Tooth eruption, epithelial root sheath and craniofacial profile in hyper-IgE syndrome: report of two cases

K.B. BECKTOR, I. KJÆR, C. KOCH

Summary. Patients with hyper-IgE syndrome (Job Syndrome) have elevated serum IgE values and a characteristic face. Problems with retention of primary teeth have been reported, and these may be associated with the persistence of Hertwig’s epithelial root sheath. Aim. The purpose of the present study was to analyse the dentition and the craniofacial morphology of two adolescent patients (one female, one male) with hyper-IgE syndrome. Methods. Radiographs of the dentition and the craniofacial profile were analysed. Histochemical analysis using cytokeratin KWS was conducted on sections from primary molars extracted from both patients. Results. The case reports demonstrated a persistence of an epithelial root sheath on the primary molars and retention of the primary dentition. Furthermore, the craniofacial profile was shown to have normal values in both patients.

Key words. IgE level, Tooth eruption, Epithelial root sheath, Craniofacial profile.

Introduction

Hyper-IgE syndrome is a rare congenital disorder associated with extremely high serum IgE levels, which may exceed values of 40,000 IU/mL (normal value: < 150 IU/mL). The condition is characterised by recurrent staphylococcal skin infections, pneumonia which frequently leads to pneumatocele formation [Davis et al., 1966; Donbedian and Gallin, 1983]. Other features not directly attributable to the immune system include frequent bone fractures and a characteristic coarse facies [Grimbacher et al., 1999]. The characteristics of the facial appearance are prominent brows and supraorbital ridges giving the impression of deep-set eyes. Additional anthropomorphic measurements have shown that the nose is wide at the alar base and the nasal tip is broad [Borges et al., 1998]. Most studies have focused on the immunological aspects and a highly characteristic feature is the abnormal production of specific IgE antibodies to common bacterial organisms such as S. aureus, but a range of other abnormalities involving leukocyte migration, T-lymphocyte subsets, antibody production and cytokine production have been detected. However, no specific common defect has been found [Geha and Leung, 1993]. In a recent publication [Grimbacher et al., 1999] the hyper-IgE recurrent infection syndrome was described as a multisystem disorder, with immunological abnormalities, including a variable expression of dental, skeletal and facial deviations. In this study, delayed shedding of primary teeth was described among 30 patients with hyper IgE syndrome. Delayed eruption occurred in 72 percent of the patients who were old enough to be evaluated. This failure has been further investigated recently [O’Connell et al., 2000]. As the primary teeth and permanent molars erupted normally, but the permanent incisors, canines and premolars erupted late, the conclusion was that impaired root resorption of primary teeth, rather than defective eruption, caused the abnormalities. Persistence of an epithelial root sheath was found to be unusual in hyper-IgE syndrome [O’Connell et al., 2000]. Thus the hypothesis was put forward that delayed resorption of the roots of primary teeth in the hyper-IgE syndrome may be a manifestation of
changes in the epithelial layer covering the cementum.

The purpose of the present study was to investigate the dentition radiographically and histologically, focussing on the presence of an epithelial root sheath in two subjects with hyper-IgE syndrome. In view of the fact that a characteristic coarse facies has been associated with hyper-IgE syndrome, a further purpose was to describe the craniofacial morphology. No previous quantitative analyses of craniofacial morphology were found in the scientific literature.

Case reports
Two patients with classical hyper-IgE syndrome were referred to the Copenhagen School of Dentistry for dental and craniofacial examination. Both patients had been surveyed and treated at the National University Hospital (Rigshospitalet) from time of diagnosis in early childhood. Both were on long-term prophylactic antibacterial chemotherapy primarily aimed as protection against S. aureus, but antimicrobial chemotherapy was regularly adjusted according to clinical and microbiological findings. Both patients were on continuous treatment with a combination of Histamine (H₁ and H₂) antagonists. Major clinical, paraclinical, and microbiological findings are given in Table 1.

Dental and cranial radiographs from the two patients were obtained from the dental clinics where they received dental and orthodontic care, and from the Department of Orthodontics, School of Dentistry, and University of Copenhagen. The material collected for analysis consisted of orthopantomograms, profile radiographs, frontal radiographs and hand radiographs. After the first report by Grimbacher et al. [1999] describing the association between impaired root resorption in hyper-IgE syndrome, the remaining primary molars from subject A and B were extracted. A second lower primary molar from each subject was obtained and examined histologically and immunohistochemically from the two subjects.

