HED (Hypohidrotic Ectodermal Dysplasia): A Review

Michele Callea[1]*, Francisco Cammarata Scalisi[2], Izzet Yavuz[3,4,5], Mehmet Sinan Dogan[5], Colin Eric Willoughby[6], Murali Dharan Bashyam[7]*

1. Unit of Dentistry, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy.
2. Regional Hospital of Antofagasta, Chile.
3. Dicle University, Faculty of Dentistry, Department of Pediatric Dentistry. Diyarbakir, Turkey.
4. Adjunct Professor, Faculty of Dentistry, University of Indonesia. Jakarta, Indonesia
5. Harran University, Faculty of Dentistry, Department of Pediatric Dentistry. Sanlıurfa, Turkey.
6. Genomic Medicine, Ulster University, Northern Ireland, UK.
7. Laboratory of Molecular Oncology, Centre for DNA Fingerprints and Diagnostics (CDFD), Uppal, Hyderabad 500039, India.

Abstract

The ectodermal dysplasias (EDs) are a heterogeneous group of inherited, developmental disorders characterized by alterations in two or more ectodermal structures including the hair, teeth, nails and sweat glands. Currently, more than 200 types of ectodermal dysplasias have been described. Anhidrotic or hypohidrotic ectodermal dysplasia (AED/HED), the most common ED, is characterized by three cardinal features: hypotrichosis, hypohidrosis and hypodontia. We review the genetic and pathogenetic mechanisms of AED/HED and report on the management of clinical manifestations driven by embryology, anatomy and physiology.

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Introduction

The ectodermal dysplasias (EDs) are a heterogeneous group of inherited, developmental disorders characterized by alterations in two or more ectodermal structures including the hair, teeth, nails, sweat glands.[1] Other structures of ectodermal derivation such as mammary glands, melanocytes, external ear and ocular glands are equally involved.[2,3] This group of disorders results from alterations in the primordial external germ layer and the epithelial-mesenchymal junction. The ectodermal-derived organs can be affected in isolation or in association with other complex clinical manifestations involving either the mesoderm or the endoderm.[3]

Epithelial-mesenchymal interaction is an emerging topic in developmental and patho-physiological conditions, and also in stem cell specification and/or differentiation.[4]

Corresponding author:
Michele Callea,
Unit of Dentistry, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy. E-mail: mcallea@gmail.com
Murali Dharan Bashyam
Center for DNA Fingerprinting and Diagnostics (CDFD), Uppal, Hyderabad, India. E-mail; bashyam@cdfd.org.in

The communication/interaction process between germ layers represents a key-regulatory mechanism governing both differentiation and tissue development which is mediated mainly by secreted signal molecules and growth factors such as Transforming Growth Factor β, Fibroblast Growth Factor and others as well as by signal pathways including Wnt and Hedgehog[3-5]. Coordinated signalling occurs through ligand binding to specific cell-surface receptors followed by potentiation of an intra-cellular cascade that ultimately culminates in the cell nucleus resulting in regulation of gene expression.

Currently, more than 200 types of ectodermal dysplasias (EDs) have been described.[6] Anhidrotic or hypohidrotic ectodermal dysplasia (AED/HED), the most common ED, is characterized by three cardinal features: hypotrichosis, hypohidrosis and hypodontia. HED comprises four subtypes: 1) X-linked HED or Christ-Siemens-Touraine (CST) syndrome; 2) autosomal recessive HED; 3) autosomal dominant HED (ADHED); and 4) the immunodeficiency HED (HED-ID)[6]. These HED subtypes are clinically indistinguishable as they all share the same phenotypic features: anodontia/hypodontia, hypohidrosis and

hypotrichosis, but they differ in their inheritance pattern.[3-7] The biological basis for the phenotypic similarities in HED originates from genetic perturbations in common developmental and signalling pathways. A molecular genetic diagnosis is therefore essential to accurately diagnose HED and to understand the molecular basis of individual clinical manifestations as well as to provide genetic counselling to affected families. In this review we discuss the mechanism and management of HED with special regard to ADHED based upon embryology, anatomy and physiology of the affected structures/organs.

