A novel mutation in the EDA gene in a Filipino family with X-linked hypohidrotic ectodermal dysplasia

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X-linked hypohidrotic ectodermal dysplasia (XLHED) is a rare genetic disorder that affects the development and function of several structures of ectodermal origin, such as hair, teeth and sweat glands. It is associated with ectodysplasin-A (EDA) gene mutation, necessary for ectodermal development.

We present a case of two brothers who were referred to our clinic due to recurrent fever and rash. Prior to referral, patients had multiple admissions due to fever and underwent a series of tests to determine the cause of fever but to no avail. Upon examination, erythematous scaly papules and plaques on the extremities, alopecia, absence of dermatoglyphic patterns, and atypical facial features were noted. Skin biopsy revealed absence of eccrine glands. Genetic analysis revealed EDA mutation in exon 8 that resulted in a delayed termination codon rather than a premature termination codon, causing XLHED. This novel mutation has never been reported in the literature.

INTRODUCTION

X-linked Hypohidrotic ectodermal dysplasia (XLHED; MIM 305100) is a rare genetic disorder that affects the development and function of several structures of ectodermal origin, such as hair, teeth and sweat glands. Hypohidrotic ectodermal dysplasia is associated with mutations in genes that encode ectodysplasin-A (EDA), EDA receptor (EDAR), EDA receptor-associated death domain (EDARADD), and WNT10A. Mutations in any of these genes affects the NF-κB signal transduction pathway necessary for initiation, formation, and differentiation of skin appendages. HED is a rare X-linked recessive genodermatosis with a low prevalence worldwide, with an incidence rate of 0.001% in the Philippines according to the Philippine Dermatological Society (PDS) central registry.

The characteristic findings of XLHED are hypotrichosis, hypodontia and reduced sweating. Lack of sweating leads to an increased body temperature, presenting as recurrent fever or collapse. Hence, we were able to determine the cause of the ‘fever of unknown origin’ of a young boy with a history of multiple admissions and consults due to recurrent febrile episodes through the dermatologic findings and genetic testing.

Several mutations in the EDA gene have been reported in XLHED, although none has been reported from the Philippines. Here we report the clinical, histopathological and molecular findings of a Filipino family with HED. Furthermore, we found in this family a novel mutation in exon 8 leading to a frameshift and a delayed downstream termination codon, an unusual consequence even in the global database of all pathogenic mutations.

CASE REPORT

A 3-year-old boy was referred to our clinic in May 2016 suffering from recurrent fever and rash. He was born to nonconsanguineous parents, with an uneventful perinatal history. His younger brother (6-month old) had similar dermatologic findings and thermoregulation disturbances (Figure 1) but no other family members, including both parents, had any other relevant history.

Figure 1. Family pedigree. The proband is a 3-year old boy (1) who has a similarly affected 6-month old younger brother (2).
The two brothers had several consults and admissions due to fever, although their guardian could not recall the diagnoses made on these occasions. In all these visits, the patients were given medications for fever, including antibiotics. Their latest visit to their pediatrician was for a 2-week fever accompanied with a rash. Multiple diagnostic tests, including hematologic, biochemical, radiologic and bacterial cultures were done by their attending doctor but no cause for the fever was identified. He was subsequently referred to our clinic for review of some skin lesions.

Upon examination, his face revealed prominent features comprising frontal bossing, large nostrils, wide cheek bones, scanty eyebrows & eyelashes, low-lying and anteriorly placed ears, thick everted lips with delayed dentition and conical incisors (Figure 2). Dermatologic examination revealed erythematous scaly papules and plaques on the extremities (Figure 3). The scalp showed patchy alopecia, and dermoscopy revealed sparse, lightly pigmented short hairs (Figure 4). Nail findings were normal, but there was an absence of whorls and ridges in the patient’s fingerprints (Figure 5). The patient’s younger brother also had a similar facial appearance and dermatologic findings (Figure 6). There were no developmental and motor delays observed in the brothers. We were not able to examine the parents, since both of them work abroad.
Following informed consent, a skin biopsy of the patient’s palms revealed a normal epidermis but an absence of eccrine structures (Figure 7). Genetic and molecular analyses on the two brothers’ blood specimen were done following consent from the patients’ guardian. DNA was isolated from peripheral blood leukocytes of the patients. We noted a hemizygous single nucleotide deletion, c. 1131delC, in exon 8 of EDA. This mutation led to a frameshift and a delayed downstream termination codon, designated p.Thr377Thrfs*37 (Figure 8). These molecular data support a diagnosis of X-linked hypohidrotic ectodermal dysplasia (XLHED).

The patient and family were managed with multidisciplinary care. Dermatologic management involved use of emollients and mild corticosteroids (hydrocortisone 1% cream) twice a day for one week with complete resolution of lesions. Future plans for the hair and dental defects will focus on wigs and orthodontic prosthesis.

