Ectodermal Dysplasia – An Overview and Update

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Abstract

Ectodermal dysplasias are a heterogeneous group of disorders that are characterized by abnormal development of ectodermal structures like hair, teeth, nails, and sweat glands. Alhough they were earlier classified according to the structures affected and hence the clinical manifestations, recent developments inch towards a genetic basis for classification. They are currently divided into four groups of disorders based on the pathway involved, which includes the ectodysplasin/nuclear factor-kappa B (NFKB) pathway, wingless-type MMTV integration site family, member 10 ([wingless related integration site] WNT10), tumor protein p63 (TP63), and the structural group. In spite of attempts at the segregation of the various disorders, there is a great degree of overlap in clinical features among the conditions, which makes a thorough history-taking and clinical examination important in helping us arrive at a diagnosis and judge the various systems involved. A multidisciplinary approach forms the crux of the management of patients with ectodermal dysplasias and their families, with a focus on education, counseling, prosthesis, and an overall rehabilitative outlook. Special attention must also be paid to screening family members for varying severities of the disorders, and an attempt must be made at a genetic diagnosis with genetic counseling.

Keywords: *Ectodermal dysplasia, genetic, hypohidrotic, multidisciplinary approach*

Introduction

Ectodermal dysplasias (ED) are a group of inherited disorders affecting the development or homeostasis of two or more ectodermal derivatives,[1] including hair, teeth, nails, and other structures like glands, retina, cochlea, central nervous system (CNS), and adrenal medulla. Advances in molecular genetics and developmental biology have led to the identification of the causative genes and developmental pathways in at least 80 of the EDs.

Definitions and Classification

"Pure ectodermal dysplasias" are entities with only ectodermal signs without disturbances derivatives of other embryonic layers. On the other hand, "syndromes of ectodermal dysplasia and malformation" present ectodermal signs and also defects of another embryonic origin, such as cleft lip/palate. Freire-Maia offered the most common major classification scheme in 1971, with primary emphasis on grouping the disorders based on the involvement of hair, teeth, nails, or eccrine sweat glands, which were termed as 1,2, 3, and 4, respectively. This was referred to as the 1-2-3-4 system, where the nomenclature of the subgroup depended on the structures involved. For example, if hair and teeth are involved, the subgroup would be named 1-2.[2] This classification finally came to include around 154 entities,[3] amongst which multiple entities belong to other classifications like pachyonychia congenita, dyskeratosis congenita, and Rothmund-Thompson syndrome. Continuous revision of the classification systems has been attempted, and a shift has occurred to classifying these disorders based on the genetic defect or the developmental pathway involved which helps in offering a better understanding of these disorders.[4] The classification described by Wright *et al*.[1] groups these disorders broadly into defects of the ectodysplasin A (EDA)/nuclear factor kappa B (NFKB) pathway, wingless related integration site (WNT) pathway, tumor protein p63 (TP63) pathway, other structural defects, and unknown causes [Table 1]. Figure 1 demonstrates the inter-relationships between the various molecules and pathways and the associated

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Table 1: Classification of ectodermal dysplasia based on molecular pathways affected (Adapted from Wright *et al.*)

Disorder	Gene
EDA/NF kappa B pathway	
X-linked hypohidrotic ectodermal dysplasia (ED1); Christ-Siemens Touraine syndrome	Ectodysplasin A (EDA)
AR hypohidrotic ectodermal dysplasia 10A	Ectodysplasin A Receptor (EDAR) or EDARADD
AD hypohidrotic ectodermal dysplasia 10B	Ectodysplasin A receptor (EDAR) or EDARADD
Incontinentia pigmenti; IP	*IKBKG*
Ectodermal dysplasia and immunodeficiency 1	IKBKG
WNT pathway	
Focal dermal hypoplasia (Goltz syndrome)	*PORCN*
Odonto-onycho-dermal dysplasia	WNT10A
Schopf-Schulz-Passarge syndrome	WNT10A
TP63 pathway	
Acro-dermato-ungual-lacrimal - tooth syndrome (ADULT syndrome)	TP63
Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC)/Hay–Wells syndrome	TP63
Rapp-Hodgkin syndrome	TP63
Ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome 3 (EEC3)	TP63
Limb-mammary syndrome	TP63
Structural Group	
Ectodermal dysplasia, ectrodactyly, and macular dystrophy syndrome	Cadherin 3
Ectodermal dysplasia 4, hair/nail type	*Keratin 85*
Ectodermal dysplasia/skin fragility	*Plakophilin*
Monilethrix	Keratin 81, 83, 86
Hidrotic ectodermal dysplasia (Clouston syndrome)	GBJ6
Cleft lip/palate-ectodermal dysplasia (CLPED1)	*Nectin 1*
Unknown	
Arthrogryposis and ectodermal dysplasia	Unknown
Dermo-odonto dysplasia	Unknown

