

Case Report



A Novel EDA Variant Causing X-Linked Hypohidrotic Ectodermal Dysplasia: Case Report

Nastaran Eivazi,¹ Erfan Zaree,² Elham Safarzadeh,^{3,4} Rassol Molatefi^{3,1*}

¹Department of Pediatric, Bouali Children's Hospital, Ardabil University of Medical Sciences, Ardabil, Iran

²Students Research Committee, Ardabil University of Medical Sciences, Ardabil, Iran

³Cancer Immunology and Immunotherapy of Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

⁴Department of Microbiology, Parasitology, and Immunology, Ardabil University of Medical Sciences, Ardabil, Iran

*Corresponding Author: Rasol Molatefi, Email: rmolatefi@yahoo.com

Summary

X-linked hypohidrotic ectodermal dysplasia (XL-HED) is a rare hereditary disorder affecting the development or function of two or more ectodermal derivatives, including teeth, hair, nails, and sweat glands. It is defined by the triad of signs that consists of abnormal or missing teeth (anodontia or hypodontia), sparse hair (atrachosis or hypotrichosis), and inability to sweat because of absence of sweat glands (anhidrosis or hypohidrosis). Their vast clinical inconsistency and etiological heterogeneity may lead to complications for the establishment of a syndromic diagnosis. In the study, we aim to report a clinical characteristic of a patient affected by EDA, which is a caring deletion at exon 2 in the *Ectodysplasin A (EDA)* gene on ChrX:69176876-69176977.

A 12-month-old boy was referred to Bou-Ali Children's Hospital with complaints of fever, cough, dyspnea, and lethargy. On clinical examination, he has sparse hair, conical teeth, scanty eyebrows, and low-set and overfolded ears. He had a history of recurrent hospitalization episodes (4 times) due to lobar pneumonia treated with intravenous antibiotics without abscess formation or effusion. Based on history, clinical features, and biopsy, genetic study with whole exome sequencing (WES) demonstrated a hemizygous deletion of exon 2 in EDA on ChrX: 69176876-69176977, whereas his parents did not have this deletion.

Based on history, clinical features, biopsy, and genetic study, ED was diagnosed with hemizygous deletion, while his parents do not have this deletion. Molecular genetic analysis of whole exome sequencing (WES) and Sanger sequencing demonstrates hemizygous deletion of exon 2 in EDA on ChrX: 69176876-69176977.

Keywords: Ectodermal dysplasia (ED), Recurrent pneumonia, X-linked genetic diseases, Ectodermal layers

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Introduction

X-linked hypohidrotic ectodermal dysplasia (XL-HED) is a rare developmental condition defined by congenital abnormalities in two or more ectodermal origin tissues, such as teeth, skin, hair, mucous membrane, sweat glands, and nails. The estimated incidence of ED is about seven cases per 100,000 people, and more than 150 distinct varieties have been documented in ClinVar.¹ During embryonic development, the expression of the Ectodysplasin A (EDA) gene is essential for the formation of skin appendages. EDA gene is a distinct member of the tumor necrosis factor (TNF) family.^{2,3} The EDA signaling pathway is regulated by EDA, EDAR, and EDARADD, which comprise a distinct complex mostly localized to the skin appendages.⁴ There are two primary categories of ED that are distinguished by the level of sweat gland function. The first kind is known as a hypohidrotic form, characterized by hypodontia, hypohidrosis, and hypotrichosis in a classical triad pattern. The second form, known as the hydrotic (Clouston's syndrome) type, does not involve the sweat glands and is passed down as an autosomal dominant. A mutation in the connexin gene, either GJB6 or connexin-30, is the root

cause of hydrotic ED.⁵

To date, three genes have been identified as mutated under distinct conditions: *EDA*, *EDARADD*, and *EDAR*. Over 90% of cases occur due to mutations in the X-linked gene, whereas most autosomal inheritance cases involve the *EDARADD* and *EDAR* genes.⁶ HED with immunodeficiency (HED-ID or EDAXID) is caused by mutations in the NF-κB essential modulator (NEMO), which is encoded by the X-linked *IKBKG* gene, even though EDA pathway abnormalities have no apparent effects on the immune system. The inhibitor of the NF-κB kinase complex, which regulates the phosphorylation of IκB and subsequently permits nuclear translocation of NF-κB, contains NEMO as a key component.^{7,8} Due to the critical involvement of NF-κB signaling in innate and adaptive immunity, HED-ID is distinguished by exceptional vulnerability to pyogenic bacteria, herpesviruses, and mycobacteria. Because of this, the phenotypes of HED with immunodeficiency are varied and dependent on mutation, with the potential to affect T-cell activity, immunoglobulin class switch recombination, and toll-like receptor (TLR) function. Noteworthy is the fact that NF-κB is a crucial



downstream component of the VEGFR-3, EDA, and RANK-ligand pathways; as a result, several reported manifestations in HED-ID include ectodermal dysplasia, osteoclast abnormalities, and lymphedema.^{8,9}

