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Hypohydrotic ectodermal dysplasia- Genetic basis and treatment- A case report

Srinivas Nallanchakrava; Pratej Kiran Kanumuri*; Dwitha Animi Reddy; Ganta Naga Sribala

***Pratej Kiran Kanumuri**
Panineeya institute of dental sciences, Hyderabad, India
Email: pratejkiran@gmail.com

Abstract

Ectodermal dysplasia is a group of disorders defined by the abnormal development of two or more structures derived from the ectodermal layer. The most frequently reported manifestation of ectodermal dysplasia is hypohidrotic dysplasia, also termed Christ-Siemens-Touraine syndrome and an hidroticdysplasia. Patients with this form of ectodermal dysplasia exhibit the following clinical traits: hypotrichosis, hypohidrosis, and cranial abnormalities. The disease is inherited by autosomal-dominant, autosomal-recessive, or x-linked genetic transmission. These disorders are relatively rare and occur in 1 in 10,000 to 1 in 100,000 births. It is both physically and emotionally devastating to the patients; hence early diagnosis and treatment are very much necessary rehabilitate the function, aesthetics and emotional stability. This case report outlines the genetic basis of Hypohidrotic ectodermal dysplasia using "InhT1-ectodermal dysplasia" test, Sanger sequencing method and also the prosthetic restoration of function and aesthetics for a 10 year-old boy with ectodermal dysplasia.

Keywords

ectodermal dysplasia; hypotrichosis; hypohidrosis

Introduction

The ectodermal dysplasia's (EDs) comprise a large, heterogeneous group of inherited disorders that are defined by primary defects in the development of hair, teeth and more tissues derived from the embryonic ectoderm [1,2,3].

The most frequently reported manifestation of ectodermal dysplasia is hypohidrotic dysplasia, also termed Christ-Siemens- Touraine syndrome and anhydrotic dysplasia. Patients with this form of ectodermal dysplasia exhibit the following clinical traits: hypotrichosis, hypohidrosis, and cranial abnormalities [4]. X-linked hypohidrotic ED (Christ-Siemens-Touraine syndrome) is the most frequent form; the diagnosis is usually made with the identification of hypotrichosis, characteristic facial features such as midface deficiency, sparse hair, depressed nasal bridge, frontal bossing hypohidrosis (and more rarely anhydrosis), and teeth abnormalities. The nails are usually normal. Abnormalities in the development of tooth buds result in hypodontia and peg shaped teeth [5].

Dental defects represent a core clinical feature of many EDs: anodontia, polydontia, dysplastic teeth, retained primary teeth, deficient enamel development (amelogenesis imperfecta), dentine

deficiency (dentinogenesis imperfecta), and under development of the alveolar ridge are seen [6].

The prevalence of EDA is unknown; however, the incidence in male is estimated at 1 in 100,000 births although the condition is usually overlooked in infants (Bergendal et al. 1998) [7]. This X-linked recessive disorder affects males and is inherited through female carriers. This carriers-incidence is probably 17.3 in 100,000 women (Chugh 2016) [8]. The autosomal dominant and autosomal recessive inheritance of EDA is an extremely rare condition.

Case Report

A 10 year old boy, presented to the department of Pedodontics and Preventive Dentistry, PMVIDS, Hyderabad for the evaluation of hypodontia, craniofacial abnormalities, alopecia, absence of sweat glands, pitting of nails and also had history of parchment like skin (FIG: 1 A, B, C, D).

Clinical examination of the patient revealed a fine, sparse eyebrows and eyelashes with perioral and periorbital hyperpigmentation and wrinkling of the skin (FIG: 1 D).

Oral examination revealed reduced number of teeth and conical in shape with prominent lips. Facial features noticed were frontal bossing, prominent supraorbital ridges with depressed nasal bridge. Patient's mother also gave history of recurrent high fevers during summer season with no sweat secretion (FIG: 2 E,F,G).

Orthopantomograms, lateral cephalogram and diagnostic casts were taken to assess the unerupted and missing teeth, facial growth pattern, shape and form of alveolar process for further diagnosis along with the child's blood sample which has been sent to “STRAND CENTER for GENOMICS and PERSONALIZED MEDICINE,” BANGLORE, to assess the gene responsible for ectodermal dysplasia (FIG: 2H,I).

