Dental Manifestations of a Pediatric Patient With Hyperimmunoglobulin E Syndrome: A Case Report

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ABSTRACT

A 7-year-old girl with hyperimmunoglobulin E syndrome (HIES) presented to our clinic with tooth agenesis in both primary and permanent dentitions. The patient's serum immunoglobulin E level was elevated at 17,091 IU/ml, and her medical history indicated the occurrence of HIES, numerous skin abscesses, and recurrent infection by bacteria and/or fungi such as Candida from birth. She also suffered from heart disease. Dental manifestations included extensive caries, impaired root resorption of primary mandibular central incisors and absence of primary mandibular canines and permanent mandibular lateral incisors. Intraoral phenotypes in HIES patients have already been reported in detail, but no previous report has described abnormalities in the number of primary teeth in HIES patients. The purpose of this report was to describe the dental manifestations in the primary dentition of a hyperimmunoglobulin E syndrome patient and to emphasize the importance of preventive dental management from early childhood in compromised children, such as those with HIES. (J Dent Child 2012;79(2):100-4)

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KEYWORDS: HYPERIMMUNOGLOBULIN E SYNDROME, TOOTH AGENESIS, DEFICIENT ROOT RESORPTION OF PRIMARY TEETH

Hyperimmunoglobulin E syndrome (**HIES**, or Job's syndrome) is a rare immunodeficiency disorder characterized by chronic eczema, recurrent staphylococcal infections, increased serum immunoglobulin E (IgE; usually >2,000 IU /ml), and eosinophilia. It is reported very rarely, with an incidence of 1 in 1,000,000 people.[1] IgE is one of the 5 subclasses of antibodies. The antigen-IgE complex associating with Fc receptors on the surface of mast cells can cause the release of histamine and cytokines, which are capable of triggering significant immune reactions. The normal serum level of IgE in adults is less than 130 IU per milliliter.[2]

Generally, adult IgE levels are achieved by 5 to 7 years old.[3] IgE levels from 10,000 to as high as >100,000 IU /ml are characteristic of HIES, but the levels are not static.[1,4] High levels of IgE are not correlated with the level of eosinophilia or susceptibility to severe infections, and the importance of the elevated IgE in the pathology of HIES is still not clear.[1,4] HIES typically first manifests with a newborn rash. The rash usually starts as papules or pustules on the scalp and face and later progresses over the rest of the body.[4] Although some cases of familial HIES with autosomal dominant or recessive inheritance have been reported, most cases of HIES are sporadic.[2,5]

In many cases of HIES, abnormalities in hard tissue are also common.[1,4,6] Skeletal abnormalities include scoliosis, osteopenia, minimal trauma fractures, and craniosynostosis.[2,7,8] Dental features as well as skeletal abnormalities have been reported.[2,4,6-9] Dental features include failure of shedding of primary teeth, supernumerary teeth, microdontia, and a high, arched palate. Deficient or delayed root resorption of primary teeth has been reported at a frequency as high as 64%, 72%, and 75% in HIES patients.[2,6,9] Reduced resorption of primary tooth roots leads to prolonged retention of

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primary teeth, which in turn prevents the appropriate eruption of permanent teeth.[9]

Recently, mis-sense or in-frame deletion in transcription factor STAT3 was identified as the etiology for HIES; pathological conditions in multiple systems were suggested to be caused by signaling abnormalities of cytokines, such as interleukin 6 (IL-6).[10,11] Cytokines are thought to link the dental and other immunologic and skeletal features of this disorder.[9-11] The various manifestations of HIES, however, remain poorly understood.

In this case report, we describe the dental management of a 7-year-old girl with HIES, who exhibits tooth agenesis in both primary and permanent dentitions in addition to deficient root resorption of primary teeth.

CASE DESCRIPTION

A 7-year, 8-month-old girl, suspected to have HIES, was referred to the Department of Pediatric Dentistry, Nagasaki University Hospital, Nagasaki, Japan, for treatment of tooth decay. A physical examination revealed numerous skin abscesses and pruritic dermatitis on her scalp, face, all 4 limbs and body trunk. Figure 1 shows the skin lesions on her upper arm, which are widespread. The skin disorder had been difficult to manage. She was under topical anti-staphylococcal agent therapy and occasional topical steroid therapy, as prescribed by her physician. According to her medical history, she had numerous skin abscesses and recurrent infection by bacteria and/or fungi such as Candida from early infancy. Although not considered a feature of HIES, the present patient also suffered from heart disease, dilated myocardiopathy, and mitral regurgitation. Because of heart disease, her cardiorespiratory function was assessed as New York Heart Association Class II[12] and her medication included furosemide and spironolactone. She had a healthy younger brother; none of her immediate family members had infections or other HIES features.