HED is the most frequent form of ectodermal dysplasia, which affects ectoderm development, identified by dysplasia of various skin appendages. Clinical characteristics of ED include Nail deformities, reduced sweating, thinning hair, hypotrichosis, malformed teeth, and meibomian gland dysfunction. High fevers are common in ED patients because of impaired sweating.¹⁰ Facial deformities are common among adults with XL-HED, and they are more likely to develop problems with their eyes, ears, and teeth.¹¹ Since ED affects several systems, physicians must overcome many treatment challenges, and unfortunately, XL-HED has no curative treatments. Therefore, the family must have proper genetic counselling and a prenatal diagnosis to be guided through understanding the dangers associated with XL-HED.¹² In the study, we aim to report a clinical characteristic of a patient affected by EDA, which is carrying deletion in exon 2 of EDA on ChrX

Case presentation

A 12-month-old boy was referred to Bou-Ali hospital with complaints of fever, cough, dyspnea, and lethargy. He was admitted for the diagnosis of bacterial pneumonia. The patient had an unusual face and a history of 4 hospitalizations due to pneumonia. On clinical examination, he has sparse hair, conical teeth, scanty eyebrows, and low-set and overfolded ears. The nasal bridge is depressed, consistent with a saddle nose. His current weight is 9500 g, height is 73 cm, and head circumference is 44 cm. The patient has a normal neurodevelopmental history. The echocardiography was normal, with no abnormality in the shape and function of cardiac valves.

The child, the result of a consanguineous marriage, was born at term from a healthy pregnant mother. His birth weight was 2700 g, height was 47 cm, head circumference was 35 cm, and history of NICU hospitalization was negative. The mother had no hypothyroidism or gestational diabetes mellitus, no prenatal infection, and no specific drug history apart from vitamins and some safe antibiotics in pregnancy. He is the first child with a negative family history of immune deficiency. The BCG vaccine, as per the Iranian children's vaccination protocol, was injected at birth with no complications up to now. Live polio vaccines (OPV) were administered without complications at birth, two months, and four months. He has a history of oral thrush once in the neonatal period without relapse or resistance. The history of frequent diarrhea was negative.

He had a previous history of recurrent hospitalization episodes (3 times) due to lobar pneumonia treated with IV antibiotics without abscess formation or effusion. The patient also had a history of being hospitalized at 5 months of age for hyperthermia and lethargy. Also. According to the abnormal appearance and hair, the skin punch biopsy from his palm revealed skin without an eccrine gland, suggestive of anhidrotic ectodermal dysplasia. The hair shaft shape

under the microscope was normal. The patient's multiple complete blood counts with differentiation showed no neutropenia, lymphopenia, or thrombocytopenia. Serum immunoglobulins, IgG, IgA, IgM, and IgE levels were 555 mg/dl, 22.6 mg/dl, 250mg/dl, and 15.8 IU/ml, respectively. Nitro blue tetrazolium test and C3, C4, and CH50 levels were normal. Based on the flow cytometry result, the percent of CD4⁺ and CD8⁺ T cells, CD19⁺ B cells, and NK cells in total leukocytes were 35%, 23%, 29%, and 10%, respectively. Based on history, clinical features, biopsy, and genetic study, ED was diagnosed with hemizygous deletion, while his parents do not have this deletion. Molecular genetic analysis of whole exome sequencing (WES) demonstrates hemizygous deletion of exon 2 in EDA on ChrX: 69176876-69176977.

Discussion

Ectodermal dysplasia, or ED as it is commonly known, is a condition that is seen with abnormal development of ectodermal derivatives in the early stages of embryogenesis. The most common type of ED is X-linked HED (XL-HED).^{13,14} The XL-HED type (also known as Christ-Siemens-Taurine syndrome) is characterized by facial dimorphism in addition to the typical triad of hypodontia, hypohidrosis (abnormal sweating) and hypotrichosis. The possible hair manifestations are numerous, ranging from sparse, short, fine and dry hair to no hair at all and decreased density of the eyebrows.¹⁵ The other form, the hidrotic type, is characterized by onychodysplasia, palmoplantar hyperkeratosis, and hypotrichosis without dysfunctions of sweat glands.¹⁰