Subject A
A female patient surveyed from age 6 years and 3 months to 14 years. The hand radiograph was assessed according to Helm et al. [1971], and the skeletal age at the last visit was MP3u (correlates to approximately two years after maximum growth spur). The dental files revealed that the majority of the primary teeth had been extracted in the incisor region due to impaired shedding. The majority of the primary molars were, however, extracted in connection with abscess formation. Only the upper right and lower left second primary molars were extracted due to impaired shedding. Furthermore, the patient often suffered from fungal infection of the mucosa and had a high caries activity.

Subject B
A male surveyed from age 8 years and 9 months to 17 years and 11 months. The skeletal ages in this period according to Helm et al. [1971] were PP2= to MP3u (correlates from approximately two years before maximum growth spur until two years after). The dental files revealed a healthy dentition, but the permanent canines and premolars had not erupted by the age of 17 years and 11 months.

Radiographic methods and findings
From the orthopantomograms, the eruption pattern and dental maturity were analysed. The dental maturity was assessed according to

<table>
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<th>A</th>
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<tr>
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</tr>
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<td>Eosinophils (milliar./L)</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Other findings</td>
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Table 1 - Findings in two patients with hyper-IgE syndrome.
Demirjian standards [Demirjian et al., 1973]. The craniofacial morphology was evaluated from profile radiographs. Cephalometric analysis was carried out according to the method developed by Björk [1960].

**Subject A**

**Dental maturation** The permanent upper incisors were approximately one year late in maturation, otherwise the dental maturation was within the normal range (Figs. 1, 2).

**Dental morphology** Large invaginations in the permanent upper laterals (Fig. 1).

**Eruption pattern** Slightly delayed eruption of permanent incisors, otherwise within normal ranges. Permanent teeth erupted in many cases adjacent to the primary one. At 14 years all deciduous teeth had been shed or extracted, and all permanent teeth, except the third molars, were erupted or under eruption.

**Caries activity** Extremely high in the primary dentition (Fig. 1).

**Craniofacial profile** The analysis showed a craniofacial profile within normal variations and without specific morphological signs of malformation (Fig. 3).

The cephalometric measurements are indicated in Table 2.

**Subject B**

**Dental maturation** Within normal range, although the lower permanent second molars formed late (Fig. 4a, 4b).

**Dental morphology** Long roots were observed in the primary dentition, on the incisors and the first molars in the permanent dentition. The premolars and canines were fully developed with a rounded apex, even though they had not erupted at age 17 years and 11 months (Fig. 4c).

**Eruption pattern** Delayed eruption of

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**Fig. 1** - Intraoral radiographs of upper incisors in subject A at age 6 years 3 months (a, b) and 8 years 1 month (c-e). Note the late maturation of the upper permanent central incisors in radiographs a and b, and the pronounced cingulum pits in the radiographs c and e (arrows). Radiographs d and e show the eruption of the right permanent lateral incisor next to the right primary lateral incisor.

**Fig. 2** - Orthopantomogram of subject A, age 12 years 4 months; 3 second premolars and 1 permanent canine have not yet erupted. The erupting teeth have not fully developed apically.

**Fig. 3** - Craniofacial profile of subject A (14 years).
permanent incisors, canines and premolars.

The canines and premolars had not erupted by age 17 years and 11 months, and the corresponding primary teeth had not loosened.

Caries activity Free of caries.

Craniofacial profile The analysis showed a craniofacial profile within normal variations, only the cranial base angle was significantly increased (Fig. 5). The cephalometric measurements are indicated in Table 2.

Histologic methods and findings
A primary lower second molar from each subject was analysed histologically and immuno-

<table>
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<tr>
<th>Subj.</th>
<th>Age</th>
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<th>s-n-ss</th>
<th>s-n-pg</th>
<th>ss-n-pg</th>
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<td></td>
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<td>3.3</td>
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<td>-1.1</td>
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<td>-0.4</td>
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</table>

SD, standard deviation from angular mean values according to Björk, 1960.
Standard unit: \( \frac{x - \bar{x}}{\sigma} = SV \), where \( x \) is the observation and \( \bar{x} \) is the mean.

