

“Under the Skin of the Teeth” - Ectodermal Dysplasia A Review

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Abstract

Ectodermal dysplasias are hereditary disorders which involves congenital defects of two or more ectodermal structures. Its occurrence is mainly attributed to disturbance in the ectoderm of the developing embryo. Most prominent feature includes hypoplasia or aplasia of structures such as skin, hair, nails, teeth, sweat glands, parts of the eye and ear and other organs. Two major forms can be commonly distinguished (1) Hypohidrotic form in which sweat glands are either absent or reduced (2) Hydrotic form in which sweat glands are normal. However more than 150 types of different pathological clinical conditions of ectodermal dysplasia have been recognised, significantly encountered types have been described in this article. Since various forms of Ectodermal dysplasias are diagnosed it becomes very essential to identify which type the individual or the family is affected. Treatment involves a multi-disciplinary approach involving pediatric professionals, psychologist, ENT specialist and speech therapist and dentists, who play a major role in improving physical, and psychosocial development and improving speech, mastication and overall esthetics.

Keywords: Ectodermal Dysplasia; Autosomal Dominant/ Recessive; Hypodontia; Hypohydrosis; Hypotrichosis

Introduction

The term Ectoderm is derived from Hellenic language *ektos* refers to outside, and *derma*, refers to skin [1]. It forms the outermost layer of germ cells during embryogenesis phase, which subsequently differentiates to form the nervous system, tooth enamel, epidermis, skin, nostrils, sweat glands, hair [2]. Dysplasia refers to abnormal development of a tissue. Ectodermal dysplasia collectively, represents a group of inherited conditions in which two or more ectodermally derived anatomic structures fail to develop [3]. Occurrence is either during the first trimester of pregnancy or before the sixth week of embryonic life [4].

By the phrase under the skin of the teeth we are emphasizing that ectodermal dysplasia is not barely a deformity involving ectodermal tissues such as skin, teeth [6] but rather we are highlighting on a prime factor, which is the role of genetic mutations involving genes *EDA1*, *EDAR*, *EDARADD*, *WNT10A* responsible for various forms of ectodermal dysplasia [7-12].

Historical evidence

Thurnam in 1848 described ectodermal dysplasia [13]. Charles Darwin's documentation in 1875 described a Hindu family of Scinde, where 10 men in a family over a course of 4 generations were affected [14]. In 1921, Thadani ascertained the cause of ectodermal dysplasia to the X chromosome [15-17]. In 1895 Nicolle and Hallipre first described Hydrotic Ectodermal Dysplasia in French-Canadian Family [18]. It was In 1929 Clouston established hereditary basis, when five generations of a French-Canadian family settled in Québec were affected [19-21].

Prevalence

Prevalence of Hypohidrotic ectodermal dysplasia is estimated as 1 in every 10,000 to 100,000 live births [3,16]. Incidence rate of Hypohidrotic form of ectodermal dysplasia is 1 in 17000 people worldwide [22]. Higher prevalence is observed among the caucasians race [6]. Skin is the most frequently affected around 93%, followed by hair and nail disorders (86%) [23,24]. Although familial segregation of Hidrotic Ectodermal Dysplasia is more among the French-Canadian origin [25]. other ethnic groups such as Chinese, Japanese, British and African-American has also been affected [26].

Classification

Ectodermal dysplasia is referred to Pure when only ectodermal structures are involved, whereas it is called as complex when structures other than the ectoderm are involved. Ectodermal Dysplasia syndromes manifests, ectodermal sign, as well as disturbances of other embryonic origin [27].

Freire-Maia and Pinheiro in 1971. based their definition on the four “classical signs” associated with EDs:

- ED 1: Trichodysplasia,
- ED 2: Dental Defects,
- ED 3: Onychodysplasia,
- ED 4: Dyshidrosis.

Group A includes those disorders with signs affecting at least two of the classical structures.

Subgroup 1: Hair, Subgroup: 2 teeth, Subgroup: 3 nails and Subgroup: 4 sweat glands.

Group B includes disorders involving one of the classical structure plus another ectodermal structure (subgroup 5).

Other ectodermally derived structures like thyroid gland, thymus, anterior pituitary, adrenal medulla, central nervous system, external ear, melanocytes, cornea, conjunctiva, lacrimal gland and lacrimal duct may be involved [9,27].

Lamartine J in 2003 classified the ectodermal dysplasia causative genes into four major functional subgroups: cell-cell communication and signalling; adhesion; transcription regulation; and development [28].

Priolo and Lagana (2005) EDs classified based on defects in developmental regulation/epithelial - mesenchymal interaction and defect in cytoskeleton maintenance and cell stability [29]. Nelson included five categories, namely Hypohidrotic (anhidrotic), Hydrotic (Clouston's syndrome), EEC (Ectodactyly ectodermal dysplasia) syndrome, Rapp - Hodgkin syndrome and Robinson's disease [13,30].

More than 150 different syndromes in ectodermal dysplasias have been recognised [31]. Some of the most common types have been described below in this article.