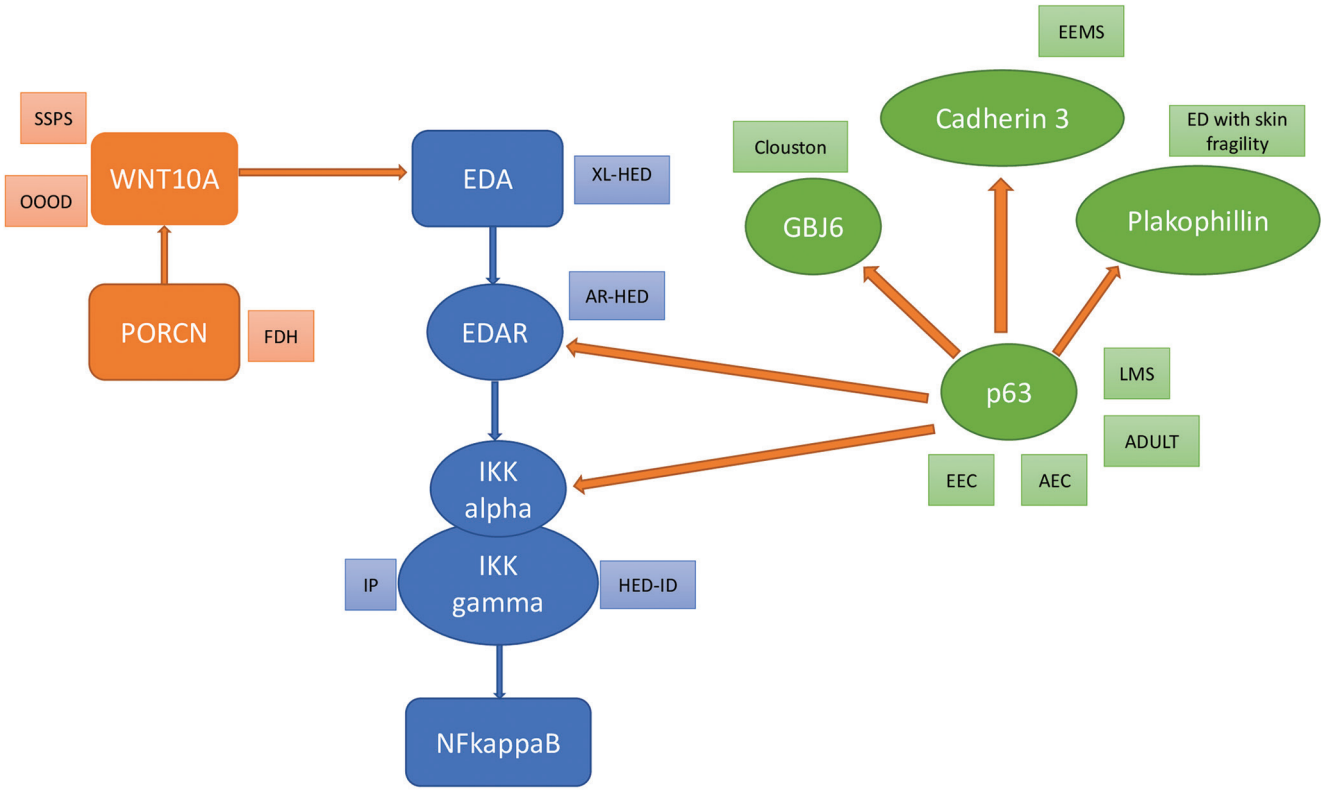

Figure 1: Schematic diagram demonstrating the inter-relationships between the various molecules and pathways in ectodermal dysplasias and the associated disorders

disorders. This system, however, excludes entities that have been included in other classification systems, like palmoplantar keratodermas or poikilodermas. The most recent classification was proposed by Peschel *et al*.[5] as a part of the five-yearly update on EDs. This system adhered to the previous genetic scheme of classification while adding 15 new entities or genes that have been recently studied.

(A) Disorders of the EDA/NFKB pathway

Hypohidrotic ectodermal dysplasia (HED)

It is classified further based on the mutated gene and the type of inheritance[6]: (a) X-linked HED-EDA1 mutation (also known as Christ–Siemens Touraine syndrome) [X-linked recessive] (b) EDAR (EDA receptor) mutation- autosomal dominant and recessive (c) EDARADD (EDAR associated death domain encoding gene) mutation- autosomal dominant and recessive (d) X-linked HED with immunodeficiency- NEMO (NFKB essential modulator)/IKBKG (inhibitor of NFKB kinase subunit gamma) gene. As the X-linked form is the most common, males are predominantly affected, although female carriers of an X-linked variant can manifest partial symptoms in a mosaic pattern due to random X-inactivation or lyonisation.

