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The dental management of a patient with hyperimmunoglobulinemia E syndrome: a case report

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Summary. Hyperimmunoglobulinemia E recurrent infection syndrome (also known as Job's syndrome) is a rare multi-system primary immunological disorder in which non-immunological abnormalities of the dentition, bones and connective tissue are also seen. A previous study has reported the occurrence of dental abnormalities in three-quarters of individuals diagnosed as suffering from this condition. The present authors report the case of a boy whose prolonged retention of the primary dentition was associated with delayed eruption of permanent teeth. They emphasize the need for early intervention in order to help minimize later orthodontic problems.

Introduction

First described prior to the discovery of immunoglobulin E (IgE), the hyperimmunoglobulinemia E syndrome (HIES) was originally called Job's syndrome on account of the cutaneous 'cold abscesses' which were observed in this condition [2]. In 1972, Buckley and co-workers [3] reported its correlation with elevated IgE levels. The condition is characterized by recurrent skin abscesses, pneumonia with pneumatocele formation, eczema, pruritic dermatitis and mucocutaneous candidiasis. It is inherited as a single-locus autosomal dominant trait with variable expressivity [4], a recent genetic linkage study having demonstrated that the proximal 4q region contains the disease locus [5]. The disorder affects both males and females, and does not seem to have a predilection for any particular ethnic group.

Immunologically, the syndrome presents with a marked elevation of serum IgE levels [6], defective chemotaxis [7], cytokine imbalance [8] and abnormal antibody production [9], although immunological screens of different patients do not produce a specific or consistent picture. Sufferers are typically maintained on antibacterial and antifungal agents, infections being treated aggressively as and when they arise.

Individuals with HIES also present with a number of nonimmunological abnormalities. Most will have a characteristic coarse facial appearance, the prominence of the supraorbital ridge and brow giving the appearance of deep-set eyes. The alar base is wide, and the nasal tip tends to be broad and fleshy. The mandible is usually prognathic and the lower lip may be larger than the upper one. A high arched palate is a common finding [1], and the occurrence of craniosynostosis has been reported in the literature [10]. Many patients suffer from frequent fractures and scoliosis because of cytokine-mediated bone resorption [11]; they may also have hyperextensible joints [2].

Dental abnormalities have previously been recognized as a complication of HIES [1]. Many patients present with what appear to be 'double rows' of teeth because of the failure of primary teeth to exfoliate on the eruption of the permanent dentition. However, in other cases, failure of the primary dentition to exfoliate results in delayed eruption of the permanent dentition. In a study by Grimbacher and co-workers [4], most of the patients who were studied reported the need for extraction of eight or more primary teeth in order to allow the permanent teeth to erupt.

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Case report

LD, a boy aged 9 years and 7 months with a confirmed diagnosis of HIES, was referred to the Paediatric Dentistry Unit of the University Dental Hospital, Cardiff, UK, regarding the prolonged retention of his primary teeth. In addition to providing the diagnosis of HIES, the referring consultant respiratory physician stated that LD suffered from bilateral bronchiectasis, gastro-oesophageal reflux and recurrent severe impetigo. His daily medication consisted of Domperidone, Ranitidine, sodium cromoglycate, Loratadine, Itraconazole, Tobramycin, DNAase, Flixotide and Linezolid; he received intravenous immunoglobulin every 3 weeks.

At LD's first attendance in the Paediatric Dentistry Unit, intraoral examination showed no evidence of soft-tissue pathology, although his mother reported a history of recurrent oral candidal infection. His oral hygiene was poor, with an associated mild chronic plaque-induced marginal gingivitis. The teeth listed in Table 1 were present.

Radiographic examination demonstrated the presence of a complete permanent dentition including the third permanent molars in all quadrants (Fig. 1). From the development of the permanent dentition, LD's dental age was adjudged to coincide with his chronological age.

LD presented with a Class I type malocclusion in the early mixed dentition, with significant crowding potential in both arches. The maxillary primary incisors and mandibular primary lateral incisors were retained and firm, with the permanent mandibular lateral incisors erupting lingually. Radiographically, the maxillary primary central and lateral incisors showed little evidence of root resorption.

Following interdisciplinary assessment by consultants in both Paediatric Dentistry and Orthodontics, LD was referred to his general dental practitioner for extraction of the retained primary incisors and mandibular primary canines, the extraction of the latter being prescribed to facilitate alignment of the permanent mandibular lateral incisors. The extractions were carried out under local anaesthesia with appropriate antibiotic prophylaxis.

