Hypohidrotic Ectodermal Dysplasia. Clinical genetic aspects and future perspective. A short comprehensive review

Michele Callea[1], Andrea Avendano[2], Francisco Cammarata-Scalisi[2], Diah Ayu Maharani[3], Lindawati S Kusdhany[4], Yasemin Yavuz[5]*

1. Unit of Dentistry, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
2. Unidad de Genética Médica. Departamento de Puericultura y Pediatría. Universidad de Los Andes. Mérida, Venezuela.
3. Department of Preventive and Public Health Dentistry, Faculty of Denstistry, Universitas Indonesia.
4. Prosthodontic Department, Faculty of Dentistry, Universitas Indonesia.
5. Turkish Goverment, City Health Management, Diyarbakır.

Abstract

Ectodermal dysplasias are a wide group of skin diseases characterized by defects in appendages of ectodermal origin. Patients with hypohidrotic ectodermal dysplasia, the most common type of ectodermal dysplasia, usually present the clinical triad constituted by hypodontia, hypotrichosis and hypohidrosis, caused by mutations in genes coding to components for tumor necrosis factor (TNF)-like signaling pathway. Lack of genotype-phenotype correlation and a broad genetic variability make diagnosis difficult; in order to establish the inheritance pattern and to confirm the clinical diagnosis direct sequencing and now next generation sequencing represent option for the molecular aspect.

Paediatric dentists may be the first specialist to propose the diagnosis, since the observation of lack of teeth due to multiple tooth agenesis; in this review authors aim is to highlight clinical and molecular aspects of the disease underlining the dental features of the syndrome.

Review (J Int Dent Med Res 2017; 10(2): pp. 397-400)

Keywords: Hypohidrotic ectodermal dysplasia, hypodontia, EDA gene.

Received date: 15 April 2017 **Accept date:** 16 June 2017

Introduction

EDA gene (MIM#300451) mutations are known to cause both X-linked Hypohidrotic Ectodermal Dysplasia (XL-HED, MIM#305100), and X-linked selective tooth agenesis (MIM#313500)[1,2,3].

The term ectodermal dysplasias (EDs) indicate a heterogeneous group of inherited, developmental disorders that affect several tissues of ectodermal origin. EDs are defined as alterations in two or more ectodermal structures: skin, hair, teeth, nails, and sweat gland function, and can be associated with malformations in other organs and systems[4,5].

The overall prevalence of EDs syndromes is unknown, but appears rare with a presumed cumulative frequency of approximately 7/10,000[4]. More than 200 clinically and/or genetically distinct EDs have been catalogued and the mode of inheritance varies amongst the different disorders. The most common form of EDs is Hypohidrotic Ectodermal Dysplasia (HED), which is characterized by hypodontia, hypotrichosis, and partial or total eccrine sweat glands absence. HED is a heterogeneous group of inherited disorders and is estimated to affect at least 1 in 17,000 people worldwide[6].

The most prevalent form of HED is inherited with an X-linked recessive pattern; however, autosomal dominant (AD) and autosomal recessive (AR) forms of the disorder have been described, albeit at a much lower frequency[7].

In this review we provided the most recent information about HED, establishing the molecular mechanism and the most outstanding clinical characteristics in patients reported until now underlining the dental features, in order to make more suitable the patients management.

***Corresponding author:**
Dr. Michele Callea
Mailing address: Unit of Dentistry, Bambino Gesù Children's Hospital, IRCCS, Viale San Paolo 15, 00146, Rome, Italy.
E-mail: mcallea@gmail.com

Genetic aspects:

HED is caused by mutations that affect components of a tumor necrosis factor (TNF)-like signaling pathway. Activation of this pathway is initiated by binding of the TNF-like ligand ectodysplasin (EDA) to its transmembrane receptor (EDAR), which connects to a canonical TNF signaling cascade through a dedicated adapter protein, ultimately leading to the stimulation of NF-κB[8]. The gene responsible for X-linked HED (XL-HED;MIM#305100) is named ectodysplasin-A (*EDA*; MIM#300451; Xq12-q13) which encodes a protein that is involved in the normal development of ectodermal appendages including hair, teeth, and sweat glands. Mutations in the same gene can cause X-linked selective tooth agenesis (MIM#313500)[1,2,3].

Defects in the molecular structure of ectodysplasin-A may inhibit the action of the epidermal-specific TNF-R family member ectodysplasin receptor (EDAR). EDAR acts through ectodysplasin receptor-associated adapter protein (EDARADD) and activate the IKK complex, necessary for normal development of the ectoderm and/or its interaction with the underlying mesoderm. Mutations in the ectodysplasin-A receptor (EDAR; MIM#604095; 2q12.3), which forms a ligand-receptor pair with ectodysplasin, and EDAR-associated death domain (EDARADD; MIM#606603; 1q42-q43). This in turn interacts with the death domain of EDAR and links the receptor to signaling pathways downstream, which are associated with both autosomal dominant and autosomal recessive forms of HED. Mutations in *EDAR* can result in autosomal dominant HED (MIM#129490) and autosomal recessive HED (MIM#224900) whether mutations in *EDARADD* result in autosomal recessive HED (MIM#614940)[9,10].

