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REVIEW ARTICLE

Ectodermal dysplasias

Displasias ectodérmicas

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Abstract

Ectodermal dysplasias are a heterogeneous group of rare inherited disorders. Molecular findings and clarification of cell signaling processes and ectodermal-mesenchyme interaction enabled the development of a clinical-functional model, which in turn helps to explain clinical signs, with variability in severity, associated non-ectodermal abnormalities and overlap seen in many patients. We herein review the current state of knowledge regarding this distinct entity and illustrate with an elucidative case report. The need for early multidisciplinary intervention is highlighted, and further studies will focus on genetically-target therapeutic approaches.

Keywords: Ectodermal dysplasia. Genodermatosis. Genetic testing.

Resumo

As displasias ectodérmicas representam um grupo heterogéneo de doenças hereditárias raras. Os achados moleculares e o esclarecimento dos processos de sinalização celular e da interação ectoderme-mesênquima permitiram compreender os sinais clínicos. Estes caracterizam-se por gravidade variável, observando-se associação a anomalias não ectodérmicas e sobreposição clínica em muitos pacientes. No presente trabalho resumimos o estado atual do conhecimento sobre as displasias ectodérmicas e apresentamos ainda um relato de caso ilustrativo. Salientamos a necessidade de intervenção multidisciplinar precoce, sendo necessários estudos futuros com enfoque em abordagens terapêuticas geneticamente direcionadas.

Palavras-chave: Displasia ectodérmica. Genodermatose. Teste genético.

Introduction

The term ectodermal dysplasia (ED) designates a heterogeneous group of rare inherited disorders characterized by abnormal development of ectodermal tissues (hair, nails, sweat glands, and teeth). In addition, non-ectodermically derived structures may also be affected[1]. To date, approximately 200 conditions are described, and the causative mutation has been identified in some cases[2,3]. Clinical knowledge and the unravelling of molecular mechanisms has therefore led to the development of classification systems[4,5].

We herein review the current expertise on this topic, regarding etiology, evaluation and management options, highlighting the importance of multidisciplinary strategies for improved outcomes. We further illustrate with a clinical case.

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Historical perspective

EDs have long been recognized, with the earliest reports dating from 1792 by Danz[6], with subsequent descriptions made by Wedderburn in 1838, Thurnam in 1948[7] and Charles Darwin in 1875[8]. Later on, the term "hereditary ectodermal dysplasia" was introduced by Weech in 1929, who coined as "anhidrotic" those with inability to perspire[9]. In 1944, Felsher further changed the adjective to "hypohidrotic," as these individuals were not truly devoid of sweat glands[2]. Since then, several cases have been reported and disease comprehension originated classification schemes.

Etiology and epidemiology

The word ectoderm comes from the Greek ektos meaning "outside" and derma meaning "skin." Indeed, it represents the outermost primary germ layer, formed in early embryonic development, superficial to the mesoderm (the middle layer) and the endoderm (the innermost layer). At around the third week of development, it differentiates to form neural (neuroectoderm) and epithelial tissues (epidermis, epidermal appendages and tooth enamel). As such, the ectoderm originates not only the hair, teeth, nails and sweat glands, but also the central and peripheral nervous system, eyes, ears and nose, along with the eccrine, mammary and pituitary glands[10]. Moreover, the ectoderm interacts with the mesoderm during development, which explains that abnormalities in mesodermal structures (such as the musculoskeletal and genitourinary system) may feature EDs[5].

ED is thus defined by a congenital defect in at least two of the major ectodermically derived structures (hair, nails, sweat glands, and teeth), and represents single-gene disorders with a variable mode of inheritance[1,2,11]. They result from the mutation or deletion of certain genes located on different chromosomes, responsible for cell signaling processes involved in the induction and development of ectodermal structures and their interactions with the mesoderm. They are usually inherited, but *de novo* mutation is also possible[2,3].

EDs are considered rare conditions, with an estimated incidence of 7:10000 births[12]. Approximately 200 conditions are known. The commonest variant is hypohydrotic ED, which is frequently X-linked with full-blown expression seen only in males[1,2,11].