HED is characterized by a triad of hypohidrosis or anhidrosis, hypotrichosis, and hypodontia.[7] Typical features include sparse and lustreless hair on the scalp as well as the torso and limbs, along with conical or peg-shaped incisors[7,8] [Figure 2]. Dentition is often delayed, and the lack of teeth leads to hypoplastic alveolar ridges and midface hypoplasia [Figure 2]. Other features that may be present are hair shaft defects like pili torti, pili canaliculi, and trichorrhexis nodosa, absent dermatoglyphics, xerosis, and periorbital wrinkling and hyperpigmentation [Figure 2]. An association with atopic eczema is often observed in two-thirds of the patients.[9]

Figure 2: A 12-year-old girl with hypohidrotic ectodermal dysplasia showing (a) peg-shaped teeth and hypodontia (b) Spock-like ears. Mid-face hypoplasia, sparse scalp hair, eyebrows and eyelashes, and periorbital hyperpigmentation can also be appreciated

The most common complication that one should be aware of is hyperthermia,[7,10] as a result of diminished sweating, which may result in heat stroke in infants, which can even lead to death. Abnormalities in mucosal glands can cause very thick nasal secretions that can predispose the patient to the development of respiratory tract infections,[10-12] and thick cerumen in the ear canal may lead to obstruction of the external auditory canal and hypoacusis. Abnormal meibomian glands lead to dry eye symptoms, including superficial punctate keratitis.[12]

Even though the diagnosis is primarily clinical, supportive modalities can be used, like starch iodine test to demonstrate the absence of sweating, trichoscopy and trichogram to demonstrate the hair shaft abnormalities and reduced hair follicle density, and confocal microscopy to assess the density of sweat glands.[13,14] Histopathology, though not routinely needed, shows a thinned-out epidermis with the absence of rete ridges, reduced sweat glands, and pilosebaceous units.[13]

The management should be individualized based on the clinical features and complications and often requires a multidisciplinary approach. Treatment is primarily directed at preventing hyperthermia and restoring oral function. Preventive measures include avoiding hot environments and strenuous physical activities, using air conditioning, cooling vests, and hand-operated cool misters and fans. Parents, children, teachers, and friends must be taught the signs and first-aid management of hyperthermia. For the management of alopecia, topical minoxidil has been used with favorable results in a few patients.[15] Wigs can be employed for cosmetic benefit. In one report, topical cetirizine and oral vitamin D supplementation improved hair density in three girls with HED.[16] Emollients and topical corticosteroids may be needed for patients who have xerosis or eczema. Nasal saline rinses may be prescribed at an early age. Avoidance of environmental smoke and other irritants must be practiced.

Fc-EDA is a recombinant fusion protein that binds to the EDA receptor and activates the signaling pathway for normal ectodermal development. It showed promising results on prenatal administration in animal models[17,18] and three human fetuses;[19] however, postnatal administration did not show any improvement as expected.[20] It is currently being investigated for prenatal pharmacotherapy in a multicentre trial.[21]

Overall, with proper monitoring, prevention of complications, and multidisciplinary management, the prognosis of growth and lifespan is excellent.

HED with immunodeficiency (HED-ID)

It is a form of X-linked HED that is seen in males due to hypomorphic mutations (small deletions or non-sense mutations in the zinc finger domain) in the gene for inhibitor of nuclear factor kappa B kinase

subunit gamma (IKBKG) (NF-kappa-B essential modulator [NEMO]).[22] Incontinentia pigmenti (IP) is allelic to this disorder and is caused by a deletion, in *IKBK*.

Clinical features are similar to HED, but milder. Males may rarely have a vesiculo-papular eruption similar to that seen in IP. Mothers of affected children have skin lesions reminiscent of IP, as well as variable manifestations of HED.

Various immune defects can be present, including natural killer cell dysfunction, hypogammaglobulinemia, and hypergammaglobulinemia M. As a result, these patients suffer from severe, recurrent infections of the lower respiratory tract, skin and soft tissues, bones, gastrointestinal, and meninges due to *Staphylococcus aureus, Streptococcus pneumonia, Pseudomonas, Mycobacterium, Pneumocystis,* viruses, or *Candida*. Inflammatory colitis can also occur along with significant failure to thrive.

The diagnosis can be confirmed via molecular genetic testing (*IKBKG* sequencing) and a thorough immunodeficiency evaluation.

Management involves prompt antibiotic treatment and intravenous immunoglobulin (IVIG) therapy. Allogenic hematopoietic stem cell transplantation (HSCT) is the only curative modality at present, with a 74% survival rate.[23] The prognosis for long-term survival is hence poor without HSCT, with death often occurring in childhood to adolescence.

Incontinentia pigmenti (IP)

IP, also known as Bloch–Sulzberger syndrome, is caused by loss-of-function mutations in the IKBKG/NEMO gene that impair cell survival, inflammation, and immunity.[24,25] It is inherited in an X-linked dominant fashion ("de novo" in 65% of cases).[25] Null mutations are lethal in utero in males, whereas females survive because of lyonization, and hence, most cases of IP occur in females. Rarely males may be affected in association with somatic mosaicism or XXY karyotype (Klinefelter syndrome).[26]

There is considerable heterogeneity in the clinical presentation, with no clear genotype-phenotype correlation due to lyonisation.[27] The classic cutaneous presentation occurs in four stages[28]:

Stage 1 (vesicular) – Tense vesicles and/or pustules, overlying an erythematous base along the Blaschko lines, which occur at birth or a few days later. These lesions can recur during a febrile illness, laser treatment, or vaccination.[29]

Stage 2 (verrucous) – Lesions become more papular or wart-like and can last for a few months to years.

Stage 3 (hyperpigmented) – By 6 to 12 months of age, infants show brown or grey-brown, linear and/or swirling macules that last through adolescence [Figure 3].

