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REVIEW ARTICLE

GENETIC REVIEW OF ECTODERMAL DYSPLASIA

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ABSTRACT

Genodermatoses are congenital skin disorder often grouped into three categories: chromosomal, single gene, and polygenetic. Several of these disorders are isolated and also has oral phenomenon, called oral genodermatoses. Among these Ectodermal dysplasia (EDs) is a large group of an inherited disorders represented by a primary defect in hair, teeth, nails or function of sweat gland, in collaboration to another abnormality in an ectodermal derived tissue e.g. ears, eyes, lips, mucous membranes of an oral cavity or nose, central nervous system. The diverse forms of ectodermal dysplasia are caused by the mutation or deletion of specific genes located on different chromosomes. The signs and symptoms differ markedly among the different forms of the condition and rely on the structures that are affected. Presently there are about 150 different forms of ectodermal dysplasias. The commonest forms are Hypohidrotic (anhidrotic) Ectodermal Dysplasia and Hidrotic Ectodermal Dysplasia. The frequency of the different ectodermal dysplasias is highly variable in a given population. There is no particular treatment, only disease management is accessible.

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INTRODUCTION

Dermatology, being the particular study of skin diseases, constitute of a relevant subdivision of the system of medicine not only because of the different primary diseases influencing the skin, but also because of the general cutaneous phenomenon of deeper visceral or systemic diseases (Rajendran, 2012). There are various dermatologic disorders that have an inherited etiology or a genetic predisposition. Such genetically resolved skin disorders are subtitle as "genodermatoses" (geno: genetic + dermatoses: skin lesions) (Rimoin, 1996). Genodermatosis ascribe to inborn genetic skin disorder contemporary with multisystem entanglement (Babu, 2015). A genodermatoses can be entitled as "a cutaneous phenotype precipitate by a single mutation, which may be a chromosomal aberration, point mutation, or deletion (Kumar, 1996)."

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Numerous of these disorders is isolated and also has oral phenomenon, called oral Genodermatosis. The amelodentinal (the enamel and dentine) fundamental of the teeth and epidermis of the skin are derived from a general embryologic neural source of the ectoderm. As a consequence, there survive many primary cutaneous diseases which find their indication in the mouth influencing the oral mucosa and dentition.[5] Therefore, it is of greatest importance for a dental surgeon to identify that not only few dermatoses exhibit associated lesions of the oral mucous membranes but also demonstrations of some diseases may be preceded by oral lesions.

Classification of oral genodermatoses (Oji, 2009)

Genodermatoses affecting teeth and dentition

- Ichthyosis
- Sjogren-Larrson syndrome
- Incontinentia pigmenti
- Ehlers Danlos syndrome
- Focal dermal hypoplasia syndrome
- Gardner syndrome

- Ectodermal dysplasia
- Hyperimmunoglobulin E syndrome (Job syndrome)

Genodermatoses affecting periodontium and gingiva

- Ichthyosis
- Sjogren-Larrson syndrome
- Papillon Lefevre syndrome
- Tuberous sclerosis
- Chediak-Higashi syndrome
- Ehlers Danlos syndrome
- Focal dermal hypoplasia syndrome

Genodermatoses affecting oral mucosa

- Darier's disease
- Neurofibromatosis type 1 and 2
- Chediak-Higashi syndrome
- Ehlers Danlos syndrome
- Lipid proteinosis
- Focal dermal hypoplasia syndrome
- Multiple hamartoma syndrome (Cowden syndrome)
- Pachonychia congenita
- Epidermolysis bullosa
- Multiple endocrine neoplasia syndrome
- White sponge nevus

Genodermatoses affecting jaw bones and facies

- Mccune-Albright syndrome
- Ehlers Danlos syndrome
- Marfan syndrome
- Focal dermal hypoplasia syndrome
- Gardner syndrome
- Basal cell nevus syndrome
- Orofacial digital syndrome type I