Genetic pathogenesis[2,3,5]

Biomolecular investigation has enabled the identification of causative mutations, that can be categorized under two broad pathogenic mechanisms (see classification section below)[5]:

Defective interaction between the ectoderm and the mesenchyme

Changes in the signaling pathways that modulate activity of nuclear factor kappa-light-chain-enhancer of activated B cell (NFκB).

EDA/EDAR/EDARADD pathway

The EDA, EDAR and EDARADD genes provide instructions for making proteins that work together during embryonic development. Mutations in these genes result in defective ectodysplasin (EDA) formation, which is critical for the interaction between the ectoderm and the mesoderm. In sum, EDA protein binds to an EDA receptor (EDAR) in the cell membrane. EDAR has an extracellular region, a transmembrane region, and a death domain in its intracellular region. A death domain is a protein interaction module that interacts with the death domains of other proteins and triggers metabolic cascades that are often implicated in regulating apoptosis and inflammation through the NFκB cascade. EDAR death domain binds to the death domain of EDAR-associated death domain (EDARADD)[13].

Finally, certain mutations in the WNT10A gene, whose product is a member of the Wnt signaling pathway (implicated in embryonic development and cell differentiation), have also been implicated in certain forms of ED.

Mutations in only 4 genes (EDA1, EDAR, EDARADD and WNT10A) are responsible for most cases of ED, through improper formation of ectodermal structures, leading to the characteristic features of hypohidrotic ED (Table 1)[14].

NFκB signaling pathway

NFκB is a transcription factor that regulates the expression of multiple genes implicated in immune and inflammatory responses, reaction to stress, cell adhesion, and protection against apoptosis[15]. In most cells, NFκB is kept in an inactive state through cytoplasmic sequestering by the NFκB inhibitory protein (IkB). Several stimuli lead to activation of the cell membrane receptors of the TNF family (such as EDAR). Activation of these receptors leads to degradation of IkB, allowing NFκB translocation to the nucleus and

Table 1. Classic ectodermal dysplasias.

	Hypohidrotic ED	Hypohidrotic ED-immune deficiency	Hidrotic ED	Witkop tooth and nail syndrome
Inheritance (associated gene)	XL (EDA); AD, AR (EDAR > EDARADD)	XL recessive (IKBKG/ NEMO); AD (NFKBIA)	AD (GJB6)	AD (MSX1)
Protein product	Ectodysplasin A; EDAR; EDARADD	NF-κB essential modulator; NF-κB inhibitor- α	Connexin 30	Muscle segment homeobox 1
Scalp hair	Sparse to absent; often lightly pigmented in children	Sparse	Wiry, brittle; patchy alopecia; often lightly pigmented	Normal to thin
Teeth	Hypodontia, conical	Hypodontia, conical	Normal	Hypo- or anodontia of secondary teeth; primary teeth regular or small/ peg-shaped
Sweating	Markedly decreased	Mildly decreased	Normal	Normal
Nails	Normal	Normal	White and small during infancy; thickened, distal separation	Koilonychia improves with age; toenails are worse than fingernails
Other	Characteristic facies; neonates may have collodion-like membrane; eczema common; thick nasal secretions and cerumen; frequent respiratory tract infections	Intertrigo, seborrheic-like dermatitis, erythroderma; colitis; recurrent infections (pyogenic or opportunistic); ↑ IgM and IgA, ↑ IgG; rare osteopetrosis and lymphedema, arthritis, and/or (esp. in AD form) autoimmune cytopenias and endocrinopathy	Stippled palmoplantar keratoderma; the grid-like array of tiny acral papules; blepharitis, conjunctivitis	Prolonged retention of primary teeth

AD: autosomal dominant; AR: autosomal recessive; ED: ectodermal dysplasia; EDAR: ectodysplasin A receptor; EDARADD: EDAR-associated death domain; GJB6: gap junction β6; IKBKG: inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ; XL: X-linked. Adapted from H. Itin et al.[1].

culminating in inflammatory and immune responses with development of T and B cells, and induction of osteoclast function and growth of epidermal cells[16]. NFκB essential modulator (NEMO) is a subunit of IkB, that if absent impairs NFκB response to stimuli[17]. Mutations in 2 genes, NEMO and IkB (subunits of IkB) have been shown to give rise to a heterogeneous group of genetic disorders that include some forms of ED (X-linked hypohidrotic ED (HED) with immune deficiency; autosomal dominant HED with immunodeficiency; and osteopetrosis, lymphedema and HED with immunodeficiency) (Table 1)[18].