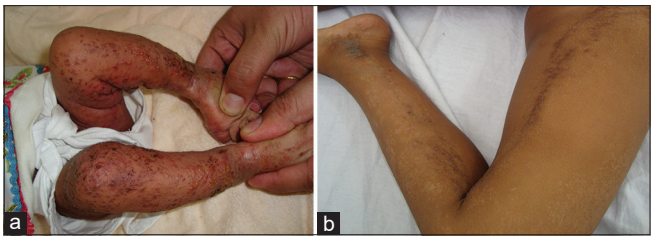

Figure 3: (a) Vesicular lesions of incontinentia pigmenti, arranged in a blaschkoidal pattern seen in a 2-month-old-girl (b) Verrucous and hypopigmented lesions along the lines of Blaschko observed simultaneously in a 7-year-old girl

Stage 4 (atrophic/hypopigmented) – Hypopigmented and slightly atrophic, linear macules/patches are seen, often associated with alopecia.

The onset, duration, and degree of overlapping of these stages vary among patients.

The mother of a child with IP may present with hypopigmented, atrophic streaks along the Blaschko's lines, along with nail dystrophy.

Other cutaneous features include cicatricial alopecia, nail dystrophy,[30] and painful, subungual, dyskeratotic tumors.[31]

Extracutaneous findings:

- Dental and oral anomalies like delayed dentition, pegged or conical teeth, anodontia or hypodontia, and cleft or high-arched palate occur in almost all patients.[32]
- Breast and nipple hypoplasia and aplasia, supernumerary nipples can occur.
- Ocular anomalies like proliferative retinopathy,[33] microaneurysms, macular occlusive disease, non-perfusion, and rarely microphthalmia.
- Neurologic symptoms include lethargy, poor feeding, seizures, neurocognitive impairment, and stroke.[33]

A diagnostic criteria was also established in 1993 by Landy and Donnai and was revised in 2014 by Minic.[34] A skin biopsy may be helpful if obtained during the vesicular stage as it reveals eosinophilic spongiosis, intraepidermal vesicles containing eosinophils, and apoptotic keratinocytes.[28] The pathologic changes seen in later stages are less specific. Molecular testing must be performed, if available, in suspected cases to identify the common deletion of exons 4 to 10 in IKBKG, which is present in ~70–80% of cases.[35] In male patients, karyotyping should be considered as well, due to the possibility of IP in the setting of Klinefelter syndrome.

Management of cutaneous lesions involves only gentle wound care and emollients in the vesicular stage. Topical corticosteroids[36] and topical tacrolimus can also be used. Local or systemic antibiotics might be needed in case of superadded infection. Emollients or topical retinoids may be tried for the verrucous stage. No treatment is generally needed for stage 3 or 4 skin lesions. Eye examinations are recommended monthly until age four months, then every

3 months from age 4 months to 1 year, every 6 months from age 1 to 3 years, and annually after age 3 years.[35] A dental consultation is indicated in all patients with IP at the time of teeth eruption or by the age of 6 months. Neurological evaluation and imaging must be performed in case of neurological symptoms with rigorous follow-up.[35]

(B) Disorders of the WNT pathway

Focal dermal hypoplasia (FDH)

Also known as Goltz syndrome or Goltz–Gorlin syndrome,[37] FDH is an X-linked dominant disorder that is caused by deletions in the porcupine O-acyltransferase gene (*PORCN*), which is required for the secretion of WNT proteins.[38] It predominantly occurs in females and is lethal in utero for males, except mosaicism for a de novo mutation or in association with Klinefelter syndrome.

It is characterized by skin atrophy with fat herniation typically following the lines of Blaschko at birth.[39] Crusting, erosions, hypopigmentation, or hyperpigmentation may develop over these areas. Other features include raspberry-like papillomas in the perioral area and groin, patchy alopecia, nail changes including longitudinal ridging, micronychia and anonychia, and palmoplantar keratoderma. Papillomas may be present in the upper respiratory tract and oral cavity as well,[40] causing respiratory distress and dysphagia. A variety of craniofacial manifestations can be present, including microcephaly, cleft lip/palate, ocular abnormalities, dental anomalies, speech problems, and central nervous system (CNS) abnormalities. Limb defects are common, including syndactyly and ectrodactyly, leg length discrepancy, osteopathia striata, and short stature.[41] Malformations of the gastrointestinal and urogenital systems may also occur.

Similar to IP, clinical diagnostic criteria have also been proposed.[42] Histopathologic findings in areas of dermal hypoplasia include increased capillaries in the papillary dermis, attenuated dermis, and fragmentation of elastic fibers.[43] Fatty tissue almost reaches the epidermis due to scarce collagen in the dermis (heterotopic fat).

Confirmation of diagnosis can be obtained by the identification of a PORCN mutation. No specific treatment is available other than surgical excision of papillomas.