Table 1. Laboratory Values*

	Normal value	Patient's value
White blood cell (μL)	6,000-15,000	12,000
Neutrophils (%)	54-62	43
Lymphocytes (%)	25-30	42
Eosinophils (%)	1-3	11
Basophils (%)	1	1
Monocytes (%)	0-9	4
Red blood cell (million/μL)	4-6	4.55
Hemoglobin (g/100 mL)	12-18	8.0
Hematocrit (%)	35-50	28.1
Platelets (mL)	140,000-340,000	456,000
Immunoglobulin A (mg/100 mL)	80-350†	213
Immunoglobulin G (mg/100 mL)	620-1400†	1,650
Immunoglobulin M (mg/100 mL)	45-250†	34.3
Immunoglobulin E (IU/mL‡)	≤ 130[2]	17,091

** Source: http://www.aapd.org/media/policies.asp.*
† Source: http://www.lymphomation.org/tests-immunoglobulins.htm.
‡ To convert values to microgram per liter, multiply by 2.4.

An intraoral and radiographic examination revealed poor oral hygiene, grossly carious primary molars in all 4 quadrants, and retained primary mandibular central incisors in a labial position, and permanent mandibular central incisors in line with the other teeth (Figure 2). Bilateral primary mandibular canines were missing, and the panoramic radiograph showed that tooth buds of the permanent lateral incisor were also absent (Figure 3). The patient had no previous dental experience, with her first visit involving the chief complaint of toothache. There was no relevant dental history, including extraction or trauma.

Because the patient was uncooperative, treatment of the multiple carious teeth was planned under general anesthesia. A hematological examination revealed that the WBC count was 12,000 cells/μL with 43% neutrophils,

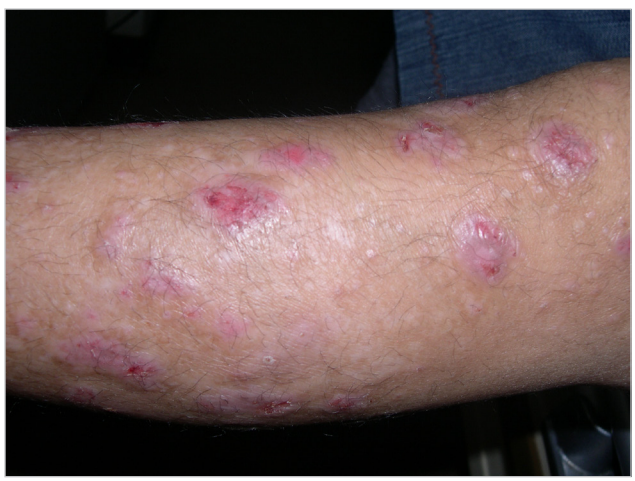

Figure 1. Numerous skin abscesses and pruritic dermatitis on the upper arm of the patient with hyperimmunoglobulin E syndrome.

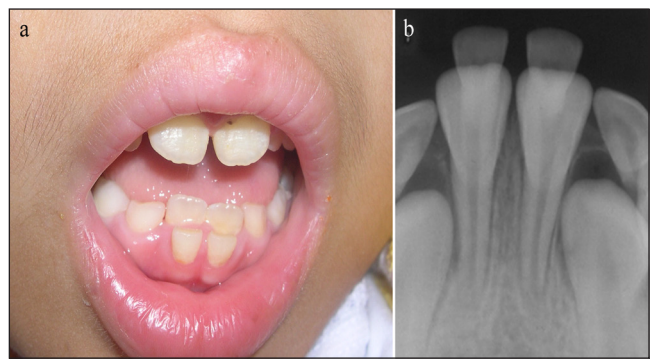

Figure 2. (a) Over-retained primary mandibular incisors and erupted permanent incisors at the first visit (7-years, 8-months) in the patient with hyperimmunoglobulin E syndrome. Permanent central incisors were positioned in the row of the primary teeth and retained primary central incisors in a labial position with no signs of mobility. Bilateral primary mandibular canines were absent. (b) Dental radiograph showing retention of primary incisors.

and the eosinophil count was elevated at 11%. A reduction in hemoglobin and hematocrit was noted at 8.0 g/dl and approximately 28%, respectively. The serum IgE level was elevated at 17,091 IU/ml, the IgM level was decreased at 34.3 mg/dl, and the level of other immunoglobulins was within the normal range (Table 1). In view of the clinical and laboratory findings, the patient was diagnosed as having HIES by her physician. Delayed hypersensitivity response to a variety of skin test antigens including latex, 2% xylocaine, polymerized composite resin, and root filling material containing iodoform paste were negative. Following interdisciplinary assessment advised by the patient's physician, antibiotic prophylaxis was recommended in view of her compromised immune system and heart condition. She was administered ampicillin 1 g intravenously 1 hour before thenprocedures. Extracted primary central incisors revealed impaired root resorption (Figure 4).