Regulatory changes in transcription and/or expression of genes such as p63

The p63 our TP63 (tumor protein 63) gene encodes the transcription factor protein p63, which is expressed very early during embryogenesis and plays an essential role in inducing epidermal differentiation and proliferation. As such, lack of expression during the early development of ectodermal tissues might block interactions between the epithelium and the mesenchyme, thereby impairing normal morphogenesis[19]. In addition, p63 regulates the expression of P-cadherin, a critical regulator of hair development[20].

The regions of greatest biological importance are the DNA binding domain, the sterile alpha motif (SAM) and the transactivation inhibition domain (TID)[19]. Heterozygous mutations in the p63 gene are responsible for at least 6 different syndromes that combine ED, orofacial clefts, and limb malformations, with a strong genotype-phenotype correlation that is dependent on the location of the p63 mutation (Table 12)[21]. Ankyloblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome will be further presented in this review (see Clinical Manifestations section).

Abnormal function of a structural protein in the cell membrane

Examples of structural proteins include nectin 1, connexins and plakophilin, whose role in adhesion and cell-cell communication is essential for tissue

homeostasis and cell growth, development and response to stimuli. Clinically, these disorders feature skin abnormalities (such as palmoplantar keratoderma), with or without involvement of highly differentiated epithelia associated with deafness or retinal dystrophy. Hidrotic ED is caused by mutations in connexin 20, and it is characterized by hair loss, nail dystrophy, and palmoplantar keratoderma (Table 1)[22].

Finally, it should be mentioned that some inherited abnormalities limited to one ectodermal structure have a genetic basis related to that of EDs (e.g., hypodontia due to heterozygous WNT10A mutations versus ED syndromes due to biallelic mutations in the same gene), that should nonetheless not be confused with a true ED.

Classification

There have been many classification schemes proposed over the years. The initial descriptive clinical categorization by Pinheiro and Freire-Maia[4] distinguished four primary ED defects:

- ED1: Tri hodysplasia (hair dysplasia)
- ED2: Dental dysplasia
- ED3: Onychodysplasia (nail dysplasia)
- ED4: Dyshidrosis (sweat gland dysplasia)

The ED were then further categorized into eleven subgroups according to the primary defects:

- Subgroup 1-2-3-4
- Subgroup 1-2-3
- Subgroup 1-2-4
- Subgroup 1-2
- Subgroup 1-3
- Subgroup 1-4
- Subgroup 2-3-4
- Subgroup 2-3
- Subgroup 2-4
- Subgroup 3
- Subgroup 4

The complex classification of ED has later evolved in an attempt to integrate clinical and genetic data. In 2009, Priolo[5] established a clinical-functional model, based on the understanding of the processes of cell signaling involved in the induction and development of ectodermal structures as well as their interactions with mesodermal structures. As such, two groups have been defined:

- Group 1: defective epithelial-mesenchymal interaction with a resulting phenotype of hypoplasia or aplasia of structures derived from the ectoderm —considered "pure EDs" without other dermatologic signs nor skeletal anomalities).
- Group 2: altered cell-cell adhesion and communication–regarded as "dermatologic EDs" (featuring skin abnormalities such as palmoplantar keratoderma), with possible involvement of other ectodermal structures or highly differentiated epithelia (e.g., associated with deafness or retinal dystrophy). In this regard, some of the conditions that might be included in this group have not been traditionally thought of as EDs because their recognition and diagnosis are based upon another primary manifestation (keratoderma, ichthyosis, aplasia cutis congenital, or skeletal dysplasia). Indeed, defects in ectodermal appendages should be the major clinical features used to classify and diagnose EDs[1].

In sum, EDs are nowadays distinguished based on the types of ectodermal abnormalities, associated non-ectodermal anomalies, and mode of inheritance, as well as the underlying genetic defect.

