

Co-Occurrence of Hypohidrotic Ectodermal Dysplasia and Food Protein-Induced Enterocolitis Syndrome: A Report of a New Ectodysplasin A Variant

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Established Facts

- X-linked HED is the most frequent form of ED and is caused by variants in *EDA*.
- The prevalence of atopic manifestations in patients with ED is higher than in the general population.

Novel Insights

- We report a new c.100dupG variant in *EDA* responsible for HED.
- We report the co-occurrence of a FPIES which could possibly be part of the clinical heterogeneity of HED or a dual diagnosis in a context of atopy.

Keywords

Hypohidrotic ectodermal dysplasia · Food protein-induced enterocolitis syndrome · *EDA*

Abstract

Introduction: Ectodermal dysplasias (EDs) are a large group of rare and complex genetic disorders, affecting the development of two or more ectodermal structures. Hypohidrotic

ED (HED) is the most frequent ED's phenotype and is characterized by hypodontia, hypotrichosis, and hypo/anhidrosis, leading to heat intolerance and hyperthermia. **Case Presentation:** We report a case of a 2-year-old girl with hair and teeth abnormalities associated with severe digestive symptoms responsible for failure to thrive. Genetic analysis by mass sequencing in parallel on a 4,867-gene panel was performed in duo (index case and her mother). The girl showed the presence of a new de novo c.100dupG variant in *EDA*

responsible for HED associated with a diagnosis of food protein-induced enterocolitis syndrome (FPIES). **Conclusion:** We describe a patient with HED and a new *EDA* variant associated with a diagnosis of FPIES, both implicating increased intestinal permeability. The inclusion of FPIES as a possible digestive symptom of HED can be suggested, although it may occur only in a context of atopy.

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Introduction

Ectodermal dysplasias (EDs) are a group of heterogeneous genetic disorders, affecting the development of two or more ectodermal structures, including the teeth, skin, nails, and eccrine/sebaceous glands. Hypohidrotic ED (HED) is the most frequent type of ED. Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergy that occurs with gastrointestinal symptoms and is reported to be associated with an increased risk of atopy [1]. The prevalence of atopic manifestations among ED patients is higher than in the general population [2]. However, the association of these 2 conditions has never been reported. Herein, we report the case of a patient with a new *EDA* variant and a diagnosis of FPIES. We discuss the relevance of this syndrome as part of the clinical heterogeneity of HED or as a manifestation of atopy.

Case Report

We report the case of a two-year-old girl who presented with hair and dental anomalies associated with major digestive disorders leading to failure to thrive. She was hospitalized at the age of 1 month for severe dehydration and metabolic acidosis and to assess a history of acute emesis, diarrhea, and weight loss.

The pregnancy was characterized by an oligoamnios and an intrauterine growth restriction. The labor had to be induced due to maternal hypertension. She was born at 38 weeks at 2,400 g (<P3) and 44 cm (<P3). Her family background revealed a history of slight atopy.

On admission, the anamnesis highlighted serious digestive symptoms such as recurrent bloody diarrhea, vomiting, and inappetence during the transition from breastfeeding to cow milk formula, leading to failure to thrive. Prick tests for cow milk and a stool culture were realized and were both negative.

An extensively hydrolyzed formula was prescribed during her hospitalization without any improvement; therefore, a milk formula containing amino acids was introduced and well tolerated. She then presented a favorable outcome. Meantime, this new formula permitted her to gain some weight and to reach the 25th percentile.

At the time of dietary diversification, recurrence of vomiting was noted in the hours following consumption of potatoes or

chicken, as well as diarrhea and digestive discomfort accompanied by intense crying. She also presented signs of IgE-mediated allergy such as hives, angioedema, and immediate digestive symptoms (diarrhea and emesis) when consuming green peas and fish.

During her follow-up, prick tests were negative for cow milk, soy milk, egg, potatoes, apple, banana, pear, green peas, poultry, beef, and various fishes, and circulating food-specific IgE levels were absent. A jejunal biopsy was performed and was banal.

Her clinical presentation suggested a non-IgE gastrointestinal-food allergy. The rapid symptoms resolution after specific dietary eviction and the reproducibility upon reexposure validated the diagnosis of acute FPIES.

At 9 months, the appearance of the first teeth was characterized by the presence of conical lower incisors (shown in Fig. 1a). At two years old, there was hypodontia and dysplasia of the upper incisors (shown in Fig. 1b). Hypotrichosis in patches was also noted with dry and brittle hair (shown in Fig. 1c). The hair shafts were normal. She did not have any facial dysmorphism. Her skin was slightly dry but without eczema. Heat intolerance with a tendency to hyperthermia in summer is reported by the patient's mother. However, the sweat test showed results within the normal range.