Mutations in *TRAF6* and *WNT10A* have been recently reported causing HED[11]. In addition to a well characterized role in ectodermal appendages development *in utero*, EDAR signaling has been demonstrated participate in adult hair cycle regulation, through the upregulation of X-linked inhibitor of apoptosis (XIAP) involved in hair follicules apoptosis-driven involution[12] and more recently, this signaling pathway has also been associated to skin wound healing[13].

Clinical features:

Newborns with HED can present with peeling skin similar to "post-mature" babies. Eccrine function (sweating), although present, is greatly deficient, leading to episodes of hyperthermia. More often, diagnosis is delayed until the teeth fail to erupt at the expected age (6-9 months) or the teeth that erupt are peg-shaped, conical, or knife-edge in shape, which may affect the ability to eat and speech. Patients also have a peculiar facies, characterized by periorbital hyperpigmentation, depressed nasal bridge (saddle nose deformity), pointed chin, frontal bossing, everted lips, midface hypoplasia. They tend to have sparse scalp and body hair (hypotrichosis) that is often light-coloured and slow-growing; eyebrows and eyelashes are sparse or totally absent[14]. Abnormalities in function of the mucous membrane leads to frequent respiratory tract infections and changes in nasal secretions from concretions (solidified secretions in the nasal and aural passages) in early infancy to large mucous clots[15]. The epidermis is xerotic, with patches of hyperkeratosis and/or eczematous. Common otorhinolaryngological manifestations include chronic infections such as rhinitis, pharyngitis, otitis media, hearing loss, epistaxis, and dysphonia. As a consequence of gastroenteric glands hypoplasia, HED patients can also suffer from dysphagy and constipation[16]. Physical growth and psychomotor development are otherwise within normal limits. In HED males are affected but female carriers may manifest milder features: congenital tooth agenesis and misshapen teeth, sparse and thin hair and some problems with sweat glands function[6].

National Foundation for Ectodermal Dysplasias (NFED) has created a database for patients which allowed to determine the most frequent clinical characteristics in a large group of patients, based on this, the most reported feature in patients with HED is hypohidrosis, followed by hypotrichosis and hypodonthia equally represented among patients. Other complications described mainly in male patients are nasal congestion with bad odor interfering with feeding, eczema and recurrent sinusitis[17].

Several times have been reported inter and intrafamilial phenotype differences in patients, presenting a wide spectrum of severity without a genotype-phenotype correlation. However, few hypomorphic mutations were described in which a genotype-phenotype correlation was stablished for sweat gland function or skin and hair signs[18,19].

Dental features:

Dental abnormalities of HED patients include tooth agenesis ranging from hypodontia (patients with up to 5 missing teeth) to olygodontia (patients with more than 5 missing teeth), teeth malformations are equally frequent as microdontia, cone shaped teeth and anomalous dental eruption[19-23].

Taurodontism is also found in HED patients, which is characterized by pulp enlargement. Moreover, the degree of taurodontism seems to be associated to the mutated gene, thus, has been proposed that could be more severe when *EDA* gene is mutated[24]. All these characteristics could lead to other anomalies such as alveolar bone resorption, osteopenia, height reduction[25].

Dental malformations can affect oral function and self-esteem of patients, therefore, dental rehabilitation at early ages is often chosen by the team of specialist dentist, being implant therapy the most used clinical technique in these patients[19,25].

Oral rehabilitation should be a multidisciplinary team effort, including paediatric dentist, orthodontist, endodontist, maxillofacial surgeon and prosthodontist in order to plan the best management of the patient. Although potential risks may arise, the use of implants seems to be the best option for these patients, thus, some consideration should be taken as best time and place for implant placement and possible consequences with regard to normal tooth eruption and normal growth of denture[26-28].

Molecular diagnosis and future treatment:

To date we have diagnosed *EDA* mutations with Sanger sequencing, although few studies on NGS (Next Generation Sequencing) detecting *EDA* mutation have been reported[6,29,30].

As the cost of exome sequencing is falling rapidly, the application of this method which is now cost effective and cheaper than the classic approach of linkage analysis followed by Sanger sequencing of candidate genes of the identified locus, could be considered in the future as a diagnostic clinic-molecular tool[11].