We present a boy patient with no family history of ED. The current case emphasizes the fact that XL-HED can occur without affected relatives, as *de novo* hemizygous deletions (like the exon 2 deletion in EDA that we identified in our patient) can spontaneously occur, an observation with significant implications for genetic counseling. His clinical symptoms were consistent with the HED classical triad. The patient's recurrent fevers and hospitalizations are consistent with the thermoregulatory failure of anhidrosis, highlighting the fact that heat intolerance is not merely a quality-of-life issue but a potentially fatal complication of this disorder if unrecognized. Heat intolerance is a common complaint due to a reduced ability of the sweat glands to function. It can be especially dangerous for children and can be fatal if left untreated. Our patient was seen at age 5 months with severe hyperthermia and lethargy. He had four hospitalizations for lobar pneumonia as well. This pattern of recurrent pulmonary infections warrants special consideration. Pneumonia is not a principal symptom or criterion for the diagnosis of this disease. Some unusual sinopulmonary infections have been reported in these patients.¹⁶⁻¹⁸

It is not clear why they are so vulnerable is not known and many suggestions have been made. Includes: dysfunction of submucosal glands of the respiratory tract, morphological and functional disorders of the palate and pharynx, concomitant atopy, and immune system

deficiencies. Recurrent pneumonia in our patient with normal anatomy and function of the pharynx or palate and normal initial immune function testing suggests that standard immunologic panels may not capture all relevant defects, particularly those affecting mucosal barrier function or local innate immunity of the respiratory epithelium. Functional defects of the acquired immune system (cellular and humoral) and defects of the innate immune system may be normal on initial examination. Therefore, in XL-HED patients with recurrent infections, a more extensive evaluation should be considered, including the assessment of mucociliary clearance, salivary and respiratory gland function, and, if clinically indicated, genetic testing for NEMO/IKBKG mutations to exclude HED-ID, even in the presence of unremarkable preliminary immune studies.¹⁹

He also shows facial manifestations such as low density of eyebrow and eyelash hair, and blond sparse hair with little distribution on the scalp. Facial features include a saddle-shaped nose, low-set ears, conical teeth, depressed nasal bridge, and everted lips. These characteristic craniofacial and dental features are often underrecognized in early infancy, and their presence should lead to early genetic assessment to facilitate diagnosis and prevent complications. An early prenatal diagnosis can be made in patients with a family history of HED using DNA-based linkage analysis and genetic testing for mutations in EDA, EDAEADD, and EDAR. Ultrasound imaging and fetal tissue biopsies are two diagnostic procedures that can be done safely in the second trimester of pregnancy.¹² Our case, however, demonstrates that even without a family history, whole exome sequencing is a useful diagnostic tool for the detection of de novo mutations and should be performed early in sporadic cases with suggestive phenotypes. Recombinant EDA-A1 is currently in Phase II clinical trials and is being given to newborn infants in an attempt to reduce some of their symptoms.²⁰ This targeted therapy is promising, but not yet widely available. Until then, management will depend on vigilant supportive care, anticipatory guidance, and multidisciplinary coordination to address the multisystemic nature of XL-HED.

Conclusion

Here, we report a sporadic case of XL-HED in a 12-month-old male with a de novo hemizygous deletion of exon 2 in EDA, confirmed by whole exome sequencing. This case highlights 3 important points: first, XL-HED should be considered even in the absence of a family history because of de novo mutations; second, recurrent lobar pneumonia can be a prominent manifestation even when it is not a classic diagnostic criterion; and third, normal initial immune studies do not completely exclude susceptibility to infection, because defects in mucosal or glandular function may underlie pulmonary vulnerability. XL-HED is a systemic disorder that requires early recognition, aggressive preventive care, and long-term multidisciplinary management by dermatology, dentistry, pulmonology, and genetics. Recombinant EDA-A1 and other targeted treatments are promising, but at present care consists

of proactive symptomatic management and caregiver education. Genetic counseling is still important in reproductive planning. This case emphasizes the necessity of integrating molecular diagnostics with thorough clinical phenotyping in an effort to improve outcomes in affected individuals.

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Artificial Intelligence Use Disclosure

ChatGPT (OpenAI) was used solely to assist with language editing and the generation and refinement of illustrative images; all AI-generated outputs were critically reviewed and revised by the authors, who take full responsibility for the final content.

Authors' Contribution

Conceptualization: Nastaran Eivazi, Erfan Zaree, Elham Safarzadeh. Investigation: Nastaran Eivazi, Erfan Zaree, Elham Safarzadeh.

Methodology: Rassol Molatefi.

Supervision: Rassol Molatefi.

Writing—Original Draft: Nastaran Eivazi, Rassol Molatefi

Writing—Review & Editing: Rassol Molatefi

Competing Interests

The authors declare no competing interests.

Ethical Approval

This study was approved by the Ethics Committee of Ardabil University of Medical Sciences, Ardabil, Iran (IR.ARUMS.REC.1402.166).

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