Onycho-odonto-dermal dysplasia

It is a rare autosomal recessive disorder that occurs due to a mutation of the WNT10A gene.[44] It is characterized by severe oligodontia, onychodysplasia, palmoplantar hyperkeratosis, dry skin, hypotrichosis, and hyperhidrosis of the palms and soles.[45] Often, a smooth tongue is seen with a marked reduction of fungiform and filiform papillae.[46]

Schopf–Schulz–Passarge syndrome

It is also an autosomal recessive disorder that occurs due to a mutation in the WNT10A gene.[47] Clinical features include diffuse palmoplantar keratoderma, hypodontia, hypotrichosis, nail dystrophy, and multiple periocular and eyelid apocrine hidrocystomas.[48] The potential risk of non-melanoma skin cancer exists in such patients and should be monitored closely.[48]

(C) Disorders of the TP63 pathway

EEC syndrome

Ectrodactyly, ectodermal dysplasia, and cleft lip/palate type 3 (EEC3) syndrome is an autosomal dominant disorder caused by missense mutations in the DNA binding domain of *TP63*.[49]

Characteristic features include split hand/foot deformity (ectrodactyly),[50] light-colored hair that is sparse, coarse, and dry, sparse eyebrows and eyelashes, thin, brittle nails, xerosis with variable sweating[51] and cleft lip/palate [Figure 4]. Other features include dental anomalies, midface hypoplasia, syndactyly, oligodactyly, absent lacrimal puncta (leading to keratitis, blepharitis, dacrocystitis, corneal ulcers), genitourinary anomalies[52] and endocrine abnormalities.

There is considerable clinical overlap and variability in the *TP63*-related disorders. Consideration of other syndromes within this family is always prudent. The prognosis is good overall.

Limb-mammary syndrome (LMS) and acro-dermato-ungual-lacrimal–tooth (ADULT) syndrome

Both these disorders are caused due to TP63 mutations at different sites. Earlier LMS was considered to present predominantly with mammary and nipple hypoplasia along with limb anomalies and bifid uvula or cleft palate rather than cleft lip as compared to EEC syndrome.[53] ADULT syndrome, on the other hand, was said to lack cleft lip/palate and presented with dermatitis and extensive freckles apart from other features similar to EEC syndrome. However, recent literature has shown considerable overlap between these three entities, which raises the question of grouping these disorders into the TP63 syndrome.

Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome

Ankyloblepharon-ectodermal defects-cleft lip/palate syndrome, also known as Hay–Wells syndrome, is an autosomal dominant disorder that is caused by mutations in the N-terminal domain of *TP63*.[54]

Neonates usually present with collodion membrane, followed by congenital erythroderma. Superficial skin erosions, most often involving the scalp,[55] are also present

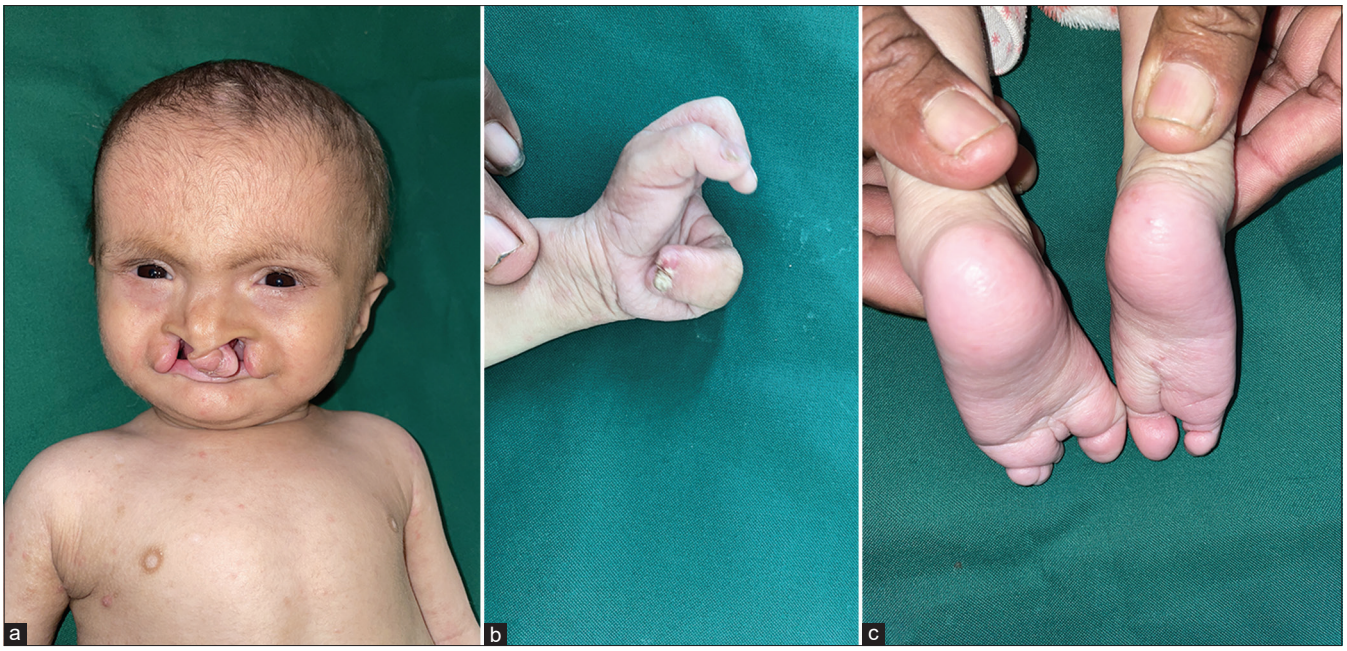

Figure 4: A 6-month-old male child suffering from ectrodactyly-ectodermal defects-cleft lip/palate syndrome. The figure shows (a) cleft lip, (b) ectrodactyly (lobster claw deformity or split hand deformity) of hand, and (c) ectrodactyly (split foot deformity) of feet. [Clinical images courtesy: Dr. Vinay Keshavamurthy]