Genodermatoses causing pigmentation of oral mucosa

- Carney complex
- Neurofibromatosis type 1 and 2
- Mccune-Albright syndrome
- Lipid proteinosis
- Pseudoxanthoma elasticum
- Peutz-Jeghers syndrome
- Congenital erythropoetic porphyria
- Hypomelanosis ofito
- Sturge-Weber syndrome
- Hereditary hemorrhagic telengiectasia

Ectodermal dysplasia: Ectodermal dysplasias (EDs) defined as an inherited disorders represented by modifications in two or more ectodermal organizations, at least one of these associating alterations in hair, teeth, nails, or sweat glands. The commonest types are Hypohidrotic (anhidrotic) Ectoderm Dysplasia and Hidrotic Ectodermal Dysplasia are the commonest form. Defective morphogenesis of cutaneous or oral embryonal ectoderm ((i.e., hair, nails, teeth, sweat glands) results in this congenital disorder. In few systems, abnormalities in mesoderm are also present.[7]Other names of Disease are: Ectodermal dysplasia anhidrotic (EDA), Anhidrotic ectodermal dysplasia, Hypohidrotic ectodermal dysplasia (HED), Christ-Siemens-Touraine syndrome (Chokshi *et al*., 2015).

Epidemiology: The prevalence of EDA is unknown; however, the incidence in males is estimated at 1 in 100,000 births although the condition is usually overlooked in infants. This X-linked recessive disorder affects males and is inherited through female carriers. This carriers-incidence is probably 17. 3 in 100,000 women (Laurikkala *et al*., 2001).

Etiopathogenesis: The abnormal production of ectodysplasin due to mutations in the *EDA, EDAR* or *EDARADD* gene prevents normal communications between the ectoderm and the mesoderm and hence results in impaired development of hair, sweat glands and teeth (Deshmukh, 2012).

Classification

EDs are divided into two groups: According to Freire-Maia's classification: Group A which consists of all the entities with defects in two or more of the standard structures Group B comprises of those with disturbances in only one of these structures plus another ectodermal defect. 11 subgroups have been included in Group A depending on the involved structures: 1-2-3-4 (hair-teeth-nails-sweat glands); 1-2-3 (hair-teeth-nails); 1-2-4 (hair-teeth-sweat glands); 1-3-4(hair-nails-sweat glands); 2-3-4 (teeth-nails-sweat glands); 1-2 (hair-teeth); 1-3 (hair-nails); 1-4 (hair-sweat glands); 2-3 (teeth nails); 2-4 (teeth-sweat glands); 3-4 (nails-sweat glands). Similarly, Group B is classified into four subgroups with number 5 added at the end, depicting that another ectodermal anomaly is present: 1-5, 2-5, 3-5, and 4-5. Other ectodermally derived structures like mammary glands, thyroid gland, thymus, anterior pituitary, adrenal medulla, central nervous system, external ear, melanocytes, cornea, conjunctiva, lacrimal gland and lacrimal duct that may also be involved in EDs (Chokshi *et al*., 2015).

Clinical Features: The three major characteristic features of EDA are sparse hair (atrichosis or hypotrichosis), abnormal or missing teeth (anodontia or hypodontia) and incapacity to sweat due to absence of sweat glands (anhidrosis or hypohidrosis) (Figure 1) (Bhadauria, 2014).

Craniofacial structures: Clinically, the forehead materialize square, with frontal bossing, eminent supra-orbital ridge and depressed nasal bridge (saddle nose deformity) is present. The midface is hypoplastic and depressed permitting it a "dished-in" appearance. There is a prominent chin, as well as hyperkeratosis of the soles and palms. Supplemental anomalies, like chronic rhinitis, pharyngitis, laryngitis, and mental disorders may escort the abovementioned symptoms in few cases (Sofaer, 1981; Bergendal *et al*., 1998)

Hair, nails, skin and skin tags: Most personals have sparse, fine, slowly developing scalp hair while few affected patients are completely bald by their middle teens, whereas others quantities have normal of scalp hair with an unusual texture. Scanty eyebrows and eyelashes were always present. Nearly all affected persons have reduced sweating, and mostly show intolerance to heat. General sites of sweating involve palms, soles and axillae. There is risk of hyperthermia delineated with mental disorders due to decreased number of sweat glands (Aswegan *et al*., 1997).