Clinical manifestations

ED develops during the first trimester of pregnancy. If severe, they occur before the 6th week of embryonic life, consequently disturbing the normal dentition. After the 8th week, the other ectodermal structures will be affected[2]. Molecular interactions among proteins mutated in EDs and altered common functional pathways will explain many clinical signs, severity variability, associated malformations, and overlap seen in some ED patients. The detailed description of the different types of ED is not under the scope of this paper and has been extensively reviewed elsewhere[1-3]. We will in turn present some key clinical and genetic features of selected classic EDs, which have a known molecular basis and/or prominent cutaneous manifestations (Tables 1 and 2)[1-3].

- Hypohidrotic Ectodermal Dysplasia (HED) (synonyms: Anhidrotic ED, Christ-Siemens-Touraine syndrome)
  HED describes a group of disorders that present with sparse or absent hair, missing or peg-shaped teeth, and decreased ability to sweat. The most common form is X-linked, which also represents the most frequent ED in general, with an incidence of 1 case per 10,0000 births. HED is caused by mutations in the ectodysplasin signal transduction pathway, namely the EDA, with no apparent genotype-phenotype relationship, and great variety among different families and within the same family

Table 2. p63-related ectodermal dysplasia syndromes

Variables	AEC	EEC	Limb–mammary	Adult
Inheritance	AD	AD	AD	AD
Typical TP63 mutations	Missense in SAM domain	Missense in DNA-binding domain	Truncating in C-terminal region	Missense in hotspot at end of DNA-binding domain
Scalp hair	Lightly pigmented, wiry; sparse with patchy alopecia	Lightly pigmented, coarse; may be sparse	Normal	Lightly pigmented, sparse; frontal alopecia
Teeth	Hypodontia, misshapen (e.g., conical) teeth	Hypodontia, enamel hypoplasia	Hypodontia	Hypodontia, small teeth
Sweating	Hypohidrosis in some patients	Usually normal	Hypohidrosis in some patients	Usually normal
Nails	Hyperconvex, thickened or absent	Transverse ridges, pitting	Variable dystrophy	Ridges, pitting
Cleft lip/palate	Almost 100%; palate ± lip	~50%; usually lip + palate	~30%; palate only	None
Digital anomalies	Syndactyly in some patients; rarely ectrodactyly	Ectrodactyly > syndactyly	Ectrodactyly > syndactyly	Ectrodactyly, syndactyly
Skin findings	Neonatal erythroderma; erosive dermatitis, esp. of scalp; flexural reticulated hyperpigmentation	Xerosis, palmoplantar keratoderma	None	Xerosis, photosensitivity, freckling
Other	Ankyloblepharon; lacrimal duct defects; ectopic breast tissue; hypospadias; GER	Lacrimal duct defects; keratopathy, corneal scarring; GU anomalies	Lacrimal duct defects, hypoplastic nipples/ breasts; GU anomalies	Lacrimal duct defects; hypoplastic nipples/breasts

ADULT: acro-dermato-ungual-lacrimal-tooth; AEC: ankyloblepharon-ectodermal defects-cleft lip/palate; EEC: ectrodactyly-ectodermal dysplasia-clefting; GER: gastroesophageal reflux; GU: genitourinary; SAM: sterile alpha motif. Adapted from H. Itin et al.[1]

group. Altered morphogenesis affecting epithelial cells in the developing tooth, hair follicle, and eccrine gland results in aplasia, hypoplasia, or dysplasia of these structures[1-3].

The scalp hair is sparse or absent with light-brown pigmentation. Affected infants have a loss of the skin's thermoregulatory function, clinically present with pyrexia of unknown origin and hyperthermia as early as the first few hours of life, with increased mortality. Furthermore, the skin appears smooth, soft, dry, and thin due to absent eccrine pores with disturbed dermatoglyphes. Atopic dermatitis is a common comorbidity. There might be a characteristic facial dysmorphism, with periorbital wrinkling, sebaceous hyperplasia of the face, saddle nose, fully-everted lips, and prominent frontal bossing. Teeth are reduced in number and usually peg-shaped. Dental caries and loss of dentition can lead to difficulty in feeding. Nails remain unaffected in HED. Other manifestations include recurrent respiratory tract infections (viscous secretions), hoarseness of voice, gastroesophageal reflux, and unilateral or bilateral breast aplasia/hypoplasia[1-3].