The test done was “InhT1-ectodermal dysplasia” which assess two genes (EDA and IKBKG) implicated in ectodermal dysplasia and the Low coverage regions in the EDA gene have been patched by Sanger sequencing which revealed “A known hemizygous 'likely pathogenic' variant, p.Arg156Leu in exon-2 of the EDA gene”.

To restore the function and the aesthetics of the teeth, removable partial denture prosthesis has been given with aesthetic modification of the conical shaped incisors and periodic follow up was done to assess the alveolar growth and the erupting teeth to modify the existing prothesis till implants are placed (FIG: 3 J,K,L,M).

Discussion

Ectodermal dysplasias (EDs) are a heterogeneous group of disorders characterized by developmental dystrophies of ectodermal structures, such as hypohidrosis, hypotrichosis, onychodysplasia and hypodontia or anodontia [1].

About 160 clinically and genetically distinct hereditary ectodermal dysplasias have been catalogued (Pinheiro and Freire-Maia, 1994) of which Anhidrotic (hypohidrotic) ectodermal dysplasia (EDA) is the most common ED (80%); it is characterized by hypoplasia of hair, teeth and sweat glands [9].

The anhidrotic (hypohidrotic) ectodermal dysplasia is often inherited as an X-linked disorder.

This X-linked recessive disorder affects males and is inherited through female carriers. The diagnostic tool is the typical clinical physiognomy. The most characteristic findings in man are the reduced number and abnormal shape of teeth. The delay in eruption of teeth is often the first step in the diagnosis. The men have an easily recognizable face, also referred to as an 'old man' faces. This can also form a clue to the diagnosis. The number of sweat glands is reduced and both scalp and body hair are sparse, with lack of eyebrows and eyelashes. The carrier female has some phenotypic expressions. The clinical findings in carrier females are the same as those in affected males. One third of the carriers appears healthy, another third of them show mild symptoms, and the rest exhibit significant symptoms, but often milder than the affected males (Sofaer et al. 1981) [10].

All the ectodermal dysplasia's appear to be genetic in aetiology. However, only a small number of ED genes have been genetically mapped or cloned. The gene for EDA was the first X chromosomal gene whose map position was suggested, based on the occurrence of an X; autosome translocation in a female patient ("Anly") with the disease phenotype. Later linkage studies confirmed the suggested position of the gene at Xq12-q13.1 (XLHED-gene) (Kere et al 1996) [10].

The recent cloning of the gene has led to the identification of a novel transmembrane protein "ectodysplasin" (TNF family ligand) and receptor "edar" (TNF receptor). This TNF ligand and receptor have a developmental regulatory role and are tightly associated with epithelial-mesenchymal interactions and signalling pathways that regulate ectodermal appendage formation and organogenesis during the initiation of development (Laurikkala et al. 2001) [11].

In the present case "InhT1-ectodermal dysplasia" test was done which assess two genes (EDA and IKBKG) implicated in ectodermal dysplasia and the Low coverage regions in the EDA gene have been patched by Sanger sequencing which revealed "A known hemizygous 'likely pathogenic' variant, p.Arg156Leu in exon-2 of the EDA gene".

This EDA gene provides instructions for making a protein called "Ectodysplasin A" which is part of a signalling pathway that plays an important role in development of ectodermal structures such as hair follicles, sweat glands, and teeth before birth [12].

Variations in the EDA gene cause hypohidrotic ectodermal dysplasia. The changes lead to the production of a non-functional version of the Ectodysplasin A protein. This abnormal protein cannot trigger chemical signals needed for normal interactions between the ectoderm and the mesoderm. Without these signals, hair follicles, teeth, sweat glands, and other ectodermal structures do not form properly, leading to the characteristic features of hypohidrotic ectodermal dysplasia [13].

The key findings obtained from the test were, the child harbours a 'likely pathogenic' variant in the EDA gene. Variants in the EDA gene are associated with Hypohidrotic ectodermal dysplasia (HED) characterized by hypotrichosis, (sparseness of scalp and body hair), hypohidrosis (reduced ability to sweat) and hypodontia (congenital absence of teeth) the features that become apparent in childhood. Deficiency of sweat results in hyperthermia in affected individuals. HED also manifests with distinctive facial features including a prominent forehead, thick lips, and a flattened bridge of the nose. The features as described in HED due to EDA gene defects are similar to the presentation in the affected child. HED is inherited in an X-linked recessive manner. Carrier females have a 50% chance of transmitting the variant

in each pregnancy. Sons who inherit the variant will be affected; daughters who inherit the variant will be carriers [14].