at birth, which can lead to infection, sepsis, electrolyte imbalances, severe scarring and alopecia. Hair, nails, and variable degrees of sweating abnormalities may be present. The characteristic feature is ankyloblepharon filiforme adnatum (fusion of the eyelids).[54] Lacrimal puncta are often absent. Cleft lip and/or palate occur in nearly all cases. Other facial features include midface hypoplasia, dental anomalies, hypospadias, and limb anomalies like syndactyly and ectrodactyly.

Rapp–Hodgkin syndrome is an allelic disorder that is now considered a variant of AEC syndrome.[56] The lack of ankyloblepharon in Rapp–Hodgkin syndrome is the only significant difference. Scalp erosions help in the differentiation of AEC from the other p63 disorders.

Apart from multidisciplinary care, skin erosions should be managed in neonatal intensive care settings with adequate fluid and electrolyte supplementation, nutritional supplementation, and antibiotics. Gentle cleansing and application of skin emollients and topical antiseptics must be practiced. Management of collodion baby and neonatal erythroderma must be undertaken in the form of careful handling, emollients, adequate hydration, and maintenance of ambient temperature and humidity. Surgical correction of ankyloblepharon must be done at the earliest. Strategies aiming at regeneration of epidermal defects using keratinocyte sheets from epidermal stem cells and corneal defects from limbal stem cells are being developed for AEC and EEC syndromes.[21] In this regard, clustered regularly interspaced short palindromic repeats (CRISPR)/Cas (CRISPR-associated) holds a lot of promise in genome editing for correction of the causative mutation. Apart from this, PRIMA-1^{MET}, a p53 reactivator, when applied topically, has been shown to augment epidermal differentiation and improve wound healing in patients with AEC syndrome.[57]

(D) Structural group of disorders

Hidrotic ectodermal dysplasia

Also known as Clouston syndrome, it is caused by mutations in the connexin-30 or *GJB6 gene*, on chromosome 13[58] and is inherited in an autosomal dominant fashion. This disorder is characterized by nail dystrophy, palmoplantar keratoderma, and abnormal hair. Sweating and dentition are normal.

Hair is usually fine, brittle, and sparse, with progressive alopecia with increasing age. Women generally have total alopecia, whereas men have patchy alopecia on the scalp. Eyebrows, eyelashes, and axillary and pubic hair are also affected, and will be sparse as well. Nails are dystrophic, short, and slow-growing, and may also be cone-shaped or triangular, hypoplastic or absent. Ophthalmologic involvement may be present, such as photophobia, strabismus, conjunctivitis, blepharitis, and premature cataracts.

Though diagnosis is mostly clinical, molecular genetic testing can be employed to confirm the diagnosis. Disorders that can pose as a differential diagnosis in such cases are pachyonychia congenita, keratitis–ichthyosis–deafness (KID) syndrome, and other forms of EDs like ectodermal dysplasia 5, hair nail type and ectodermal dysplasia 4, pure hair nail type. Management mainly involves keratolytics and emollients for palmoplantar

keratoderma. A combination of tretinoin and minoxidil may be effective for increasing hair growth.[59]

Ectodermal dysplasia-skin fragility syndrome

It is caused by a mutation in plakophilin 1, one of the proteins in the desmosomal complex. It is characterized by features of both ectodermal dysplasia like hypohydrosis, nail dystrophy, hypotrichosis, palmoplantar keratoderma, as well as epidermolysis bullosa, such as skin fragility and erosions.[60]

Monilethrix

It is an autosomal dominant disorder that occurs due to mutations of the hair keratins K81 and K86. It clinically presents as fragile, brittle hair, which on dermoscopy or hair microscopy, shows regular elliptical beading [Figure 5].[61] Minoxidil and oral acitretin have been used for management with variable results.[62]