The abovementioned features are mainly observed in males, with females ranging from a carrier state to a limited blaschkoid distribution or even a full-blown disease, depending of X-inactivation. In addition, a subset of patients presents with immunodeficiency in the form of hypogammaglobulinemia and autoimmune cytopenias, with identified mutations in the NEMO gene[1-3].

– Hydrotic Ectodermal Dysplasia (synonym: Clouston syndrome)

It is an autosomal dominant condition that is caused by missense mutations in the GJB6 gene, which encodes the connexin 30 protein. The 3 main clinical characteristics are hair loss, nail dystrophy, and palmoplantar keratoderma, with sparing of teeth and eccrine glands. Hair and nail changes manifest in early infancy and progress over time. Namely, atrichia or hypotrichosis with wiry, brittle and pale hair, and frequently patchy alopecia. In addition, sparse eyelashes predispose to recurrent episodes of conjunctivitis and blepharitis. Nails are milky-white, with gradual thickening throughout childhood. Palmo-plantar keratoderma with a cobblestone-like

pattern on the dorsal aspect resulting from the coalescence of eccrine acrosyringia has been reported in several patients, as oral leukoplakia. Facial dysmorphism is not present and general physical development is normal[1-3].

– Ankyloblepharon-Ectodermal Defects-Cleft Lip/Palate (AEC) Syndrome (synonyms: Hay-Wells syndrome, RappHodgkin syndrome)

Heterozygous mutations in the p63 gene are responsible for at least 6 different syndromes that combine ED, orofacial clefts, and limb malformations[21]. AEC syndrome has an autosomal dominant transmission pattern of non-sense mutations in the SAM domain of protein p63, with approximately 100 patients reported to date[23]. Ankyloblepharon, ectodermal defects, and cleft lip/palate make the characteristic clinical triad[1-3].

This disorder is evident at birth. Up to 90% of affected infants show a classic erythrodermic presentation with peeling skin or erosions, which can result in life-threatening infectious complications. The scalp is almost always involved in the form of chronic oozing erosive dermatitis, patchy alopecia, and wiry hair. Some degree of nail dystrophy is typically evident, with hyperconvex and thickened nail plates or anonychia. Sweating may be decreased with heat intolerance. Additional features that differentiate this syndrome include hyper granulation tissue formation, recurrent skin infections, cribriform and stellate scarring of the shoulders and upper trunk, and reticulated pigmentation of the intertriginous areas. Dental abnormalities include hypodontia and misshapen teeth[1-3].

Congenital strands of tissue are observed between the eyelids (ankyloblepharon) in approximately three-quarters of affected individuals, which may lyse spontaneously, even prior to birth, or require surgical correction. Lacrimal duct atresia may occur. Almost all patients with AEC syndrome present with a cleft palate with or without a cleft lip[1-3].

External ear malformation may be observed, leading to recurrent otitis media with secondary conductive hearing loss. In addition, gastroesophageal reflux develops in the majority of AEC patients, and in some cases results in failure to thrive and requirement of gastrostomy placement. Finally, hypospadias, supernumerary nipples, and limb abnormalities are other associated traits[1-3].

Regarding differential diagnosis, neonatal erythroderma is typically confused with bullous congenital ichthyosis. The absence of ankyloblepharon can occur in Rapp Hodkgin syndrome, which is now considered part of the AEC spectrum[11].

Evaluation

Diagnosis is first based on the typical phenotypic characteristics of ED, with special emphasis on the presence/absence of sweating, hair/nail, and teeth abnormalities. Further identification of specific syndrome/subtype requires a series of investigations. For example[1-3]:

– Atrichogram will show barcode hair in HED, which will be absent in the hydrotic variant.
– Laboratory work-up with the determination of quantitative immunoglobulin levels and B and T lymphocyte subset populations will be altered in HED associated with primary immunodeficiency.
– Sweat pore counts and pilocarpine iontophoresis may document hypohidrosis and a reduction in the number of eccrine glands.
– Even though usually unnecessary, a skin biopsy shows the absence of eccrine structures in HED or eccrine syringofibroadenomatosis in hydrotic ED.
– Other studies, such as X-rays of the limbs, may aid in diagnosing variants of ED.
– Molecular genetic testing (sequence analysis) allows for disease identification and establishment of risk of transmission.