Oral manifestations: Radiographically, delay in teething or missing teeth and an abnormal shape and structure of teeth also can be seen. Taurodontism is a general feature which frequently present in the second deciduous molars. A severe hypodontia influencing both deciduous and permanent teeth is a crucial feature (Figure 2) (Johnson *et al*., 2012; Pirinen, 1996).

Commonly occurring syndrome concomitted with Ectodermal dysplasia

- **Hidrotic ectodermal dysplasia (Clouston syndrome):** This condition is an inherited in an autosomal dominant manner in which sweat glands are present generally (Bhadauria *et al*., 2014).
- **Genetic Pathogenesis:** The disorder is due to mutation in connexin gene, GJB6 or connexin – 30 which maps on the centromeric region of the long arm of chromosome (Bhadauria *et al*., 2014).

Clinical Features: It has a variable appearance, and equally both males and females are affected. The 3 major characteristic features of the disorder include Hair loss, nail dystrophy, and palmoplantar keratoderma. Teeth and sebaceous gland function are normal in comparison to Hypohidrotic ectodermal dysplasia (HED).Hair abnormalities are present as atrichia (absence of hair) or hypotrichosis (less hair). Females are entirely bald, whereas men represent expression that varies from focal alopecia to complete baldness. The eyebrows and eyelashes are sparse or absent, as is axillary and pubic hair. Nail disorders varies from normal appearance to micronychia or anonychia; the nail plate may represent thickening, desquamation, and changes in colour, striation, and onycholysis. Nail abnormalities in these patients may be reminiscent. (Figure 3) (Chokshi *et al*., 2015).

Hypohidrotic ectodermal dysplasia (Christ-siemens-touraine syndrome/Ahidrotic ectodermal dysplasia): It is the commonest form in which sweat glands are either absent or significantly reduced in number.

Genetic Pathogenesis: Mutations in the autosomal gene, Ectodysplasin A receptor (*EDAR*) mapped to 2q11-q13, have been implicated in an autosomal dominant and recessive form of hypohydrotic ectoderm dysplasia that is clinically similar to X-LHED. EDAR acts as a receptor for ectodysplasin. Mutations in EDARADD gene have been recognized in the autosomal recessive form of HED. *EDARADD* is an intracellular adaptor protein that assists in transmitting signals from the activated EDA receptor to the nucleus of the cell. Certain cases show X-linked nuclear factor-κB essential modulator (*NEMO*) gene, the regulatory subunit of the *IκB* kinase complex, is a critical component of the NF-κB pathway is found to cause HED and immune defects (Klaus Wolff *et al*., 2008).

Clinical features: The characteristic clinical features include skin, tooth, and sweating abnormalities. Alopecia is generally the first noticeable clinical feature. Children will have fine, scanty, light-colored hair which thickens and darkens as patient grows up. The eyebrows and beard hair are also scant, but the hairs of eyelashes, armpit and pubic area might be normal. Hair from other body part is sparse or even absent (Rajendran, 2012).