At the recall examination when the patient was 8 years, 1 month old, the patient's mother reported shedding of the primary mandibular right lateral incisor; the exfoliated tooth revealed normal root resorption (Figure 5).

DISCUSSION

The clinical manifestations of HIES involve the immune system, skeletal tissue, connective tissue, and dentition. Pediatric dentists are often approached for management of failure of primary teeth exfoliation,[7] tooth decay,[8] and severe periodontitis[13] in HIES patients. It was reported that extractions of retained primary teeth were carried out under antibiotic prophylaxis,[7] and all primary teeth with severe periodontitis in a 5-year-old girl were extracted due to poor prognosis and risk of systemic infection.[13] Furthermore, it was reported that an untreated periapical abscess led to the development of a serious head and neck infectious disease.[14] This indicates that, in HIES patients, a chronic odontogenic infection can quickly progress into a life-threatening emergency in a short period. These reports emphasize, for dental management of HIES patients, the dentist must remember these individuals are compromised people with an immunological disorder of unknown etiology.

In addition to compromised immunity, our patient also suffered from heart disease, dilated myocardiopathy, and mitral regurgitation. Prevention of infective endocarditis (**IE**) must also be considered. IE is an uncommon but life-threatening infection, and antimicrobial prophylaxis to prevent IE in patients who undergo a dental procedure has been emphasized. According to the modification in the guidelines for endocarditis prophylaxis guidelines in 2007[15], prophylaxis for a dental procedure is not recommended, except for patients whose underlying cardiac conditions are associated with the highest risk of adverse outcome. Patients with a compromised immune system, however, may not be able to tolerate a transient bacteremia following a dental procedure such as extraction.[16,17]

HIES patients are known to be vulnerable to *Staphylococcus aureus* and fungi.[14] On the other hand,

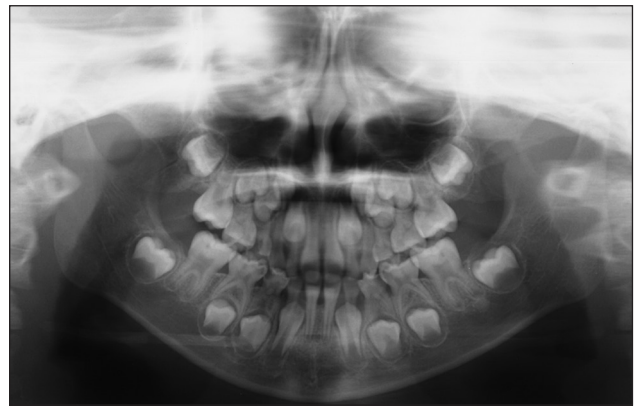

Figure 3. Panoramic radiograph taken at the first visit (7 years, 8 months) showing absence of bilateral primary canines and bilateral permanent lateral incisors in the mandible in the patient with hyperimmunoglobulin E syndrome.

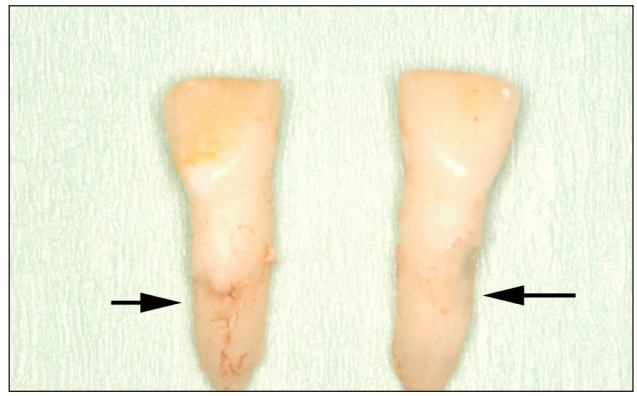

Figure 4. Lingual side of the roots of extracted primary mandibular central incisors showed little evidence of root resorption (arrow) in the patient with hyperimmunoglobulin E syndrome.

