Case Report
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Hyper IgE (Job's) Syndrome: A Primary Immune Deficiency with Oral Manifestations

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Abstract

Objectives: Hyper-immunoglobulin E syndrome (HIES), also known as Job's syndrome, is a rare primary immunodeficiency disorder characterized by a classic triad: elevated immunoglobulin E (IgE) levels, recurrent pneumonia with pneumatocele formation, and recurrent cold skin abscesses.

Case: A 5-year-old girl was referred to the pediatric dentistry department for tooth decay and multiple dental abscesses. Her medical history revealed elevated serum IgE levels, and she was receiving treatment with warfarin due to a history of jugular vein thrombosis. Clinical examination showed numerous skin abscesses alongside multiple eczemas. Angular cheilitis, de-papillation of the tongue, deep furrows on the tongue, numerous intraoral ulcerated lesions, poor oral hygiene, and gingivitis were seen in the intraoral examination.Due to the systemic conditions and the child's non-cooperation, treatment under general anesthesia was planned.

Conclusion: Dentists play an essential role in the early diagnosis of HIES and in monitoring their oral health conditions. Timely extraction of over-retained primary teeth can reduce the necessity for complex treatments, thereby facilitating the management of patients with Job's syndrome.

Keywords: Hyper IgE syndrome; Job's syndrome; Immunodeficiency; HIES; Retained primary teeth; Primary immunodeficiency

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Introduction

Hyper-IgE syndrome (HIES), also known as Job's syndrome, was first identified by Davis et al. in 1966 when they reported on two sisters exhibiting eczema, cold abscesses, and pneumonia.[1] This condition is a primary immunodeficiency disorder that can be inherited in an autosomal recessive (AR) or autosomal dominant (AD) manner, caused by mutations in the STAT3 or DOCK8 genes.[2] Although rare, HIES affects both males and females equally, with the majority of cases having an autosomal dominant inheritance (AD-HIES).[3]

Symptoms typically emerge during the neonatal period, often at birth or within a few days, and almost always by 18 to 20 months of age.[4] The autosomal dominant form of HIES is notably characterized by a triad of elevated serum IgE levels, recurrent skin abscesses due to Staphylococcus aureus, recurrent pneumonia with pneumatocele formation, and eczematous dermatitis. Blood tests reveal increased IgE concentrations and specific IgE antibodies against inhaled substances, bacteria, fungi, and food allergens, often accompanied by impaired neutrophil chemotaxis and eosinophilia.[4]

Individuals with HIES have a higher susceptibility to autoimmune and neoplastic diseases, including non-granulating lymphoma and Hodgkin's disease.[5] Oral examinations frequently reveal a predisposition to mucosal lesions such as chronic candidiasis, hyperkeratosis, and tongue fissures.[6,7] Dental anomalies may include retained primary and deciduous teeth, enamel hypoplasia, and dentin defects. By the age of eight, 72% of patients exhibit dental issues like retained teeth, persistent deciduous teeth resulting in a double row appearance, and extra teeth (supernumerary teeth).[8] The presence of skeletal abnormalities, pathological fractures, dental anomalies, and distinctive facial features is indicative of the dominant inheritance pattern seen in HIES.

The present case involved a child displaying the classic symptoms of Job's syndrome. Owing to its rarity, this case report aimed to highlight the clinical features, investigative dental procedures and management strategies utilized, thereby contributing to the limited pediatric literature on Job's syndrome.

Case Report

A girl aged five years and three months was referred to the pediatric dentistry department of Shahid Beheshti Dental School, Tehran, Iran, presenting with tooth decay and multiple dental abscesses. Her medical history indicated an immune system deficiency, specifically hyper IgE syndrome, and she was receiving treatment with warfarin due to a history of jugular vein thrombosis.

During the clinical examination, a significant number of skin abscesses and numerous instances of eczema were observed on the patient's skull, face, limbs, and trunk. Facial and intraoral examinations revealed a coarse facial appearance, a prominent forehead, thick facial skin, deep-set and widely spaced eyes, a wide and fleshy nasal tip, a broad nasal bridge, and an aged appearance (Figure 1). Additionally, angular cheilitis, de-papillation of the tongue, deep furrows on the tongue, numerous intraoral ulcerated lesions, poor oral hygiene, and gingivitis were noted (Figure 2).