Removal of the retained primary incisors and mandibular primary canines resulted in spontaneous permanent incisor eruption over the following 18 months (Fig. 2). However, at 11 years and one month of age, the maxillary permanent central incisors showed significant mesiolabial rotation. These teeth were in cross-bite with the labially positioned mandibular permanent central incisors, associated with which there was a minimal amount of labial attached gingiva. Therefore, a short course of sectional fixed appliance therapy was provided in which the maxillary central incisors were aligned and the associated cross-bite corrected. For the future, the eruption of the permanent canines and premolars will be monitored, and the primary molars will be removed if eruption is impaired.

Table 1. Teeth present when the subject was 9 years and 7 months old.*

6	E	D	C	B	A	A	B	C	D	E	6
6	E	D	C	B	1	1	B	C	D	E	6

*Teeth numbers: 11, 55, 54, 53, 52, 51; 61, 62, 63, 64, 65, 26; 36, 75, 74, 73, 72, 31; 41, 82, 83, 84, 85, 46.

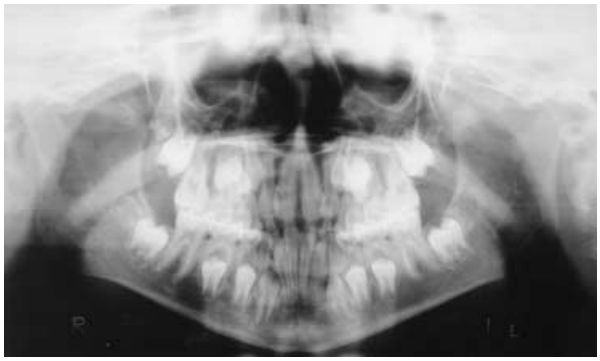

Fig. 1. Panoramic radiograph taken when the subject was 9 years and 7 months old.

Discussion

The present case reinforces the observations of two groups of researchers, O'Connell and co-workers [1], and Grimbacher and co-workers [4].

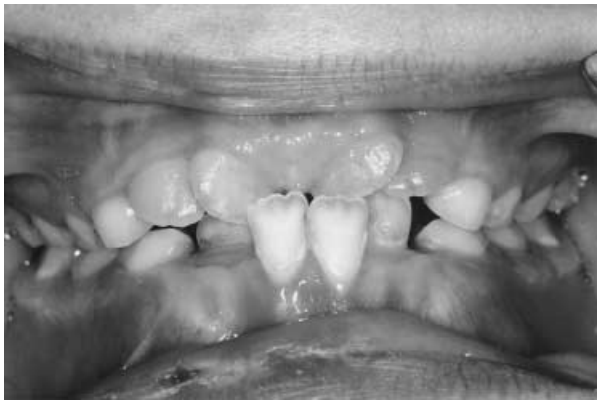

Fig. 2. Photograph of the upper and lower arches in occlusion taken when the subject was 11 years and one month old.

O'Connell *et al*. [1] found that 75% of patients older than 7 years reported problems with the eruption of the permanent dentition, although none of the patients had experienced problems with the eruption of primary teeth. These authors considered that, as in the case reported above, the reported problems were the result of a delay in the exfoliation of the primary dentition, as opposed to a delay in the formation of the permanent dentition. By way of explanation, O'Connell *et al*. suggested that the unusual persistence of Hertwig's epithelial root sheath on the root of a primary tooth might have some association with their delayed resorption.

Grimbacher *et al*. [4] showed that, unlike patients with other systemic diseases who may have a generalized delay in tooth development, patients with HIES have dental ages which coincide with their chronological ages. However, tooth eruption is significantly delayed (by as much as two standard deviations) in comparison with standards for age-matched healthy children. The eruption of teeth without predecessors (i.e. all the primary teeth and the permanent molars) occurred on time.

The failure to shed primary teeth in HIES contrasts with the early loss of primary teeth as a result of periodontal infection in other diseases of host defences, most notably defects in leucocyte adhesion. The factors which control physiological root resorption are undefined, but may involve the activation of osteoclasts and/or macrophages by cytokines, these latter also mediating local inflammation. Grimbacher *et al*. [4] suspected that delayed resorption of primary teeth in HIES may be a manifestation of the same defect that results in ineffective inflammatory responses and the formation of pneumatoceles.

The present case outlines the need for both awareness of the dental problems which may occur in association with HIES and continuous monitoring of patients with the condition. As suggested by Grimbacher *et al*. [4], removal of retained primary teeth has led to easier management and reduction in, or avoidance of, the need for complex orthodontic treatment later in life. However, we should also emphasize that monitoring such patients for dental caries is also paramount because dental infections can have serious effects. Indeed, Vigliante *et al*. [12] described a case in which a child with HIES developed a life-threatening cervicofacial infection as a result of a dental abscess. The dentist must also bear in mind that these patients tend to be maintained on life-long therapeutic doses of penicillinase-resistant penicillin. This prolonged use of antibiotics often leads to mucocutaneous candidiasis, which may present in the oral cavity and require (as in this case) the regular use of antifungals.