Figure 1. The child suffering from Ectodermal Dysplasia

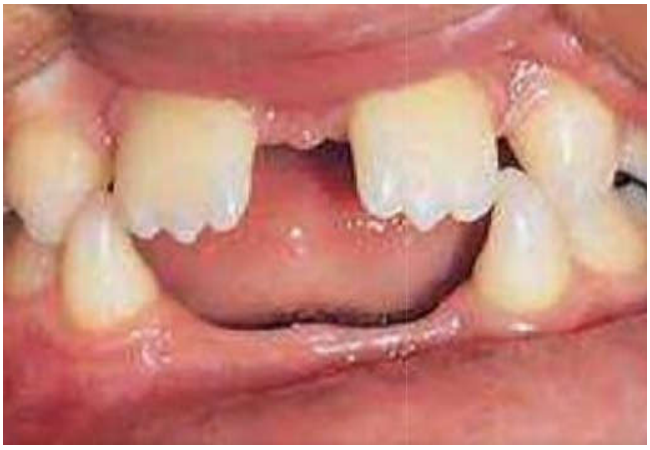

Figure 2. Showing missing teeth or peg shaped teeth.[10]

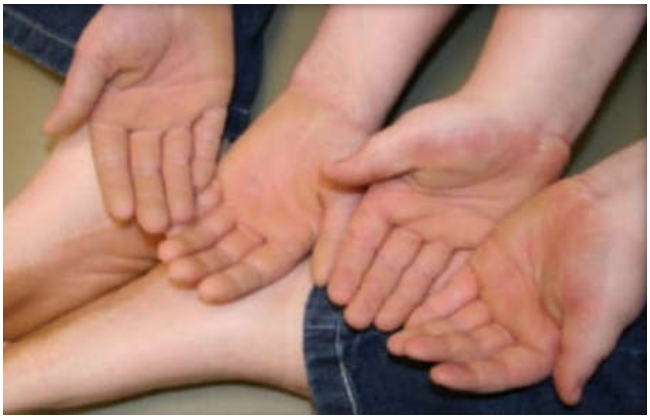

Figure 3. Showing features of Hydrotic ectodermal dysplasia (HED) (palmoplantar hyperkeratosis)

Oral Manifestations: Tooth abnormalities may become apparent during lactation as hypoplasia of the alveolar crests. Within the families, same family or between the sexes a great degree of variation can be seen regarding the number of missing and malformed teeth. In comparison to the posterior teeth the anterior teeth will exhibit more morphologic discrepancies. Commonest example would be a tooth with cone or peg shaped crown (Lu, 2008; Blüschke *et al*., 2010).

Ectodactyly-ectodermal dysplasia (EEC SYNDROME): EEC syndrome (also known as "Split hand–split foot–ectodermal dysplasia–cleft syndrome") is an inherited

developmental disorder distinguished by ectrodactyly, ectodermal dysplasia, and orofacial clefts (cleft lip/palate).It is categorized as multiple congenital anomaly syndrome because it has considerable involvement of constructions other than ectodermally derived (Chokshi, 2014; Bhadauria, 2014).

Genetic pathogenesis: Mutations in *p63* a tumor suppressor gene located on chromosome 3q27. EEC is an autosomal dominant syndrome with variable expression and reduced penetrance. Intra and interfamilial difference in severity is observed (Chokshi *et al*., 2015; Bhadauria *et al*., 2014).

Clinical features: The most frequent abnormalities are malformations of the limbs like ectodactyly and syndactyly, ED associated with sparse, hypo-pigmented or light colored hair, absence of eyebrows and eyelashes, and alopecia, and oro-facial cleft, followed by tear duct abnormalities, genital malformations, and deafness, although the clinical manifestations vary greatly within and among families. Perioral lesions and angular cheilitis may be present in the oral commissures as a result of anatomic changes caused by reconstructive surgery for cleft lip/palate (Jan *et al*., 2014; Pierre-Louis *et al*., 2010).

Oral Manifestations: Tooth abnormalities such as hypodontia or anodontia have also be reported, as well as a propensity to tooth decay due to defective enamel and changes in the salivary gland function (Fete *et al*., 2009).

Ankyloblephar on filiforme adnatum-ectodermal dysplasia cleft palate syndrome (Hay-wells syndrome): It is an ectodermal dysplasia syndrome with describing features of ankyloblepharon filiforme adnatum (AFA), aberrancy in ectoderm and a cleft lip and/or palate (Bhadauria, 2014).