Clinical features

ED is a congenital condition, but features may not manifest until the emergence of the teeth or hair growth. The typical manifestations are reduced (hypohidrosis) or absent (anhidrosis) sweating, which result in unexplained fever, heat intolerance and febrile seizure in infancy and childhood. A mortality rate of about 30% is reported in early childhood due to febrile episodes and respiratory infections.[8] The skin can be abnormal at birth (in affected X-linked HED males the skin can have an ichthyosis-like appearance with collodion membranes and scales) and subsequently is dry with patches of hyperkeratosis and/or eczematous-like changes. Affected individuals have sparse body and scalp hairs (hypotrichosis) which are hypochromic, brittle and slow-growing. Frequently, the diagnosis is delayed until dental anomalies present (including delayed eruption or hypodontia with conical or knife or peg shaped teeth. Patients with X-linked HED have a characteristic facial appearance with periorbital hyperpigmentation, depressed nasal bridge and malar hypoplasia. Abnormalities in mucosal secretions lead to respiratory infections, chronic rhinitis and gastrointestinal problems. Ear Nose Throat (ENT) manifestations commonly include otitis media and hearing loss.[9] Abnormalities in the meibomian glands are the commonest ocular manifestation of HED with total or partial absence reported.[10-13] Most patients show features of an evaporative dry eye with a rapid tear film breakup time and abnormal meibography.[10] Corneal changes are usually mild and consist of an age-related pannus. Infantile glaucoma is a rare association.[11]

Genetics and Biochemistry

Mutations in four genes account for 90% of HED cases; these include a) Ectodysplasin A1 (*EDA-A1* MIM #300451; Xq12-q13), b) EDA receptor (*EDAR* MIM #604095; 2q11-q13), c) EDAR-associated death domain (*EDARADD* MIM #606603; 1q42-q43) and d) *WNT10A* (MIM# 606268;). *Wnt10A* mutations also cause two additional types of ectodermal dysplasias namely Odonto-onycho-dermal dysplasia (OMIM #257980) and Schopf-Shulz Passare syndrome (OMIM #224750) (Borhring et al., 2009, Am J Hum Genet). In addition, a variant of HED called EDA-ID (EDA with immmune deficiency) may be caused by mutations in gene encoding NEMO (*IKBKG* MIM# 300248). Incontinentia pigmenti (IP) is an X-linked dominant ectodermal dysplasia associated with defects in NEMO function resulting from mutations which lead to a truncated NEMO.[8-15] Despite current research on NEMO associated diseases IP and EDA-ID (Hypohidrotic Ectodermal Dysplasia associated with Immuno Deficiency) cannot be precisely distinguished because distinct geno-and phenotypes of EDA-ID cannot be assigned confidently to these diseases.[15-19] in *EDAR* and *EDARDD* can result in autosomal recessive and dominant HED.

The first three genes viz. *EDA-A1, EDAR and EDARDD* encode proteins that constitute a cardinal signalling cascade important for generation of ectoderm during development. The EDA-A1 ligand belongs to the TNF family of ligands, is expressed as a membranous protein and is activated and secreted into the extra cellular space by Furin based cleavage. The ligand then binds to its cognate receptor viz. EDAR which further transduces the signal to Nuclear Factor (NF)-κB through EDARDD (by virtue of its death domain receptor) and other cytoplasmic signalling proteins. Being located on the X chromosome, mutations in *EDA-A1* cause X-linked type of HED (XLHED).

Autosomal Dominant and recessive forms of HED) are caused by heterozygous and homozygous mutations in *EDAR*/*EDARDD*/*WNT10A*, respectively. Although individuals diagnosed with autosomal dominant form of HED are expected to have at least one affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early

death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Though it is also possible to have a *de novo* mutation in the proband.

Family counseling

The clinical phenotype of HED resulting from mutations in different genes is indistinguishable as the same developmental pathway is impacted at the molecular and cellular level. A careful assessment of family members in HED may identify an inheritance pattern but a formal diagnosis requires molecular genetic testing. The clinical assessment of the family requires multiple specialists and is best coordinated by the local clinical genetics team who can help ascertain the inheritance pattern, instigate molecular genetic testing and counsel patients and families about risk of transmission, prenatal diagnosis and potential treatments.[21]

HED patient management

The management of HED requires a multidisciplinary team with a clinical geneticist acting as case manager. The management consists of two main components: surveillance and treatment.[21-27]

Surveillance is mainly addressed to prevent complications from hypo/anhidrosis and is based upon embryology, anatomy and physiology of the affected tissues/organs. The first symptom to control is hyperthermia that can cause febrile seizure or even early death. Hyperthermia is due to a defective thermoregulation owing to the absence/paucity of sweat glands that are of eccrine or apocrine types. Both types are located in the skin. The eccrine type reverses the secretion directly to the extern through a duct, whilst the apocrine type secretes the sweat into the hair follicle (modified variants of sweat apocrine glands are found in axilla, inguinal and perineum). The management consists mainly of a logical approach encompassing application of all possible mechanisms to maintain a cool environment for the patient. These may include air conditioning not only at home but also in the school; liquids allowed in places where they are usually prohibited (special liquids should be prescribed by the Physician), cool vests, adequate supply of fresh water and wigs or special hair care formulas for sparse, dry hairs. Educational training should be provided to caregivers, family members and affected individuals. X-linked patients can present at birth with colloid membranes and scales or hyperkeratosis with an ichthyosis-like appearance. These features are due to the concomitant insufficiency/dysfunction of the apocrine sebaceous glands that are anatomically associated with the hair follicles. The disturbance in ectodermal or ectodermal/mesenchymal development process leads to the absence of both sweat and sebaceous glands, thus resulting in dryness and absence of lubrification of the skin. The latter reduces the protection of the skin from bacterial aggression.