Hypohidrotic (anhidrotic) Ectodermal Dysplasia

Synonym: (Christ-Siemens- Tourine Syndrome)

Is the most commonly encountered form, which exhibits an X-linked mode of inheritance with the gene mapping to Xq12-q13. It includes a classical triad of hypodontia, hypotrichosis and hypohidrosis. Extraoral features include sparse, lustreless hair over the scalp, heat intolerance, frontal bossing, sunken cheeks, depressed nasal bridge, thick everted protuberant lips, hyper pigmented periorbital skin and a large low set of ears [32,33].

Hydrotic type ectodermal dysplasia

Synonym: Clouston syndrome

Hydrotic type is an autosomal-dominant genetic disorder, caused by mutations in the GJB6 gene (connexin gene) which is located on chromosome 13 (locus 13q11-q12.1) [34,35]. Characterized by a triad of palmoplantar hyperkeratosis, hair abnormalities and nail dystrophy, sweat glands are normal [36,37]. Hair abnormalities include hypotrichosis, reduced eyebrows and eyelashes. Nail disorders range from micronychia; nail plate thickening, color changes. Diffuse palmoplantar keratoderma on the knees, and elbows [38,39].

Ectrodactyly-ectodermal dysplasia-cleft syndrome

Synonym: split-hand/split-foot malformation

An autosomal dominant form due to mutations in tumor suppressor gene p63 located on chromosome 3q27 [40], characterized by the triad of ectrodactyly, ectodermal dysplasia, and facial clefts [41]. Other findings include hypodontia, sparse hair, dry skin, tear duct malformation, and genital malformations [42-44].

Rapp-Hodgkin syndrome

Is an autosomal dominant disorder caused by a defect in P63 gene mutation [45]. Hair appears steel wool, reduced sweat glands, absence of lacrimal punctae, epiphora. Oral features include hypodontia, abnormal tooth shape, and cleft palate [46].

Hay-Wells syndrome

Initially described by Hay and Wells in 1976. Occurs due to missense mutations in the tumor suppressor gene TP63 [47]. Characterized by ankyloblepharon filiforme adnatum, ectodermal dysplasia, and cleft palate and/or cleft lip and skin erosions [48] hypohidrosis, hypodontia, dental malformations and ocular abnormalities [49-51].

Margarita Island ectodermal dysplasia

Affects the population of Isla de Margarita, located in the south-central Caribbean.

Autosomal recessive disorder caused by mutations in PVRL1 gene which encodes for nectin 1, characterized by unusual facies, dental anomalies, hypotrichosis, palmoplantar hyperkeratosis and onychodysplasia, syndactyly, and cleft lip/cleft palate [52].

Naegeli-Franceschetti-Jadassohn Syndrome

Synonym: Naegeli syndrome

Rare autosomal dominant form of ectodermal dysplasia, caused by mutations in the keratin 14 (KRT14) gene, located on chromosome 17q12-21. Characterized by hypohidrosis, hypodontia, skin pigmentation, and hyperkeratosis of the palms and soles. One of the most striking features is the absence of fingerprint lines on the fingers [53,54].

Jackson-Sertoli syndrome

Synonym: Pachyonychia congenita type II

Is an autosomal dominant disorder caused by a defect in the genes KRT6B or K17; gene KRT17 encoding keratin 6B; clinical manifestations include plantar keratoderma, with nail changes [6].

Goltz syndrome

Synonym: Focal dermal hypoplasia

Focal dermal hypoplasia [55] is a multisystem disorder caused by mutations in the PORCN (Protein-serine O-palmitoleoyltransferase porcupine) gene. Features include yellow-pink bumps on the skin, shortness of stature and epilepsy [6].

Ellis-Van Creveld Syndrome

Synonym: chondroectodermal dysplasia

Ellis-van Creveld syndrome follows an autosomal recessive transmission pattern due to mutations in the EVC or EVC2 genes. Clinical features include orofacial abnormalities, nail dysplasia, and bone abnormalities. Patients appear short in stature, acromesomelic limb shortening, Polydactyly, syndactyly, genus valgum [56].

McGrath syndrome

Synonym: Ectodermal dysplasia/skin fragility syndrome

Autosomal recessive genodermatosis caused by loss of functional mutation in the plakophilin gene 1 (PKP1). Characterized by skin fragility usually trauma-induced, defective sweating, erythema, alopecia, and palmoplantar keratoderma [57].

Witkop Syndrome

Synonym: tooth and nail syndrome

Autosomal dominant condition caused by mutation in the MSX1 gene, located on chromosome 4 (locus 4p16.1). Typical clinical characteristics are nail dysgenesis and hypodontia, and hair abnormalities [58].

Rosselli-Gulienetti syndrome

Synonym: Bowen-Armstrong

Syndrome follows an autosomal dominant pattern of inheritance, caused by mutation of the p63. Defining features include cleft lip and/or palate, fused eyelids, absent nails, delayed bone growth and dry skin [59,60].

Diagnosis

Since various forms of Ectodermal dysplasias are diagnosed it becomes very essential to identify which type the individual or the family is affected.