Because of the importance of an early diagnosis, families with X-linked EDA should be offered genetic counselling. This implies a calculation of the risk of having an affected child. For genetic counselling the diagnosis of female carriers is very important. The advantage of diagnosing female carriers of EDA includes the optimization of neonatal and paediatric care for affected male infants, who may be at substantial risk of death in infancy. There is substantial mortality and morbidity in male infants, with about 30% dying in the first two years of life, because of fever or a chest infection (Clarke and Burn, 1991) [15]. So it is important for carrier females to be aware of their 1/4 risk of having an affected child, for the sake of their child's health. For the calculation of the risk for a particular female to be a carrier, both clinical and pedigree information are necessary.

Genetic counselling and carrier testing by Sanger sequencing is also recommended for the parents and the first degree relatives of this child. Data from this test is based on currently available scientific information. This data can be reassessed annually for the presence of any variants that may be newly linked to established genes associated with the patients phenotype or to newly identified disorders since the date of this report [16].

To restore the function and aesthetics, removable prosthesis should be given which is periodically replaced to accommodate the alveolar growth and also to facilitate the eruption of teeth till implants are placed.

It is commonly agreed that osseo-integrated implants should not be placed before cessation of growth. Even in young adults, alveolar growth can be remarkable. There are several published cases of early implant placement in toothless EDA patients; the success, however, has been variable (Bergendal et al. 1998) [7,17]. But in the present case as child is partially edentulous, removable prosthesis was considered as treatment option.

Conclusion

Early diagnosis based on genetic testing can help both the patient and parent to recognize the problems associated with the disease, which could motivate them for early treatment like the prosthetic rehabilitation which restores the function, aesthetics and more importantly emotional stability and they can lead a relatively normal life. Prenatal genetic counselling along with pedigree chart counselling of the affected families also can help the parents to understand the risk of inheriting the disease in their offspring.