Conclusion

In summary, the present case serves as a reminder to every dentist of the importance of monitoring the developing dentition in patients diagnosed as suffering from HIES. Many of the potential problems associated with this syndrome can be avoided with vigilant monitoring and good care.

Résumé. L'hyperimmunoglobulinémie E (Hyper-IgE) est un syndrome infectieux récurrent (également appelé syndrome de Job), un désordre immunologique primaire multisystémique rare, dans lequel des anomalies non-imunologiques de la denture, des os et des tissus conjonctifs sont rencontrées. Une étude précédente [1] a rapporté la présence d'anomalies dentaires dans les 3/4 des cas diagnostiqués. Nous rapportons un cas au cours duquel la rétention prolongée de la denture primaire a été associée à une éruption retardée des dents permanentes. Nous faisons ressortir la nécessité d'une intervention précoce afin d'aider à minimiser les problèmes orthodontiques ultérieurs.

Zusammenfassung. Hyperimmunoglobulinämie E (Hyper-IgE) Syndrom (auch Job Syndrom) ist ein seltener primärer Immundefekt, daneben werden Veränderungen an Zähnen, Knochen und Bindegeweben beobachtet. Die Häufigkeit von Zahnanomalien bei dieser Erkrankung wurde mit drei Viertel angegeben. Im vorliegenden Fallbericht wurde eine verlängerte retention der Milchzähne und die verspätete Eruption der bleibenden Zähne beobachtet, dies macht eine rechtzeitige kieferorthopädische Intervention erforderlich, um spätere kieferorthopädische Komplikationen zu vermindern.

Resumen. El síndrome de infección recurrente hiperinmunoglobulinemia E (Hiper-E), (también conocido como síndrome de Job), es una rara alteración inmunológica primaria multisistémica, en la que también se ven anomalías no inmunológicas de la dentición, huesos y tejido conjuntivo. Un estudio previo (1) ha informado de la aparición de anomalías dentarias en tres cuartas partes de los

diagnosticados como afectados por esta alteración. Aquí informamos de un caso en el que la retención prolongada de la dentición primaria se asoció a retraso de la erupción de los dientes permanentes y se subraya la necesidad de una intervención temprana para ayudar a minimizar los problemas ortodóncicos tardíos.

References

1 O'Connell AC, Puck JM, Grimbacher B, *et al*. Delayed eruption of permanent teeth in hyperimmunoglobulinemia E recurrent infection syndrome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* 2000; **89**: 177–185.

2 Davis SD, Schaller J, Wedgwood RJ. Job's syndrome. Recurrent 'cold' staphylococcal abscesses. *The Lancet* 1966; **1**: 1013–1015.

3 Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 1972; **49**: 59–70.

4 Grimbacher B, Holland SM, Gallin JI, *et al*. Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. *New England Journal of Medicine* 1999; **340**: 692–702.

5 Grimbacher B, Schaffer AA, Holland SM, *et al*. Genetic linkage of hyper-IgE syndrome to chromosome 4. *American Journal of Human Genetics* 1999; **65**: 735–744.

6 Donabedian H, Gallin JI. The hyperimmunoglobulin E recurrent infection (Job's) syndrome: a review of the NIH experience and the literature. *Medicine* 1983; **62**: 195–208.

7 Hill HR, Ochs HD, Quie PG, *et al*. Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent 'cold' staphylococcal abscesses. *Lancet* 1974; **2**: 617–619.

8 Ohga S, Momura A, Ihara K, *et al*. Cytokine imbalance in hyper-IgE syndrome: reduced expression of transforming growth factor β and interferon γ genes in circulating activated T cells. *British Journal of Haematology* 2003; **121**: 324–331.

9 Dreskin SC, Goldsmith PK, Gallin JI. Immunoglobulins in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome. Deficiency of anti-Staphylococcus aureus immunoglobulin A. *Journal of Clinical Investigation* 1985; **75**: 26–34.

10 Hoger PH, Boltshauser E, Hitzig WH. Craniosynostosis in hyper-IgE syndrome. *European Journal of Pediatrics* 1985; **144**: 414–417.

11 Cohen-Solal M, Prieur AM, Prin L, *et al*. Cytokine-mediated bone resorption in patients with the Hyperimmunoglobulin E syndrome. *Clinical Immunopathology* 1995; **76**: 75–81.

12 Vigliante CE, Costello BJ, Quinn PD. Life-threatening cervicofacial infection in a child with Hyperimmunoglobulin–E Syndrome. *Journal of Oral Maxillofacial Surgery* 2001; **59**: 561–565.