If the patient has severe hypohidrosis and no immune deficiencies then we can diagnose it as X-Linked Recessive form of Hypohidrotic Ectodermal dysplasia, Autosomal Dominant - Hypohidrotic Ectodermal dysplasia or Autosomal Recessive - Hypohidrotic Ectodermal dysplasia. However along with mild to no hypohidrosis there are immune deficiencies, Hypohidrotic Ectodermal dysplasia/immune defect with deficiency in the “NF-kappa B Essential Modulator” gene can be suspected. Ectodermal dysplasias with normal appearance of teeth are seen in Clouston syndrome and skin fragility form. In abnormal appearance of teeth and no facial anomalies a diagnosis of tooth and nail, trichodontoosseous type can be established. Abnormal teeth with cleft and involvement of limb deformities Ectrodactyly ectodermal dysplasia cleft lip/palate syndrome, limb-mammary, Margarita island can be confirmed. In case if no limb anomalies are present Hay-Well, Rapp Hodgkin form can be suspected [41].

Dental panoramic radiographs

Which plays an important aid in ruling out orofacial anomalies such as clefts and hypodontias, in ectodermal dysplasia [61].

Genetic testing

Is a done to analyse a chromosomes and proteins in order to detect inherited disease-related mutations [62]. Mutations in the EDA, EDAR or EDARADD gene results in defective ectodysplasin A, which affects the development of ectodermal tissues, thereby contributing to ectodermal dysplasias [7].

Sweat pore counts

Yellow starch-iodine powder applied to palmar or dorsal skin. In Female carriers of X-linked EDA a mosaic pattern with areas of normal numbers of sweat pores along with areas of absent pores.

Skin punch biopsy

Specimen is taken from scalp and sole, hypothenar eminence of the palm and sweat pores were counted in order to assess absence or hypoplasia of sweat glands [63].

Dermatoglyphic studies

Dermatoglyphic studies using hand imprints show disruption of dermal ridges due to decrease in number of sweat pores. Slight variation in 'atd' angle was noted when compared to normal individuals, increase in number of arches and decrease in number of radials were also noted [64].

Prenatal diagnosis

Fetal skin biopsy may help identify the presence of decreased numbers of eccrine sweat glands and also pilosebaceous follicles in cases of hypohidrotic ectodermal dysplasia [6,63,64].

Treatment

Involves an multidisciplinary approach involving pediatric professionals, psychologist, ENT specialist and speech therapist and dermatologists who play a major role in improving physical, emotional and psychosocial development of affected individuals and creating a positive self-image [7,65].

In cases of hypotrichosis: Management of sparse, dry hair special hair care formulas, wigs. Topical minoxidil is found to be useful in treatment of alopecia and also showed hair growth [66].

In cases of Hypohidrosis: Individuals must have access to an adequate supply of water and a cool environment, a wet T-shirt, and/or a spray bottle of water [67].

In Cases of Hypodontia

A collaborative approach by oral surgeons, orthodontists, prosthodontists, endodontists is mandatory to improve speech mastication and facial appearance [17]. Hence, early treatment should be started as early as possible suggested. In certain type of ectodermal dysplasia associated with cleft lip or palate along with hand and limb deformities, surgical treatment is required reduce deformities and improve function [68]. Various treatment options include removable, fixed denture, complete denture prosthesis or an implant retained prosthesis [69,70]. Since it's a congenital disease, dentists must start working with the affected individuals right from the age when growth and development begins. Prosthetic treatment should be started as early as 2 or 3 years, this allows the child to accommodate to the prosthesis and improve appearance, speech, during the developmental ages [70-72].

Initially in cases of hypodontia removable prosthesis is fabricated, but removable appliances requires constant relining or remaking to accommodate growth patterns.

Post growth and development, continuous monitoring and modifications are mandatory. especially during the mixed dentition stage oral appliances needs to be will modified to accustom newly erupting permanent teeth. complete denture usually indicated in patients with ectodermal dysplasia only when abutment teeth cannot take up the load or when patient has anodontia [72,73]. Composite build-ups can improve the contour of abnormally shaped anterior teeth. Orthodontic treatment can place should be started for positioning the Misaligned teeth in a favorable position before the prosthodontic treatment [21]. In older patients, if bone support is sufficient osseointegrated implants can be used. If bone support is inadequate then bone grafting procedures are required before implant placement [13].

Recent Developments

Clinical trials have been conducted on canine and mice models where they investigated the use of Ectodysplasin-A1 (EDA-A1) replacement protein that binds to the EDA-A1 receptor (EDAR) and activates the signaling pathway that is responsible normal ectodermal development. It has found to reduce mortality and morbidity in animal models suffering from X-linked hypohidrotic ectodermal dysplasia [74,75].

Conclusion

Early recognition of the signs and symptoms occurring in the oral cavity such as anomalies involving the tooth number, form and structure which are characteristic of this disease helps in establishing a diagnosis. Timely intervention and treatment is essential to prevent psychological trauma and lack of confidence to the patient undergoes due to. It involves a multidisciplinary approach by all specialties of dentistry which focuses on significantly improving facial, esthetics appearance masticatory and phonetic function. esthetics appearance masticatory and phonetic function.

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