**TABLE 2** - Skeletal cephalometric measurements for the two subjects with hyper-IgE syndrome.

**Fig. 4** - Three orthopantomograms from subject B at age 8 years 9 months (a), 10 years 9 months (b) and 17 years 11 months (c). Note the great disparity between the dental maturation of the central incisors and the stage of root resorption of primary incisors, indicating abnormal eruption pattern (a). Note that the canines and premolars had still not erupted when the last orthopantomogram was taken at age 17 years 11 months (c).

**Fig. 5** - Craniofacial profile of subject B (17 years and 11 months). Note the flattened cranial base angle.
histrochemically. The tissue was formalin-fixed and decalcified in equal parts of 2% citric acid and 20% sodium citrate (pH 6), embedded in paraffin and serially cut in 5 μm longitudinal sections. The sections were stained with toluidine blue in 30% ethanol (pH 7).

In order to determine the amount of root sheath present on the demineralised tooth sections, an immunocytochemical method was employed to identify the presence of ectodermally derived cells. This involved the use of a polyclonal keratin antibody Keratine wide spectrum KWS (Dakopatts, Denmark), and sections were labelled for this marker using the Avidin Biotin method.

**Subject A**

The histological analysis of the left lower second primary molar showed interglobular dentine and linear traces of hypomineralization similar to developmental lines. There were sporadic signs of epithelial cell layers along the cementum (Fig. 6a).

**Subject B**

Histological analysis of one lower primary molar showed a normal morphological appearance of dentine. A pronounced epithelial cell layer covering parts of the cementum was observed (Fig. 6b, 6c).

**Comparison of the two subjects**

Subject B had a much higher peak IgE (16.124 IU/ML) compared to subject A (5.116 IU/ML). In subject B persistence of the primary canines and molars was observed, in subject A, however, frequent abscess formation had led to extractions of the primary molars. The craniofacial phenotypes were within normal values in both subjects except the cranial base angle which was increased (3.8 SD) in subject B. Differences in the thickness of the epithelial lining of the cementum were also observed in primary molars obtained from both subjects.

**Discussion**

The persistence of an epithelial root sheath, as described for the first time by O’Connell et al. [2000], was found in both subject A and, to a greater degree, in subject B. Thus our analysis of additional two patients with hyper-IgE syndrome confirmed their observation.

Subject B manifested conditions in dental maturation and tooth eruption that corresponded to the main findings described by Grimbacher et al. [1999] and O’Connell et al. [2000]. However, subject B did show delayed development of the second permanent molar, a circumstance that, according to Grimbacher et al. [1999], should be normal. The dental eruption pattern of subject A, on the other hand, was difficult to evaluate because of the high incidence of dental abscesses, which had led to early extractions of several primary teeth.

Patients with hyper-IgE syndrome are often described as having characteristic facial appearance [Borges et al., 1998; Grimbacher et al., 1999]. The face of hyper-IgE syndrome was defined with anthropomorphic measurements [Borges et al., 1998]; however, these studies were not supported by analysis of the craniofacial profile. In the present study, when the craniofacial profile was analysed for the first time, the

**FIG. 6** - Histological sections of lower primary molars showing the differences in the epithelial lining covering the cementum (KWS immunohistochemical method) in subject A (magnification x 75) (a) and subject B (b, magnification x 75; c, magnification x 120).
measurements for both patients were within normal ranges, except for the cranial base angle in subject B. However, investigation of a larger sample would be needed to confirm whether patients with hyper-IgE syndrome have a characteristic craniofacial profile or not.

The impaired shedding of primary teeth seemed more pronounced in subject B than in subject A. It would therefore be tempting to suggest that there is a connection between the IgE level and impaired resorption of the primary dentition as subject B had much higher levels of serum IgE. This association however, was not proven in the study by Grimbacher et al. [1999], as the patients' IgE levels were not related to the degree of impaired root resorption of the primary teeth.

Tooth eruption is a very complex process, which is not completely understood. It is not known whether the persistence of the epithelial layer covering the root surface is associated with impaired root resorption, but this finding, and the possible connection between elevated serum IgE and impaired shedding of the primary teeth, may contribute to our understanding of the eruption process.

It will be interesting to follow the reactivation of the eruption process in future studies. The eruption process is seemingly restored after extraction of the retained primary teeth even when the patients are much older, than the average ages for tooth eruption.

Acknowledgements
This study was supported by grants from the Danish Medical Research Council (grant no. 9601764) and from the “IMK A Imene Fond”.

References