, and the IgE levels ranged from 9.3 to 90.7 IU/mL. All the patients had a typical coarse-featured face, which was more pronounced according to the age (Figure 1). They had all been affected since age 1 year by eczema, in some cases severe and cure resistant (Figure 2). All patients were also affected by recurrent respiratory diseases, and 4 of them developed pneumatoceles. Five of them developed typical cutaneous cold abscesses, both superficial and deep. STAT3 mutation was present in 5 patients: we are still testing the sixth case. Four of 6



Fig. 1. The typical HIES facies of our 6 cases.



Fig. 2. Chronic eczematous dermatitis in case 5.

sufferers scored more than 60 on the scoring system by Grimbacher et al.¹⁷ (Table I).

Many authors reported that oral implications in HIES include anomalies in the change from primary to permanent dentition and in facial skeletal growth, and a severe susceptibility to oral infections. Our survey confirms the delayed eruption of permanent teeth with primary predecessors as a feature of AD-

HIES. The correlation between dental age and chronologic age of the patients and the normal eruption time of teeth without predecessors (all the primary teeth and the permanent molars) suggests that this defect is because of a failure of primary teeth exfoliation and not to a delayed eruption of the permanent teeth (Figure 3). The retention of the deciduous teeth acts as a “mechanical barrier.” In fact, in 5 of 6 cases the extraction of many primary teeth was necessary to allow the eruption of the permanent teeth. The underlying mechanisms of this phenomenon remain to be confirmed. O’Connell et al.¹⁶ observed the persistence of Hertwig’s epithelial root sheath on the root of a primary tooth, suggesting its role in the protection of the root from physiological resorption. Grimbacher et al.¹⁵ suspected the delayed lysis of primary teeth to be a manifestation of the same defect that results in ineffective inflammatory responses and the formation of pneumatoceles, involving disorder in the activation of osteoclasts and/or macrophages by cytokines. Nevertheless, in 2 adult cases, numerous impacted permanent teeth were found, even if the extraction of the corresponding deciduous teeth was performed (probably not at the correct time). In these cases, we advised against



Fig. 3. Extracted deciduous tooth in case 3: to notice the length of the root.

the orthodontic extrusion of the impacted elements because of the high risk of infections and the severe enamel fragility and carioreceptivity. We preferred to perform a prosthetic rehabilitation with a removable dental prosthesis and we are still monitoring the impacted elements (Figure 4). Removal of retained primary teeth at the correct time of exfoliation is highly important, not only because it allows the normal eruption of permanent teeth, leading to a reduction in the need for complex orthodontic treatment later in life,¹⁸ but also because the presence of double rows, in which permanent teeth erupt lingual of the deciduous teeth, prevent effective oral hygiene. Five cases of 6 had several cavities and/or signs of gingival inflammation owing to insufficient dental hygiene, requiring oral medications, endodontic treatments, and extractions (Figure 5). Monitoring these patients and educating them on correct oral hygiene procedures is paramount to prevent severe dental infections. Vigliante et al.¹⁹ reported a life-threatening cervicofacial infection as a result of a dental abscess in a child with HIES. The immunologic disorder and the prolonged use of antibiotics make oral candidiasis (pseudomembranous, erythematous, median rhomboid glossitis, and angular cheilitis) a common disease among patients with HIES. In our survey, only Case 1 had antifungal-resistant erythematous candidiasis. A recent study associates HIES with defective salivary activity. Conti et al.²⁰ showed that patients with HIES exhibit reduced candidacidal activity in saliva, which correlates with reduced expression of certain antimicrobial proteins with antifungal activity, namely β -defensin-2 and histatins. Domingo et al.²¹ identified asymptomatic lesions of the oral mucosa and gingiva in more than 75% of patients, mainly palatal lesions (ranging from



Fig. 4. Oral features in case 1.



Fig. 5. Oral features in case 4.

a generalized surface keratosis to a midline sagittal fibrotic bridge) and tongue lesions (consisting of multiple fissures and a midline cleft). On the lip and buccal mucosa, keratotic plaques and/or surface fissures were less common. In contrast to Domingo et al.,²¹ in our 6-year observation of 6 patients with

HIES, we found nothing abnormal in mucosal aspect and texture.

The HIES facies was evident in all but 2 patients. In cases 3 and 6, the typical facial aspect was not clearly discernible because of their young age. These 2 patients, however, had a high narrow palate, which we treated by a rapid palatal expander to correct the transversal diameter deficiency. In 3 of 6 cases, we performed an orthopedic treatment with functional appliances to optimize the mandibular growth and the vertical dimension.²²

CONCLUSIONS

Our review and the cases presented emphasize the role of the dentist both in the diagnosis and in the treatment of this syndrome.