Figures

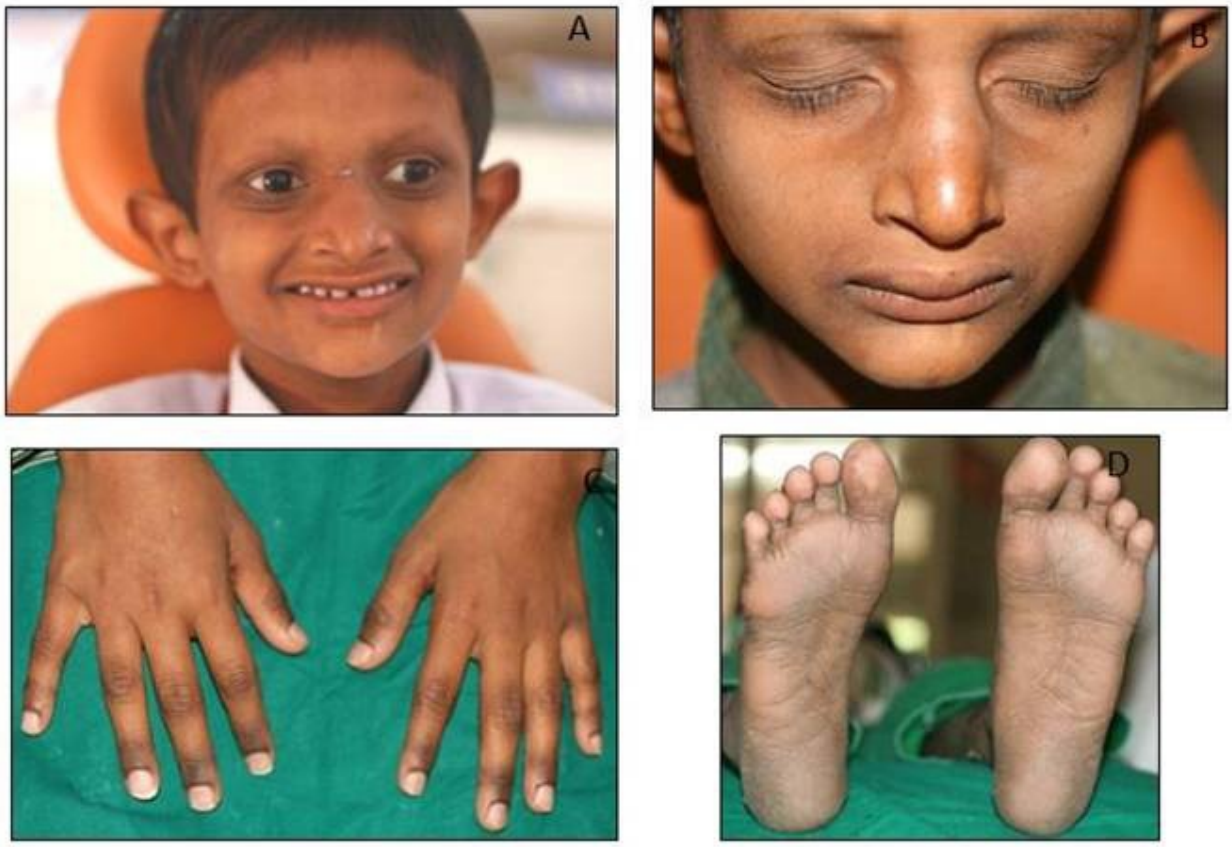

Figure 1: A- preoperative View; B- photograph showing sparse eyebrows & eyelashes, C- photographs showing pitting of nails; D- wrinkling of skin

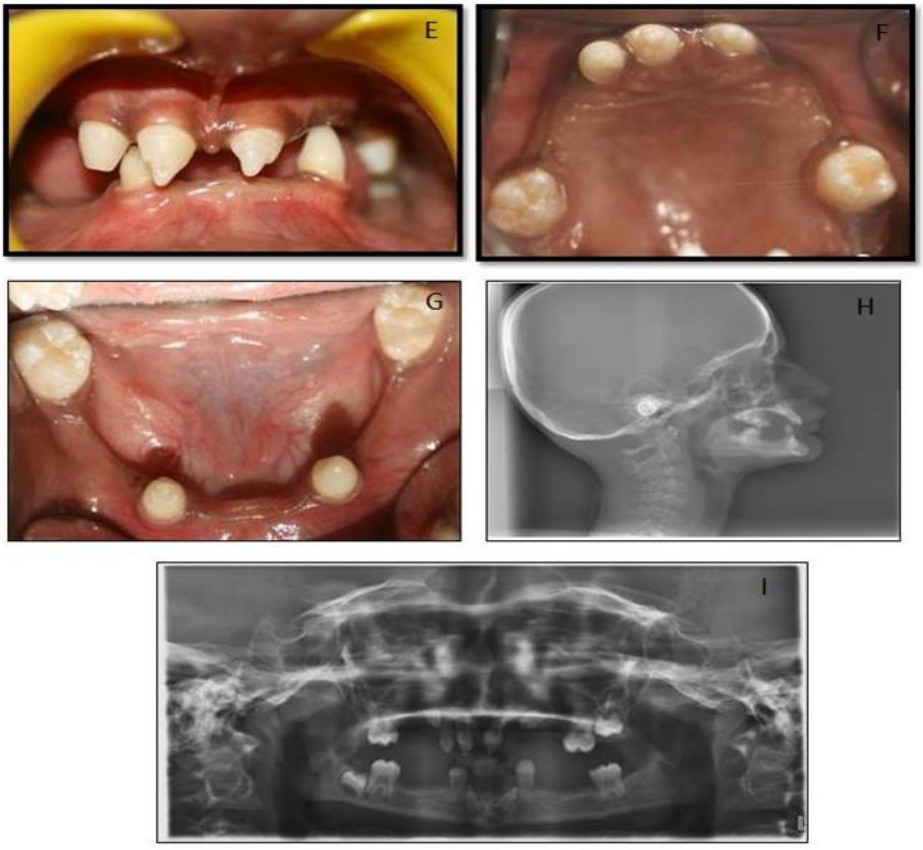

Figure 2: E- conical shaped teeth; F,G- reduced number of teeth (Anodontia); H- lateral cephalogram showing maxillary and mandibular growth patterns; I- opg showing missing teeth

Figure 3: J- removable partial denture in mandibular arch; K- removable partial denture in maxillary arch; l- postoperative frontal view; M- postoperative lateral view

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Authors Information: Srinivas Nallanchakrava; Pratej Kiran Kanumuri*; Dwitha Animi Reddy; Ganta Naga Sribala

Panineeya institute of dental sciences, Hyderabad, India

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