The proposal of new diagnostic strategies may allow a faster diagnosis giving the possibility to establish inheritance patterns useful for families, and to answer to "thirsty" Scientists.
To date, only symptomatic treatment is available for these patients. Causative therapeutic approaches to such disorders are expected to be effective in the near future[31,32].

Conclusions

HED have been associated to mutations in different genes, without a genotype-phenotype correlation well stablished leading to a challenging diagnosis and making difficult establishing the inheritance pattern without DNA sequencing.

Therefore a group of multidisciplinary specialists including paediatric dentist, dermatologist, ophthalmologist, geneticist and othorinolaryngologist are necessary for a good patient management.

Exome sequencing may be the best available approach to molecular diagnosis reducing time and cost and increasing diagnosis sensitivity. Early oral rehabilitation is mandatory in order to improve the quality of life.

Acknowledgments

Authors wish to thank ANDE (Associazione Nazionale Displasia Ectodermica) in the person of the President and Founder Giulia Fedele who since 1999 take care of all needs and necessity of the patients with Ectodermal Dysplasia and with her sweetness makes sure an accurate awareness for any needs helped by the shoulders of her Scientific Board.

In particular the corresponding author wish to thank the Medical Directorate in the person of his Director Dr. Massimiliano Raponi, and Dr. Marta Ciofi Degli Atti for their constant support in this field of Research.

Declaration of Interest

The authors report no conflict of interest.