- The high variability of presentation of HIES makes it easy to confuse the diagnosis with that of severe atopy or other rare immunodeficiencies and thus delay diagnosis. The general practitioner who identifies multiple retained primary teeth along with a highly narrow palate, the typical facies, or many dubious findings in the medical history should refer the patient to an immunologic department and to an orthodontist.
- The orthodontist should recognize the syndromic “orofacial phenotype” of HIES and follow the patients during skeletal and dental development, executing the necessary extractions at the correct time to avoid further complex orthodontic treatment, especially in patients particularly susceptible to dental and mucosal infections.
- Moreover, it is of primary importance to check the patients regularly to motivate them to careful oral hygiene. All 6 patients with HIES of this survey reached eventually good oral conditions and were then involved in a dental follow-up program.

REFERENCES

1. Davis SD, Schaller J, Wedgwood RJ. Job's syndrome. Recurrent, “cold” staphylococcal abscesses. *Lancet* 1966;1:1013-5.
2. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infections. *Pediatrics* 1972;49:59-70.
3. Hill HR, Ochs HD, Quie PG, Clark RA, Pabst HF, Klebanoff SJ, Wedgwood RJ. Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent “cold” staphylococcal abscesses. *Lancet* 1974;2:617-9.
4. Freeman AF, Domingo DL, Holland SM. Hyper IgE (Job's) syndrome: a primary immune deficiency with oral manifestations. *Oral Dis* 2009;15:2-7.
5. Buckley RH. The hyper-IgE syndrome. *Clin Rev Allergy Immunol* 2001;20:139-54.
6. Erlewyn-Lajeunesse MD. Hyperimmunoglobulin-E syndrome

with recurrent infection: a review of current opinion and treatment. *Pediatr Allergy Immunol* 2000;11:133-41.

7. Borges WG, Hensley T, Carey JC, Petrak BA, Hill HR. The face of Job. *J Pediatr* 1998;133:303-5.
8. Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, Glocker EO, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol* 2010;125:424-32.
9. Minegishi Y, Saito M. Molecular mechanisms of the immunological abnormalities in hyper-IgE syndrome. *Ann N Y Acad Sci* 2011;1246:34-40.
10. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol* 2009;124:1289-302.
11. Heimall J, Davis J, Shaw PA, Hsu AP, Gu W, Welch P, et al. Paucity of genotype-phenotype correlations in STAT3 mutation positive Hyper IgE syndrome (HIES). *Clin Immunol* 2011;139:75-84.
12. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* 2004;144:93-9.
13. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. *Immunol Rev* 2005;203:244-50.
14. Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. *Pediatr Res* 2009;65:32-7.
15. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med* 1999;340:692-702.
16. O'Connell AC, Puck JM, Grimbacher B, Facchetti F, Majorana A, Gallin JI, et al. Delayed eruption of permanent teeth in hyperimmunoglobulinemia E recurrent infection syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;89:177-85.
17. Grimbacher B, Schäffer AA, Holland SM, Davis J, Gallin JI, Malech HL, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. *Am J Hum Genet* 1999;65:735-44.
18. McAuliffe NJ, Hunter ML, Kau CH, Hunter B, Knox J. The dental management of a patient with hyperimmunoglobulinemia E syndrome: a case report. *Int J Paediatr Dent* 2005;15:127-30.
19. Vigliante CE, Costello BJ, Quinn PD. Life-threatening cervicofacial infection in a child with hyperimmunoglobulin-E syndrome. *J Oral Maxillofac Surg* 2001;59:561-5.
20. Conti HR, Baker O, Freeman AF, Jang WS, Holland SM, Li RA, et al. New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome. *Mucosal Immunol* 2011;4:448-55.
21. Domingo DL, Freeman AF, Davis J, Puck JM, Tianxia W, Holland SM, Hart TC. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. *Oral Dis* 2008;14:73-81.
22. Tecco S, Farronato G, Salini V, Di Meo S, Filippi MR, Festa F, D'Attilio M. Evaluation of cervical spine posture after functional therapy with FR-2: a longitudinal study. *Cranio* 2005;23:53-66.

Reprint requests:

Giampietro Farronato, MD, DDS
 Department of Orthodontics
 Fondazione IRCCS Cà Granda
 Ospedale Maggiore Policlinico
 University of Milan
 Via Commenda 10
 20122 Milan, Italy
 farronato@unimi.it