Approach to a case of ectodermal dysplasia

A suspicion of ectodermal dysplasia arises when developmental defects occur in the ectodermal structures like skin, hair, nails, and glands. A thorough history and physical examination must be undertaken in order to arrive at a clinical diagnosis [Figure 6]. The relevant history that must be elicited is the ability or inability to sweat**,** heat intolerance, and febrile seizures. A history of recurrent episodes of respiratory infections and soft tissue infections in the presence of other features of HED is suggestive of HED with immunodeficiency. History of dry skin, eczema, and associated atopy must also be asked. History of vision abnormalities, dry eye, difficulty in eating and mastication, speech disability, seizures, stunted growth, intellectual disability, etc., will suggest involvement of other organ systems. A history of collodion baby is often present in AEC and sometimes in HED as well. Prior history of superficial erosions, especially on the scalp, is specific to a diagnosis of AEC. Blistering at birth is associated with IP and ED with skin fragility. A thorough family history must be obtained, and a detailed pedigree chart must be drawn in order to gain a better understanding of the inheritance pattern and penetrance. Sometimes, other family members may have subtle or partial findings, hence careful probing is mandatory. Mothers of children with HED and IP must be examined as well in order to look for blaschkoidal lesions. Following history, a careful and thorough cutaneous and systemic examination must be performed. Blaschkoidal lesions are observed in IP, follicular dysplasia with hamartomas (FDH), and MIcrophthalmia, Dermal Aplasia, and Sclerocornea (MIDAS). Palmoplantar keratoderma is often associated with many of the EDs. Adnexal tumors like papillomas or apocrine hidrocystomas must be looked for in the appropriate clinical setting.

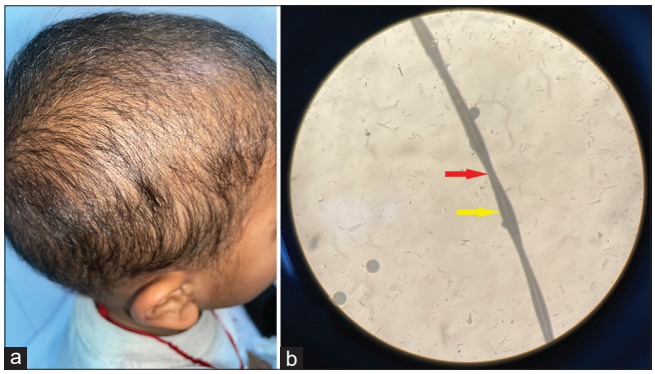

Figure 5: (a) Sparse scalp hair in a 3-year-old boy with monilethrix (b) Hair microscopy shows the regular beaded appearance of a shaft with nodes (red arrow) and elliptical internodes (yellow arrow)

Examination of hair involves noting the density, texture, length of hair shaft, distribution of hair, areas of involvement, and presence or absence of scarring. Dermoscopy and trichoscopy can also augment examination as findings like pili torti, pili canaliculi, trichorrhexis nodosa, regular beading (monilethrix), scarring alopecia, etc., can be observed. Nails in EDs can range from normal to dystrophic to anonychia. Some subtle clues are milky white nails at birth followed by thickened and hyperconvex nails in Clouston syndrome and koilonychia in ED with skin fragility and Witkop syndrome. Though varying degrees of hypodontia are seen in many EDs, conical or peg-shaped teeth with hypoplastic alveolar ridges are characteristic of HED.

The involvement of a multidisciplinary team forms the cornerstone of the evaluation and management of ED. Ophthalmological, neurological, skeletal/orthopedic, endocrinologic, and genitourinary evaluation must be undertaken at the earliest wherever applicable. Though histopathology is not routinely performed in ED, it may be useful in certain cases like eosinophilic spongiosis in IP, absence of sweat glands in HED, fat herniation and dermal atrophy in FDH and supra-basal split in ED with skin fragility. Immunofluorescence may reveal the absence of collagen 4 expression in FDH and the absence of plakophilin 1 expression in ED with skin fragility. Relevant imaging studies must be performed depending on the systemic involvement.

Genetic studies and counselling

The ultimate aim of the classification of the various molecular pathways and implicated genes is to gradually shift towards a molecular diagnosis, which will help in newer targeted avenues of treatment. Molecular testing is available to identify the specific genes and their mutations in most of the disorders.

Single-gene testing may also be considered if physical findings are classic and family history is consistent with a specific pattern of inheritance. The initial step is sequence analysis of the implicated gene, followed by deletion/duplication analysis.