References

1. Han D, Gong Y, Wu H, Zhang X, Yan M, Wang X, Qu H, Feng H, Song S. Novel EDA mutation resulting in X-linked non-syndromic hypodontia and the pattern of EDA-associated isolated tooth agenesis. Eur J Med Genet. 2008;51:536-546.
2. Tao R, Jin B, Guo SZ, Qing W, Feng GY, Brooks DG, Liu L, Xu J, Li T, Yan Y, He L. A novel missense mutation of the EDA gene in a Mongolian family with congenital hypodontia. J Hum Genet. 2006;51:498-502.
3. Tarpey P, Pemberton TJ, Stockton DW, Das P, Ninis V, Edkins S, Futreal PA, Wooster R, Kamath S, Nayak R, Stratton MR, Patel PI. A novel gln358glu mutation in ectodysplasin A associated with X-linked dominant incisor hypodontia. Am J Med Genet. 2007;143:390-394.
4. Mark BJ, Becker BA, Halloran DR, Bree AF, Sindwani R, Fete MD, Motil KJ, Srun SW, Fete TJ. Prevalence of atopic disorders and immunodeficiency in patients with ectodermal dysplasia syndromes. Ann Allergy Asthma Immunol. 2012;108:435-438.
5. Visinoni AF, Lisboa-Costa T, Pagnan NA, Chautard-Freire-Maia EA.Ectodermal dysplasias: clinical and molecular review. Am J Med Genet A. 2009;149:1980-2002.
6. Tyagi P, Tyagi V, Hashim AA. 2011. Ocular and non-ocular manifestations of hypohidrotic ectodermal dysplasia. BMJ Case Rep. pii: bcr0120113731. 2011.
7. Lind LK, Stecksén-Blicks C, Lejon K, Schmitt-Egenolf M. EDAR mutation in autosomal dominant hypohidrotic ectodermal dysplasia in two Swedish families. BMC Med Genet. 2006; 7:80.
8. Headon DJEctodysplasin signaling in cutaneous appendage development: dose, duration, and diversity. J Invest Dermatol. 2009;129:817-819.
9. Callea M, Nieminen P, Willoughby CE, Clarich G, Yavuz I, Vinciguerra A, Di Stazio M, Giglio S, Sani I, Maglione M, Pensiero S, Tadini G, Bellacchio E. A novel INDEL mutation in the EDA gene resulting in a distinct X- linked hypohidrotic ectodermal dysplasia phenotype in an Italian family. J Eur Acad Dermatol Venereol. 2016;30:341-343.
10. Lippens S, Lefebvre S, Gilbert B, Sze M, Devos M, Verhelst K, Vereecke L, Mc Guire C, Guérin C, Vandenabeele P, Pasparakis M, Mikkola ML, Beyaert R, Declercq W, van Loo GKeratinocyte-specific ablation of the NF-κB regulatory protein A20 (TNFAIP3) reveals a role in the control of epidermal homeostasis. Cell Death Differ. 2011;18:1845-1853.
11. Haghighi A, Nikuei P, Haghighi-Kakhki H, Saleh-Gohari N, Baghestani S, Krawitz PM, Hecht J, Mundlos S.Whole-exome sequencing identifies a novel missense mutation in EDAR causing autosomal recessive hypohidrotic ectodermal dysplasia with bilateral amastia and palmoplantar hyperkeratosis. Br J Dermatol. 2013;168:1353-1356.
12. Fessing MY, Sharova TY, Sharov AA, Atoyan R, Botchkarev VA. Involvement of the Edar signalling in the control of hair follicle involution (catagen). Am J Pathol. 2006;169: 2075-2084.
13. Garcin CL, Huttner KM, Kirby N, Schneider P, Hardman MJ. Ectodysplasin A pathway contributes to human and murine skin repair. J Invest Dermatol. 2016;136:1022-1030.
14. Callea M, Paglia M, Bahsi E, Di Stazio M, Ince B, Fedele G, Yavuz Y, Paglia L. Hypohidrotic ectodermal displasia: a clinical case report. Int J Dent Med Res. 2014;7:37-41.
15. Wright JT, Grange DK, Richter MK. Hypohidrotic Ectodermal Dysplasia. Gene Reviews. 2014.
16. Callea M, Teggi R, Yavuz I, Tadini G, Priolo M, Crovella S, Clarich G, Grasso DL. Ear nose throat manifestations in hypoidrotic ectodermal dysplasia. Int J Pediatr Otorhinolaryngol. 2013;77:1801-1804.
17. Callea M, Yavuz I, Clarich G, Cammarata-Scalisi F. Clinical and molecular study in a child with x-linked hypohidrotic ectodermal dysplasia. Arch Argent Pediatr. 2015;113: 341-344.
18.Schneider H, Hammersen J, Preisler-Adams S, Huttner K, Rascher W, Bohring A. Sweating ability and genotype in individuals with X-linked hypohidrotic ectodermal dysplasia. J Med Genet. 2011;48:426-432.
19. Burger K, Schneider AT, Wohlfart S, Kiesewetter F, Huttner K, Johnson R, Schneider H. Genotype-phenotype correlation in boys with X-linked hypohidrotic ectodermal dysplasia. Am J Med Genet A. 2014;164:2424-2432.
20. Montanari M, Callea M, Battelli F, Piana G. Oral rehabilitation of children with ectodermal dysplasia. BMJ Case Rep. pii:bcr0120125652. 2012.
21. Lee KE, Ko J, Shim TJ, Hyun HK, Lee SH, Kim JW. Oligodontia and curly hair occur with ectodysplasis-A mutations. J Dent Res. 2014;93:371-375.
22. Wang Y, He J, Decjer AM, Hu JC, Zou D. Clinical outcomes of implants therapy in ectodermal dysplasia patients: a systematic review. Int J Oral Maxilofac Surg. 2016:45:1035-1043.
23. Callea M, Faletra F, Maestro A, Verzegnassi F, Rabusin M, Vinciguerra A, Radovich F, Clarich G, Yavuz I, Tumen EC. Dental phenotype in a patient with hypohidrotic ectodermal displasia and severe inmunodeficiency. Int J Dent Med Res 2011;4:17-20.
24. Gros CI, Clauss F, Obry F, Manière MC, Schmittbuhl M. Quantification of taurodontism: interests in the early diagnosis of hypohidrotic ectodermal dysplasia. Oral Dis. 2010;16:292-298.
25. Yap AK, Klineberg I. Dental implants in patients with ectodermal dysplasia and tooth agenesis: a critical review of the literature. Int J Prosthodont. 2009;22:268-276.
26. Sari ME, Duran I, Ibis S. Dental implant patients with ectodermal dysplasia: current approaches. J Int dent Med Res. 2015;8:147-150.
27. Tumen EC, Hamamci N, Deger Y, Tumen DS, Agackiran E. Direct composite resin application, and prosthetic management in a patient with hypohidrotic ectodermal dysplasia: a case report. Int J Dent Med Res. 2009;2: 19-24.
28. Joseph S, Sherackal GJ, Jacob J, Varghese AK. Multidisciplinary management of hypohidrotic ectodermal dysplasia-a case report. Clin Case Rep. 2015;3:280-286.
29. Takeichi T, Nanda A, Aristodemou S, McMillan JR, Lee J, Akiyama M, Al-Ajmi H, Simpson MA, McGrath JA.Whole-exome sequencing diagnosis of two autosomal recessive disorders in one family. Br J Dermatol. 2015;172:1407-1411.
30. Sarkar T1, Bansal R2, Das P1. Whole genome sequencing reveals novel non-synonymous mutation in ectodysplasin A (EDA) associated with non-syndromic X-linked dominant congenital tooth agenesis. PLoS One. 2014;9:106811.
31. Hermes K, Schneider P, Krieg P, Dang A, Huttner K, Schneider H.Prenatal therapy in developmental disorders: drug targeting via intra-amniotic injection to treat X-linked hypohidrotic ectodermal dysplasia. J Invest Dermatol. 2014;134:2985-2987.
32. Huttner K. Future developments in XLHED treatment approaches. Am J Med Genet A. 2014;164:2433-2436.