Hydratant and lubricant creams are needed for the management. Likewise, skin care products are most useful for complications/associations such as eczema, atopic dermatitis and for protection against the exposure to heat that can exacerbate dry skin. The development of allergies requires a personalized treatment plan.[27]

Ocular manifestations result from the lack/reduction/dysfunction of all ocular glands:[28] Meibomians and Zeiss that are modified sebaceous and Moll glands that are sweat modified glands. That explains the dry eyes as a consequence of the absence/insufficiency of tears and of both the oleuos/external) and mucous (internal) layers of the trilaminar film covering the cornea.[29] Indeed these patients do not secrete enough oil into the tears. Therefore, the tear fil on the surface of the eye evaporates too quickly. The lack the endogenously physiological substances requires the use both aqueous and lipid products such as liposomal eye spay and artificial lipidic tears, to prevent the formation of a corneal pannus by age,[11] or corneal alterations as well. A good hygiene, the use of hot compresses and a meticulous cleaning of the eyelids, especially if scales are present, represent beneficial procedures. A bilateral infantile glaucoma has been also reported in HED.[12] Nose, ear and throat complications are due to the dysfunction of loco-regional glands. The nasal floor contains salivary glands of mixed (sero-mucous) type, the mucosa is plenty of mucous secreting cells and of sebaceous glands associated to vibrissae. The absence/reduction of all these components provoke dryness, lack of lubrification with consequent formation of cristae and absence of the vibrate activity for secretion flow and debris removal. Chronic rhinitis,

respiratory infections, nasal cavity obstruction and gastrointestinal problems can develop. Regular follow-up by an ENT specialist is necessary as the removal of concretion requires suction devices or forceps. Throat hoarseness is a manifestation due to the same mechanisms and as such it benefits from humidification of air ambient. The lack of lubrification secondary to the absence of ceruminous (modified sebaceous) glands causes concretion in the auditive external duct. Otitis media and hearing loss can follow. Aural like nasal concretions may require forceps and therefore may not be always removed by caregivers or parents.[27]

Dental treatment, ranging from simple restorations to dentures, must begin at an early age, for which services of an Orthodontist may be necessary. Children with HED typically need to have their dental prostheses replaced every 2.5 years. Dental implants in adults can support aesthetic and functional dentition. Dental implants in the anterior portion of the mandibular arch have proven successful only in children age seven years and older.[21,24,25] Hyposalivation is present in some individuals and predisposes to dental caries, thus requiring oral lubrication and caries control. Dietary counseling may be helpful for those individuals who have trouble chewing and swallowing despite adequate dental care. Saliva substitutes and optimal fluoride exposure may be helpful in preventing dental caries in individuals having a marked reduction in salivary flow. Other dental caries preventive approaches such as pit and fissure sealants can be beneficial as well.[26]

Research and future perspectives

Classification systems incorporating molecular etiology and molecular pathways are being developed to help in a more efficient diagnosis of the diverse ED conditions at both the clinical and molecular levels.[2,4] Understanding of the molecular basis of embryological development of skin appendages and of the role of the EDA signalling cascade including effect of modifier genes, have opened the possibility of designing intervention strategies targeting multiple levels to try and impede the disease initiation and progression without lethal effects.

In X-linked HED, the correction 'in utero' of the HED phenotype using a recombinant protein was reported in a mouse model and in 2018 in a pair of human twins treated prenatally was a significant medical advance,2 or whether novel candidate genes could result in ED.

The recent "omics revolution" is expected to lead to the detection of many new Mendelian disorders and their causative genes.31 and to the distinction of essential (lethal) genes from non-essential genes which may lead to syndromic diseases. All diseases result from the interaction between genetic constellation and environmental perturbations, leading to intermediate phenotypes, clinical syndromes and overt diseases.[32] The term "human interactome" has been created to describe this network medicine.[33]

Conclusions

Anhidrotic or hypohidrotic ectodermal dysplasia (AED/HED), the most common ED, it is characterized by three cardinal features: hypotrichosis, hypohidrosis and hypodontia. This review gives the genetic and pathogenetic mechanisms of AED/HED and report on the management of clinical manifestations driven by embryology, anatomy and physiology.

Declaration of Interest

The authors report no conflict of interest.

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