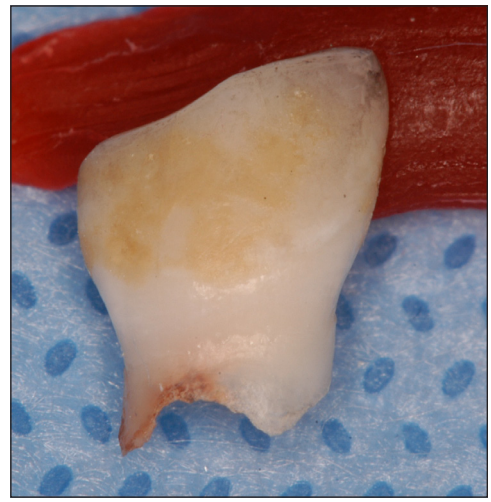

Figure 5. The spontaneously exfoliated primary mandibular right lateral incisor revealed normal root resorption in a patient with hyperimmunoglobulin E syndrome.

recently it was reported staphylococci, particularly *S aureus*, had surpassed viridans streptococci as the most common cause of IE.[18] *S aureus* is frequently part of the skin flora found in the nose and on the skin, and the risk of transient bacteremia is thought to increase due to nasal bleeding caused by nasal intubation and injection during general anesthesia. Therefore, although the cardiac condition of our patient did not come in the high-risk category, considering the immunodeficiency and immune dysregulation in HIES, prevention of IE was thought to be necessary.

To date there is no explanation for the high levels of total IgE, and the association between HIES and allergies is not clear. Although decreased delayed-type-hypersensitivity responses have been described, this was a feature in only 50% of patients tested.[19] Because our patient had no previous experience of dental treatment, it was the first time she was exposed to all dental materials. The risk of hypersensitivity to some dental materials, which has been reported to be the cause of allergy,[20-22] was screened using patch tests by her physician, and all tested materials, latex, 2% xylocaine, polymerized composite resin, and root filling material containing iodoform paste gave negative results.

Prolonged retention of the primary teeth is a consistent feature of HIES. All primary teeth of the HIES patient do not always present with root resorption deficiency,[6] which may occur in the primary molar region as well as mandibular primary anterior teeth.[8] In the present case, root resorption deficiency was confirmed in the primary mandibular central incisors, but not in the primary mandibular lateral incisors and the maxillary incisors. The roots of extracted primary mandibular central incisors showed little evidence of root resorption (Figure 4). The primary incisors in our patient seem to have migrated labially from their original location without being resorbed. Bone resorption is typically enhanced in HIES patients, but root resorption is defective.[9]

Increased bone resorption is thought to be linked to abnormal cytokine production in HIES, and the cytokines implicated include interleukin-1 (IL-1), IL-6, and tumor necrosis factor-αlpha (TNF-α).[9] On the other hand, the lack of appropriate inflammatory responses is thought to be responsible for defective root resorption[6]. However, since all primary teeth of the HIES patient do not always present with root resorption deficiency,[6] it is not clear whether the problem of inflammatory response is in the specific site or in the specific timing.

Our patient showed agenesis of primary mandibular canines and permanent mandibular lateral incisors. The prevalence of agenesis of primary teeth in the normal population is 0.5%, and the tooth most frequently affected by agenesis is the maxillary lateral incisor.[23,24] Most cases of primary tooth agenesis occur in association with cleft lip and palate or manifest as an isolated finding or part of a syndrome. To the best of our knowledge, no abnormalities of size, shape, or number in the primary dentition of HIES patients have been reported. In the permanent dentition, multiple supernumerary teeth were reported to develop in the mandible.[6,9] Tooth development is regulated by many events, and the precise molecular mechanisms are not clear, although various cytokines and growth factors have been shown to play important roles.[25] Abnormal cytokine function in HIES may affect tooth formation as well as the inflammatory response.

Each event, such as tooth formation, physiological root resorption, and tooth eruption, occurs with a specific timing during the period of growth and development, and each tooth develops in a specific site. The abnormality occurring during tooth morphogenesis can be easily identified because of the visible outcome in the tooth size, shape, number, and eruption. Further detailed reports about dental findings will be needed to understand whether the impaired cytokine function of the HIES population influences tooth formation.

Increases in the record of decayed, missing, and filled surfaces, gingival index, and plaque index were reported in the HIES population.[26] Our patient's oral hygiene was poor, and she had mild chronic plaque-induced marginal gingivitis and multiple caries. These findings, however, can also be observed in a patient without HIES and it is not clear whether our patient had increased risk for dental caries. Oral hygiene of chronically ill children tends to be neglected because of their poor physical condition. The frequent use of sweetened medications may also increase the risk for caries. Besides caries, HIES patients tend to have oral disorders from early childhood due to their defective immune systems. Pediatric dentists play an important role in recognizing the oral manifestations, including caries, gingivitis, lack of root resorption, and abnormalities of tooth size, shape, quality, and number, and can start preventive dental management as early as possible.

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