Dental abnormalities in a patient with autosomal dominant hyper-IgE syndrome: A case control study

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May 27, 2021

Abstract

Autosomal-dominant hyper-IgE (AD-HIES) is mainly characterized by eczematous dermatitis, staphylococcal skin abscesses, connective tissue defects, and elevated serum IgE. This disorder is largely associated with heterozygous dominant-negative mutations in STAT3 gene. Herein, we reported a patient with AD-HIES suffering from dental abnormality and allergic reactions.

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Authors

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Running title: Dental implications in AD-HIES.

Key Clinical Message:

Dental abnormalities and other clinical complications of HIES are largely associated with heterozygous dominant-negative mutations in*STAT3* . Early diagnosis and management of these complications can improve life quality of patients.

Keywords: Hyper-IgE syndrome, STAT3, Recurrent infections, Dental abnormality, Allergic reactions.

Introduction

Autosomal dominant hyper-IgE syndrome (AD-HIES), also known as Buckley or Job's syndrome, is a rare multisystem disorder with both immunologic and nonimmunological characteristics. [1] This disorder is largely associated with heterozygous dominant-negative mutations in *signal transducer and activator of transcription 3* (*STAT3*) gene and characterized by eczematoid rashes, staphylococcal skin abscesses, connective tissue defects, and extremely elevated IgE serum level. [2-5]

Abnormalities in the dentition are often observed in patients with AD-HIES, such as retention of primary teeth together with ectopic eruption or non-eruption of permanent teeth. [6] In addition to dental abnormalities, some oral cavity defects have been reported for AD-HIES, including deep grooves on the tongue, buccal mucosa with multiple fissures, central ridges and fissures of the palate and a high arched palate. [7]

In this report, we reported dental abnormalities observed in an AD-HIES patient suffering from dermatitis, asthma, eczema, anaphylaxis, and refractory sinusitis.

Case history

The case was a 14-year-old boy referred to the allergy and immunodeficiency clinic of Shahid Beheshti hospital, Kashan, Iran. He suffered from acute asthma attacks and eczema. He was the third child of nonrelative parents. His problems began at the age of ten days when he experienced acute erythematous papules associated with excoriations and vesicles over the skin of glans following circumcision procedure. Facial dermatitis appeared and continued to involve other parts of his body at six months of age. A skin prick test was performed which was indicative of sensitivity reactions to milk, egg, and wheat. Therefore, an elimination diet including milk, egg, and wheat was recommended and started. At the age of 18 months, he had two episodes of cough, dyspnea, and wheezing, resembling asthma attacks which were followed by more exacerbations at older ages. These exacerbations were effectively controlled by inhaled corticosteroids. At the age of 12 years, the patient experienced an episode of anaphylaxis. He also suffered from recurrent sinusitis without pulmonary infections. Growth and development of patients were normal. However, primary teeth were retained which was accompanied by ectopic eruption of permanent teeth (Figure 1). Based on these findings, an underlying immunodeficiency disorder was considered. Some laboratory tests were carried out for investigating immunological situations of our case (Table. 1). The results of these tests revealed the serum level of IgE was significantly elevated (1320 IU/ml) which in association with his previous history proposed the possibility of hyper IgE syndrome (HIES). The patient was genetically studied to determine a possible defect in the *STAT3* gene. The genetic analysis indicated that he had a heterozygous mutation in STAT3 with a nucleotide exchange of 1909G>A in the exon 21 of *STAT3* gene, leading to an amino acid change (V637M), previously known as the cause of the autosomal dominant type of hyper IgE syndrome (HIES).

Regarding the fact that our patient did not cooperate for further evaluation and only suffered from asthma, his treatment was continued by Symbicort 160/4.5 mg/inhalation one puff twice daily. Our case is presently alive and in acceptable health condition.

Discussion

STAT3 is a critical regulator of multiple processes, including cellular proliferation, survival, differentiation, fetal development, cancer, wound healing, angiogenesis, autoimmunity and inflammation.[5] Defect in its function results in multisystem disorders such as dental abnormalities and connective tissue defects.[5] In the present study, we investigated a boy with acute asthma attacks, eczema, and dental abnormalities.

Abnormalities in the dentition are frequently observed in AD-HIES, although its mechanism(s) is not well identified yet. It is reported that STAT3 as a transcription factor play indispensable roles in signaling pathways of various cytokine such as IL-6, IL-10, IL-21, IL-22, and IL-23. [8, 9] Among these cytokines, IL-6 has a positive role in bone resorption through inducing osteoclastogenesis.[10, 11] Thus, impaired STAT3 signaling may disrupt the role of IL-6 in osteoporosis and thereby contribute to the retention of primary teeth in AD-HIES. [12] In line with this notions, some reports have revealed that retention of deciduous teeth is owing to reduced resorption of tooth roots leading to failure of eruption of permanent teeth.[7] Grimbacher et al evaluated 30 patients with HIES and 70 of their relatives and reported primary teeth retention in 72% of them. [13] In another study by O'Connel et al on 34 HIES patients, it was indicated that 75% of subjects older than 7 years had problem with permanent tooth eruption, in the form of prolonged retention of primary teeth or the need for extraction of primary teeth. [14] In another report of 60 patients with the HIES, 76.7% of subjects suffered from intraoral lesions such as fibrotic bridges in the hard palate or keratotic plaques which were more prevalent than the characteristic facial traits. [15] Considering the above findings in the literature, abnormal dentition in our patient is a common feature but as the prominent finding in an adolescent is particularly noteworthy.

Asthma and anaphylaxis were two atypical presentations in this patient. According to the literature, allergic manifestations including allergic rhinitis, asthma, urticaria, and anaphylaxis are not common clinical features in these patients despite their high serum IgE concentrations. Wjst et al tested whether STAT3 mutations were responsible for increased IgE levels in asthmatic children and found it unlikely.[16] Furthermore, some studies have reported no significant association between STAT3 gene expression and either mild or severe refractory asthma. [17] However, positive findings regarding an allergic background in our case including neonatal dermatitis with positive skin prick test to milk, egg, and wheat and a favorable response to an elimination diet, recurrent asthma exacerbations, as well as a history of anaphylaxis may denote an underlying atopic predisposition.

Taken together, our findings indicate that clinical evaluations of some atypical presentations, such as asthma and anaphylaxis, along with immunological and genetic analyses can be helpful to better diagnosis and management of AD-HIES, which can improve life quality of patients. Therefore, patients suffering from allergic and infectious diseases, autoimmune disorders, and dental abnormalities should be investigated by clinical, immunological, and genetic tests to determine possible mutations in *STAT3* gene.

Acknowledgments:

The authors would like to give special thanks to Professor Bodo Grimbacher for performing the genetic study.

Conflict of interest

The authors declare that they have no competing interests.

Author contribution

Marzieh Heidarzadeh Arani and Atena Ramezanali Yakhchali contributed to the conceptualization, data curation, supervision, and writing the original draft; Mohammad Gharagozlou, Sepideh Darougar, Zahra Chavoshzadeh, and Mahnaz Jamee and Hossein Motedayyen reviewed and edited the final manuscript. All authors read and approved the final manuscript.

Ethical approval

Written informed consent was obtained from parents for the clinical data and photos of their child to be published. This study is approved by the Ethics Committee of Kashan University of Medical Sciences.

Data availability statement

All data generated or analyzed during this study are included in this published case report.

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Figure legend

Figure. 1) Dental complications in a patient with AD-HIES. Permanent teeth erupt adjacent to primary teeth (double rows of teeth).