Treatment/management

As patients with ED are usually children, parent education is of paramount importance, including day-to-day routine management in order to prevent complications. In addition, children and adults with ED must be evaluated individually by multidisciplinary teams, in order to treat multiorgan manifestations.

In general terms, it consists of temperature maintenance and management of congenital defects. For instance, older children should be instructed on physical cooling measures such as frequent drinking of cold liquids and special cooling vests for heat-generating activities. Regular use of moisturizers is useful for xerosis and collodion-like presentation. Treatment of chronic erosive scalp dermatitis (AEC syndrome) can be challenging, and the condition is deemed debilitating and refractory. A stepwise approach must be considered, with bland emollients and prevention of secondary infections. However, classic wound regimens typically fail, and even though topical and systemic antibiotics

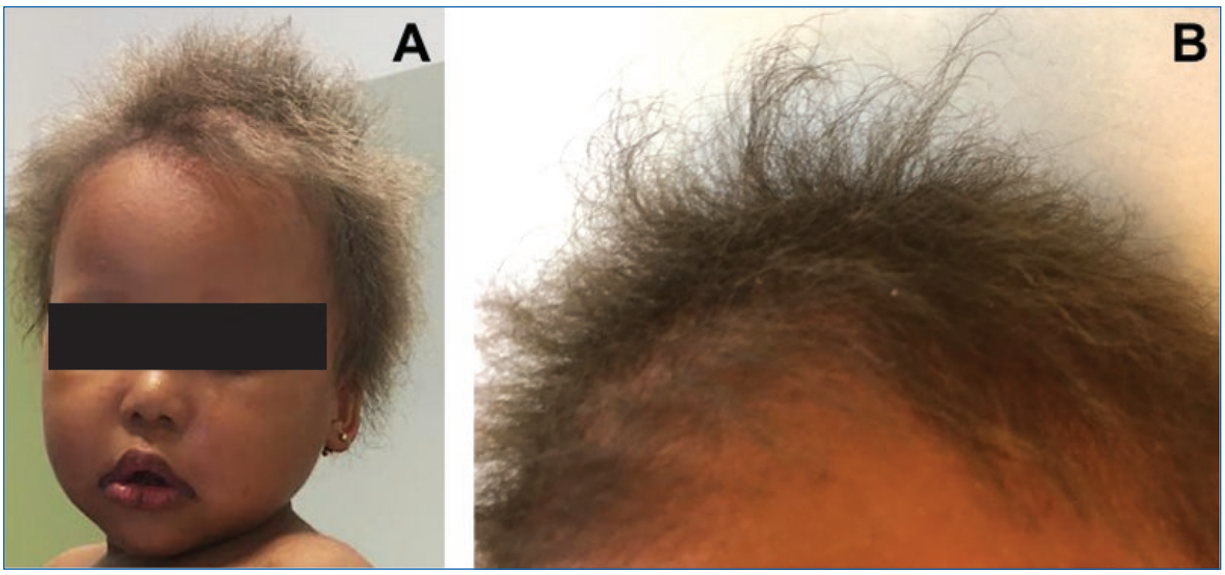

Figure 1. Hypotrichosis with thin rough hair, madarosis, and milphosis.