Clinical exome sequencing (4,867 known disease causing genes, SeqCap EZ Choice XL NimbleGen Roche) performed in duo (proband and maternal DNA, father unavailable) showed the presence of c.100dupG p.(Ala34fs) heterozygous variant in the *EDA* gene (NM_001399.4) (shown in Fig. 2), responsible for ED type 1, hypohidrotic, X-linked (MIM: 305100). No clinically significant variants were found in other genes. The presence of this variant has been validated by Sanger sequencing.

Discussion

EDs are a large group of rare and complex genetic diseases, affecting the development of two or more ectodermal structures, including hair, teeth, nails, and eccrine sweat glands [3, 4]. EDs are characterized by clinical and genetic heterogeneity, with incomplete penetrance and variable expressivity. *EDA*, *EDAR*, *EDARADD*, and *WN-T10A* genes are responsible for the HED phenotypes, each with different modes of transmission. These genes are involved in the TNF α pathway that lead to NF- κ B activation [2].

The X-linked HED subtype is the most prevalent and is characterized by hypodontia, hypotrichosis, and hypo/anhydrosis, leading to heat intolerance and hyperthermia, responsible for 30% of the mortality of this syndrome [5]. The hemizygous males present a more severe phenotype, while heterozygous female carriers present variable expression due to the level of lyonization, commonly known as X-inactivation [6].

This c.100dupG (p.Ala34fs) variant has never been reported in the literature. The null variant (frame-shift) in the *EDA* gene, causing loss of function, is a known mech-

bances in infants due to local T-cell infiltration and inflammation and imbalanced TNF α /TGF β response [10]. Our patient presented with a diagnostic of FPIES according to the diagnostic criteria of the International Consensus of FPIES [11].

Atopic children are at greater risk of developing FPIES [10, 12], and children with EDs have significantly more chances to present atopic diathesis and IgE-mediated allergies [2, 4, 6]. A study of 347 HED patients investigating the occurrence of digestive manifestations and food allergies showed that more than one-third of HED patients had allergic reactions to specific foods [4], but this study did not identify any cases of FPIES.

Both HED and FPIES implicate increased intestinal permeability and involve the TNF α /TGF β pathway. In ED, the junction may be distorted due to impaired development and that implies perturbations in epithelial-mesenchymal interactions. Therefore, the selective mucosal barrier does not operate effectively which allows enhanced sensitivities and allergies and, in this particular case, FPIES. To our knowledge, the association between ED and FPIES has not been reported yet. However, the diagnosis of FPIES is often underreported.

At present, it is not possible to know whether FPIES in patients with EDs are related to a disturbance of the barrier functions of the skin and mucous membranes or whether they are full part symptoms of ED with a variable expression [4]. Some authors [2] suggest that manifestations of atopy may be part of the ED picture and base their argument on the absence of pathogenic variants predisposing to atopy. We also did not find any variants predisposing to atopy in the clinical exome. Our patient did not have eczema or asthma despite a family history of atopy. However, it is possible that this is a dual diagnosis in the same patient.

Further reports of patients presenting similar clinical phenotypes correlated with genomic information are needed. Meantime, this might be a diagnostic lead for HED patients with nondocumented food allergy.

Conclusion

We have reported a new c.100dupG variant in *EDA* occurring in a patient with a concurrent diagnosis of FPIES. Although the underlying mechanisms have not yet been elucidated, both HED and FPIES implicate increased intestinal permeability. More reports are needed to support this association.

Statement of Ethics

Written informed consent was obtained from the patient's parents for publication of the details of their medical case and any accompanying images. This study protocol was reviewed and approved by the Ethical Committee of CHU Saint-Pierre and Hôpital Universitaire des Enfants Reine Fabiola (ULB, Brussels, Belgium) under the reference CE/18-09-10 - B076201838166.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Déborah Salik: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, visualization, and writing – original draft. Florine Moulart: conceptualization, data curation, formal analysis, visualization, and writing – original draft. Martina Marangoni: data curation, formal analysis, methodology, supervision, and writing – original draft. Dimitrios Salamouras and Marie-Sophie André: data curation, investigation, visualization, and writing – original draft. Catheline Vilain: data curation, formal analysis, investigation, supervision, and writing – original draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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