Genetic Pathogenesis: The disorder is caused by mutations in tumor suppressor gene *p63* that has been implicated in acro-dermato-ungual-lacrimal- tooth or ADULT syndrome Ectodactyly-ectodermal dysplasia- cleft lip/palate or EEC syndrome and other autosomal dominant forms of ED but the mutation causing each syndrome cluster in the different region of the gene (Bhadauria *et al*., 2014).

Clinical features: The facial features like short philtrum, thin vermillion border, broad nasal root, maxillary hypoplasia and small mandible become more apparent in childhood. Other commonest anomalies are limb changes with syndactyly, hypospadias (males 78%) and trismus (not much prevalent).[10]

Oral Manifestations: Hypodontia and cone-shaped teeth.

Rapp – Hodgkin's syndrome: The syndrome is commonly noticeable at birth but the predominance is unknown with less than 100 cases diagnosed in the disquisition so far. It is an autosomomal dominant syndrome that shares its feature with Hay Wells syndrome cleft palate with or without the cleft lip.

Genetic Pathogenesis: This type of ED is due to a mutation in the *p63* gene (also termed as the tumor protein *p73*-like (*TP73L*) gene, localized to 3q27).

Clinical Features: Characteristic facies like maxillary hypoplasia, small mouth, thin upper lip and narrow nose, hypospadias in males, obstructed lacrimal puncta or epiphora, have also been reported (Bhadauria *et al*., 2014).

Tooth and nail syndrome: Witkop syndrome / Hypodontia with nail dysgenesis Witkops syndrome is an autosomal dominant syndrome with inconstant expression and intrafamilial uncertainty.

Genetic Pathogenesis: This syndrome is caused due to mutation in *msx1* gene which plays an crucial role in the development of certain teeth (premolars, first molars, and third molars) and nails, by determining the integrity and thickness of the nail plate.

Clinical Features: The characteristic clinical features of Witkops syndrome are Nail dysplasia and hypodontia (Fete *et al*., 2009).

Diagnosis: The typical clinical physiognomy is a diagnostic tool. The reduced number and abnormal shape of teeth are the most characteristic findings in man. The first step in the diagnosis is often delayed in teething. The men have a simply noticeable facies, also attribute to as an 'old man' facies. Few infants have a untimely look with scaling of the skin. This can also produce an indication to the diagnosis. There is reduced number of sweat glands and both scalp and body hairs are scanty, with absence of eyebrows and eyelashes. The conveyor female has few phenotypic expressions. The clinical findings of both affected males and conveyor females are same. One third of the conveyor materializes healthy, another third of them is appearing mild symptoms, and the last third shows remarkable symptoms, but usually milder than the affected males (Sofaer, 1981).

Differential diagnosis: The differential diagnostic complication is the divergence of the autosomal recessive form of HED from X-linked HED. AR-HED is considerably less common than XLHED. The clinical characteristics are absolutely identical in both situations but due to the various mode of heritage AR-HED influences both males and females and the heterozygotes have no character at all (Munoz *et al*., 1997).

Treatment: To support the facial soft tissues, normalize the vertical dimension, aesthetics of the teeth and re-establish the function of teeth is the main course of the treatment. .From the age of two or three years onwards, early placement of partial or full dentures is generally recommended. The denture must be systematically adjusted as alveolar growth; erupting teeth and rotational jaw development change both the alveolar, basal and occlusal measurements. Wreckage and even loss of removable in children, is quite prevalent. It is commonly agreed that before termination of growth, osseo-integrated implants should be not placed. There are various published cases of premature implant placement in toothless patients of EDA; the achievement, however, has been inconsistent (Klaus Wolff, 2008).

Conclusion

In recent years, there has been incredible success in explanating the molecular bases of Genodermatoses. The alliance between genetics and dermatology has widened with the recognization of "new" heritable disorders, remodeled identification of phenotypic spectrums, and assimilation of clinical and molecular data to clarify disease categorization and highlight correlation between conditions.

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