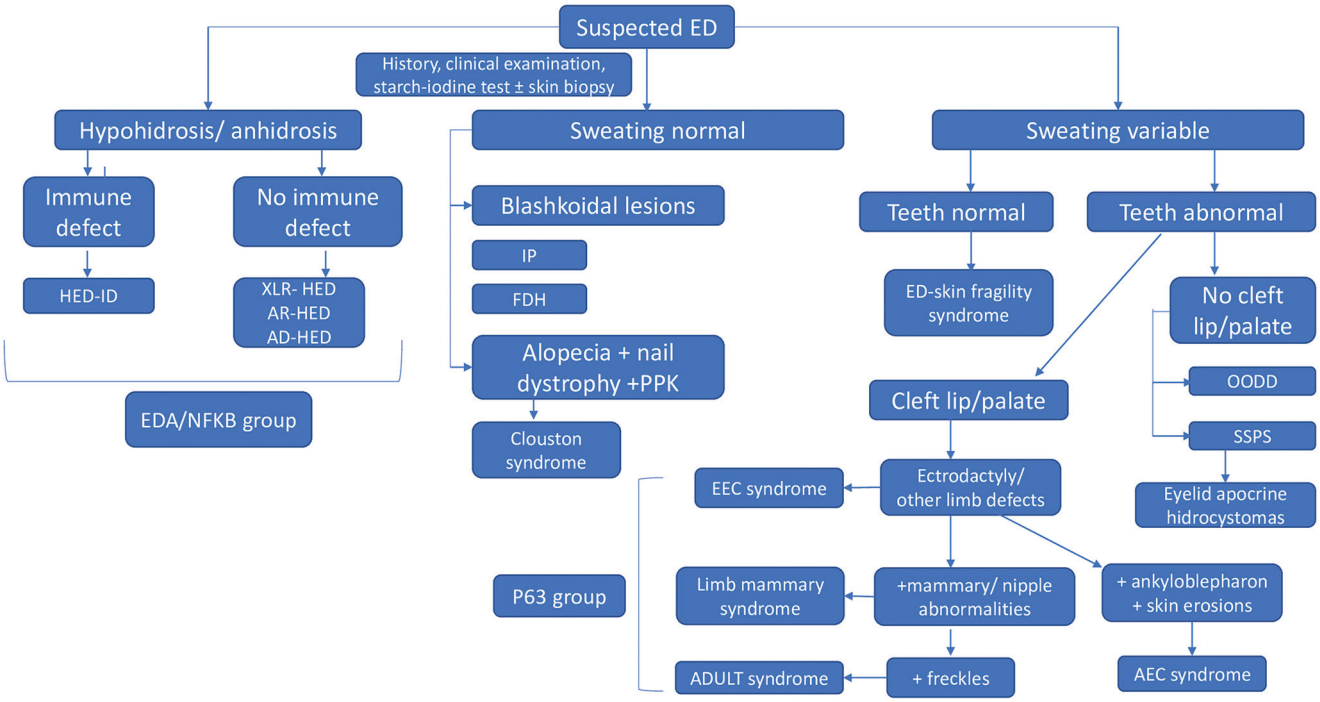

Figure 6: Schematic representation of approach to diagnosis of ectodermal dysplasias described in this article. *Abbreviations*: HED = hypohidrotic ectodermal dysplasia, XLR = X-linked recessive, AR = autosomal recessive, AD autosomal dominant, HED-ID = hypohidrotic ectodermal dysplasia with immunodeficiency, IP = incontinentia pigmenti, FDH = focal dermal hypoplasia, PPK = palmoplantar keratoderma, OODD = odonto-onycho-dermal dysplasia, SSPS = Schopf–Schulz–Passarge syndrome, EEC = ectrodactyly, ectodermal dysplasia and cleft lip/palate, AEC = Ankyloblepharon-ectodermal defects-cleft lip/palate, ADULT = acro–dermato–ungual–lacrimal–tooth

Prenatal genetic testing may also be considered via chorionic villus sampling or amniocentesis if there is a known familial pathogenic variant or suggestive features of an ED on ultrasound, such as missing tooth buds or characteristic limb anomalies.

Following a genetic diagnosis, counseling is key, including reproductive counseling and the probability of progeny being affected. For example, women affected with IP have a 50% chance of transmitting the mutated gene to their offspring. The expected ratio among liveborn children is approximately 33% unaffected females, 33% affected females, and 33% unaffected males.

Management

Once a definitive diagnosis is obtained, education of the patient and parents about the disorder, its complications, prognosis, and ultimately management of the disease becomes imperative. General guidelines for the management of ED have been enlisted in Table 2. A multidisciplinary approach forms the crux of management and ensuring quality of life. Regular follow-ups with dentists, orthodontists, ophthalmologists, ENT specialists, speech therapists, neurologists, geneticists, podiatrists, physiotherapists, orthopedic specialists, and nutritionists may be required. Nail and dental prostheses are often employed to ensure cosmesis and maintain functions and development of the oral cavity and face at an early age.

Table 2: General measures in management of ectodermal dysplasia

Regular moisturizing (bland emollients)
Avoiding overusing cleansers and soaps
Broad-spectrum sunscreens must be used
Ideally air-conditioned environment, if feasible
Wearing wet T-shirts, drinking extra fluids, having immediate access to a cool environment during sports or play-time
Swimming is a preferred sport
Avoiding damage to hair – protein-coated shampoos are preferable
Careful styling and cutting of hair and beard to improve appearance
Wigs may be preferred to improve cosmetic appearance
Keeping nails trimmed, filing with pumice stones
Adequate oral hygiene must be maintained; fluorinated toothpastes can be used
Saliva substitutes, saline nasal drops, humidification, and artificial tears help in dealing with symptoms like dryness of mouth, dry eyes, etc.
Regular monitoring of weight and height must be performed
Adequate nutrition and micronutrient supplementation must be done
*Adapted with permission from National Foundation for ectodermal dysplasias

Psychiatric support and family counseling may also be considered in individual cases. Support groups like the National Foundation for Ectodermal Dysplasias (NFED) may be employed by patients for a better understanding of the disorders.

Conclusion

ED is a rare group of genodermatoses with wide variability in clinical presentations and multisystem involvement. Careful assessment of all systemic features and involvement of the respective specialists is crucial to the management. The development of facilities for genetic analysis and prenatal diagnosis, especially at tertiary care centers, is important in order to undertake proper and timely genetic counseling and prevention of the development of the disease in further generations.

Consent

Written informed consent was taken from the parents of the patients prior to the publication

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Conflicts of interest

There are no conflicts of interest.

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