The patient was referred back to pediatrics, informed them of the diagnosis, and was made aware of the cause of
the “fever of unknown origin”. This important information will now hopefully lead to measures to prevent episodes of hyperpyrexia, consults/admissions, unnecessary antipyretic medication use, and administration of antibiotics that could lead to resistance of infection and economic burden. The family was advised about proper thermoregulation of the affected individuals with frequent cooling and hydration, especially during the summer months time. Early guidance about temperature regulation and its risks were given. Proper skin care and monitoring was also instructed to the caregivers.

Furthermore, patient/family education and genetic counseling were also provided to the family. This important process of providing the patients and family with information on the nature, inheritance and implications of their genetic condition can help make informed medical and personal decisions. Risk and prognostication to family members were provided, as summarized in Table 1.

**Table 1. Risk of transmission among family members**

<table>
<thead>
<tr>
<th>FAMILY MEMBER</th>
<th>GENE MUTATION</th>
<th>RISK OF TRANSMISSION TO OFFSPRING/S</th>
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<tbody>
<tr>
<td>Father</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Mother (Obligate carrier)</td>
<td>+</td>
<td>50%, regardless of sex - 50% (affected males) - 50% (female carriers)</td>
</tr>
<tr>
<td>Two brothers (patient 1 &amp; 2)</td>
<td>+</td>
<td>100% to all daughters, obligate carriers (show minimal manifestations) - 0% to sons</td>
</tr>
<tr>
<td>Two elder brothers, with no manifestations</td>
<td>-</td>
<td>0%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

HED or Christ-Siemens-Touraine syndrome is a rare X-linked recessive genetic condition characterized by the triad of reduced sweating, hypotrichosis, and defective dentition. To date, several different mutations in the EDA gene have been described in the literature. The EDA gene is located on chromosome X (Xq12.2-q13.1), and encodes ectodysplasins A1 and A2 (EDA-A1 and EDA-A2) involved in the differentiation of skin appendages and other ectodermal structures. ED genes provide signals for producing proteins (ectodysplasin A) that forms a signaling pathway for the interaction between the ectoderm and mesoderm cell layers (Figure 9). These interactions are essential for the formation of several structures that arise from the ectoderm, including the sweat glands, hair and teeth. Mutations in EDA will lead to improper signaling leading to the characteristic features of HED.

In our case, the mutation does not appear to have been reported in the literature. This novel mutation appears to be the most 3’ of all reported mutations in EDA this far, and furthermore, it results in a delayed termination codon rather than a premature termination codon. Potentially, this scenario could lead to a slightly less disruptive change to the protein with perhaps a milder phenotype. However, the C-terminus of the protein is a functionally important domain and so even this mutation could result in almost identical changes to the majority of other mutations reported, with similar phenotypic consequences. Identification of this mutation confirms the diagnosis of X-linked HED. Furthermore, the diagnosis could translate to a better genetic counseling to the family. Being transmitted as X-linked recessive and although we were unable to test the parents, it is highly likely that the mother is an obligate carrier of the disease-causing EDA mutation. The genetic counseling for future pregnancies indicates 4 possible outcomes: 25% will be clinically and genetically normal females; 25% will be heterozygous carrier females (clinically mostly normal but perhaps with subtle, focal dental or sweating defects); 25% will be clinically and genetically normal males; and, 25% will be males with XLHED.

The most remarkable phenotypic manifestation of HED is hypohidrosis, which can be apparent in the second year of life due to repeated episodes of unexplained fever. The inability to sweat results in intolerance to heat, leading to hyperpyrexia, precisely what our HED patients experienced. The unexplained fever may be more severe especially during the summer months.

Dermatologic findings include dry and thin skin with hyperpigmentation and appears prematurely aged, due to the partial absence of sweat and sebaceous glands.
Furthermore, there is an increased susceptibility to atopic or allergic disorders. Other phenotypic findings include hypotrichosis, due to reduced hair follicles, hypodontia with conical-shaped teeth, facial abnormalities and dermatoglyphic anomalies that were all present in our case. Significant morbidity and mortality is due to hyperthermia and risk of respiratory tract infections due to the lack of nasal, tracheal and bronchial glands, although the clinical emphasis is always on prevention of hyperpyrexia through hydration and thermoregulation.

With regards to more specific treatments, studies in mouse and dog models of XLHED using recombinant ectodysplasin A (Fc:EDA1) protein have shown partial reversal of disease, and improvement of airway infections, although a human clinical trial using recombinant protein in affected male infants failed to demonstrate clinical benefits.

Patients afflicted with this hereditary deformity suffer from poor psychological and physiologic development as a result of aesthetic and abnormal features. Early intervention with multidisciplinary collaborative efforts from dermatologists, pediatricians, geneticists, psychologists, dentists and other specialists can help rehabilitate and improve the appearance and function among these patients.

Genetic testing on the proband’s mother should be endeavored in the future to substantiate genetic counselling for this family. An ongoing surveillance of the children’s growth and development is important as this novel mutation may involve other problems such as developmental delay and/or immune deficiency in the future.

CONCLUSION

Dermatologists play a role in early recognition of this rare hereditary condition that present mainly with fever of unknown origin. The dermatologic manifestations can prompt further investigation of HED through molecular analysis. This approach confirmed our diagnosis by disclosing a novel mutation in EDA.

REFERENCES