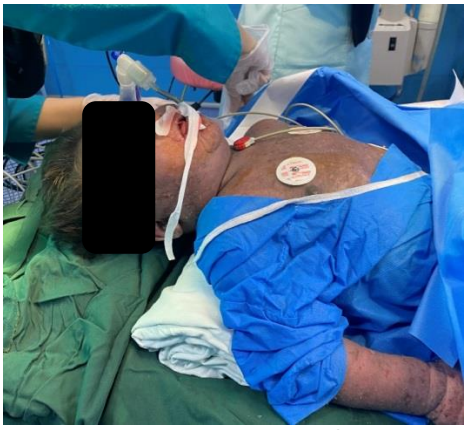

Figure 1: Clinical appearance of the patient

Figure 2: Oral and dental appearance of the patient

The patient's severe itching from skin lesions made it impossible to prepare radiographs for further examination due to extreme uncooperativeness. A blood test revealed a white blood cell count of 12,700 cells per microliter (μL), with neutrophils constituting 82%. The hemoglobin level was recorded at 9.1 g/dL, and the hematocrit was 31.7%.

Given the patient's specific systemic conditions, generalized dental caries, and her inability to cooperate, the decision was made to perform dental treatment under general anesthesia. Before this, necessary due consultations were made with specialists in cardiology, allergy and immunology, infectious diseases, and anesthesiology, leading to the conclusion that the planned treatment could be carried out under the mentioned supervision. Following the cardiologist's recommendations, several measures were taken:

- Warfarin was discontinued and replaced with heparin.
- Prothrombin time (PT), partial thromboplastin time (PTT), and complete blood count (CBC diff) tests were conducted before the surgery and after cessation of the anticoagulant medication.
- Antibiotic prophylaxis was administered (650 mg amoxicillin one hour before the operation).
- A PICU bed was reserved for the patient's postoperative care.

The dental treatments carried out were as follows:

- Teeth 51, 54, 55, 61, 74, 75, 84, 85 were extracted.
- Preventive resin restorations (PRRs) were applied to teeth 16, 26, 36, 46.
- Teeth 64 and 65 received pulpectomy treatments and were restored with stainless-steel crowns (SSCs).
- Teeth 52, 53, 62, and 63 underwent pulpectomy and were restored with composite resin materials.
- Composite restorations were also applied to teeth 73 and 83.

The child’s parents were given detailed instructions on maintaining strict oral hygiene and the importance of regular dental follow-ups.

Consent was obtained from the patient's parents to publish this report by assuring its confidentiality.

Discussion

This case report investigated dental and oral presentations in a child with Job's syndrome to enhance dental practitioners' awareness, knowledge, and astuteness and prevent dental complications in adolescence.

For patients with Job's syndrome, initiating treatment early in childhood is critical. The management of Job’s syndrome primarily involves prophylactic antimicrobials and adherence to routine skin care protocols, as no specific therapeutic interventions are recommended for this condition.[9,10] Antibiotics are prescribed for skin infections caused by S. aureus, and a broader spectrum of antibiotics may be utilized for recurrent Gram-negative infections.

Maintenance antifungals, such as fluconazole, have shown benefits for those experiencing recurrent mucocutaneous candidiasis. In parenchymal cystic lung disease, prophylactic or therapeutic management might include anti-aspergillus antifungals.[11] Skin care management typically involves topical eczema treatments and antiseptics like bleach baths or swimming in chlorinated pools. Bleach baths significantly reduce staphylococcal colonization and improve eczema symptoms.

Immunomodulators have shown varying levels of success

in treating HIES. One study aimed to assess the efficacy of levamisole, an antiparasitic agent with immunomodulatory effects, but found it less effective than a placebo. However, intravenous immunoglobulin has been beneficial for some patients, as highlighted by Kimata in 1995.[12]

Bone marrow transplantation has been attempted in several cases, yielding mixed results. One patient underwent transplantation for lymphoma and showed initial improvement in IgE levels and symptoms but died six months post-transplantation. In another case, a 7-year-old girl with severe HIES manifestations showed initial symptom improvement post-transplantation, which diminished after the reduction of immunosuppression despite successful engraftment. These cases underscore the need for further research into bone marrow transplantation's efficacy for HIES.[13,14]

Early detection and the judicious use of antibiotics and antifungals for prophylaxis remain the cornerstone of therapy. In a study by Singh et al.[15], a 13-month-old diagnosed with HIES received a prophylactic regimen of cotrimoxazole with amoxicillin-clavulanate.

In addition to over-retained primary teeth, patients with Job's syndrome are exposed to various oral lesions.[16] A study by Meixner et al.[17] reported 13 cases of STAT3-HIES and investigated the long-term outcome of related dental interventions. Two patients had mild tongue fissures.[18] In their STAT3-HIES cohort, gingivitis was observed in 31% of patients and aphthous ulcers in 15%; however, these rates were comparable to those found in the general population.

Some case reports regarding the effect of Job's Syndrome on dental and oral conditions can be found in the literature. Sepet et. al.[19] reported a case from an 11-year-old boy with Job's syndrome, in which the patient showed symptoms of angular cheilitis and delayed root resorption of primary teeth.

O'Connell et al.[16] concluded that delayed tooth eruption is among the presentations of hyper-IgE syndrome (HIES). They suggested that the failure of primary teeth to resorb might be related to the persistence of Hertwig's epithelial root sheath. McAuliffe et al.[20] reported a case involving a boy whose prolonged retention of primary teeth was associated with delayed eruption of permanent teeth.

In HIES, the inability to shed primary teeth contrasts with the early loss of primary teeth due to periodontal infections seen in other host defense disorders, especially those involving defects in leukocyte adhesion. The mechanisms controlling physiological root resorption are not fully understood but may involve the activation of osteoclasts and macrophages by cytokines that mediate local inflammation. Grimbacher et al.[21] hypothesized that delayed resorption of primary teeth in HIES could reflect the same defect causing ineffective inflammatory responses and pneumatoceles formation.

Grimbacher et al.[21] also suggested that extracting over-retained primary teeth can facilitate the management and potentially reduce or eliminate the need for complex orthodontic treatments later on. However, it is crucial to monitor these patients for dental caries, as dental infections can have severe consequences. Vigilante et al.[22] described a case where a child with HIES developed a life-threatening cervicofacial infection stemming from a dental abscess. Dentists should be aware that these patients are often on long-term therapeutic doses of penicillinase-resistant penicillin, which can lead to mucocutaneous candidiasis in the oral cavity, necessitating regular antifungal treatments, as observed in this case.

In the present case, teeth numbered 51, 54, 55, 61, 74, 75, 84, and 85 were extracted under general anesthesia. The research by Meixner et al.[17], particularly during complex orthodontic treatment, emphasized the importance of extracting primary teeth in STAT3-HIES patients within the normal physiological exfoliation period. Delayed extraction of primary teeth was associated with impaction of permanent successor teeth. As a precautionary measure, we recommend the use of antibiotic prophylaxis, such as amoxicillin/clavulanic acid, prior to complex dental procedures, in addition to the continuous medication regimen that STAT3-HIES patients receive.

Conclusion

Hyper-IgE Syndrome (HIES) is diagnosed before the patients come to the dentist for their dental treatment; the role of a specialized dentist, especially a pedodontist, is paramount. The prognosis for patients with HIES dramatically depends on the early detection and effective management of its complications. As such, dental professionals must thoroughly understand the disease's early oral manifestations. This knowledge not only aids in the early diagnosis of HIES but also in formulating a comprehensive treatment plan that addresses the condition's dental and broader health-related aspects. By recognizing and managing these oral symptoms promptly, pedodontists can significantly improve the quality of life and overall health outcomes for patients with HIES.

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Informed Consent Statement: Informed written consent to participate in this study was provided by the patient's legal guardian. Informed written consent was obtained from the patient's legal guardian for publication.
Data Availability Statement: The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.
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