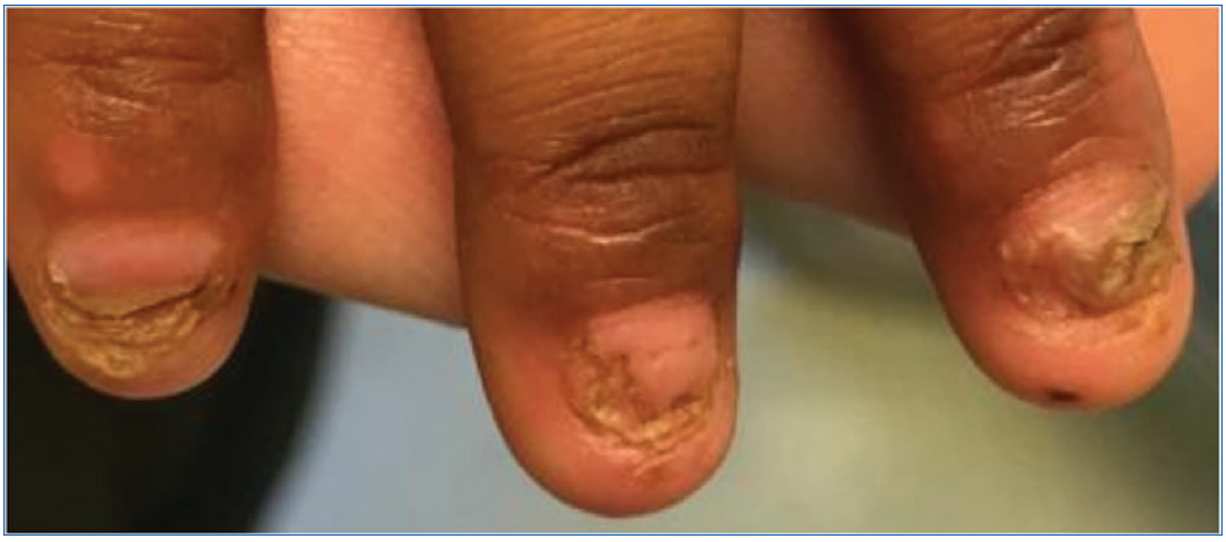

Figure 2. Micronychia.

are often used, they are usually of little benefit except in cases of overt infection[1,2,11]. Improvement with high-potency topical steroids has been advocated in case reports[24], and therefore can be considered in resistant cases.

Early and ongoing dental treatment is essential for the functional and cosmetic outcomes of the teeth. Limb defects, ocular, and other abnormalities require expert reference at the earliest suspicion. Finally, the psychological impact as a consequence of esthetics and abnormal function of orofacial structures should not be overlooked. Referral to the National Foundation of Ectodermal Dysplasias could also prove valuable[1,2,11].

Gene therapy using recombinant gene administration has been evaluated experimentally in animal studies and needs future investigation[25].

Author's experience

A 2-year-old girl presented with alopecia and dystrophic hair and nails. She was otherwise healthy, with an unremarkable familiar history. On examination, there was hypotrichosis with thin rough hair, madarosis and milphosis (Figure 1), micronychia (Figure 2), and heterogeneous skin pigmentation with hyperpigmented areas (Figure 3). There was also apparent hypodontia (Figure 3). A complementary

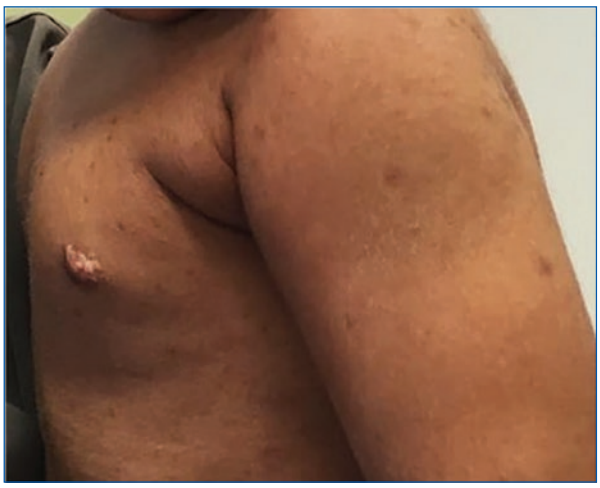

Figure 3. Heterogeneous skin pigmentation with hyperpigmented areas.

investigation revealed a normal blood workup, and primary immunodeficiency was ruled out. An ED was suspected, and genetic testing through next-generation sequencing multigene panel analysis was carried out (Agilent SureSelect Human All Exon® kit and Illumina platform®. Bioinformatics multigene panel analysis comprehending the following genes ATP6V1B2, CDH3, EDA, EDAR, EDARADD, EVC, EVC2, GJB6, HOXC13, IFT122, IFT43, IKBKG, KDF1, KREMEN1, KRT14, KRT74, KRT85, MBTPS2, MSX1, NECTIN1, NECTIN4, NFKBIA, NLRP1, PKP1, SMARCAD1, TP63, TWIST2, WDR19, WDR35, WNT10A). An heterozygous variant c.1963del (p.(Arg655Glufs*49) in exon 14 of TP63 [NM_003722.4] gene was detected. This is a null variant (frameshift), and loss-of-function is a known mechanism of disease in the TP63 gene. This variant is also absent from controls and was previously reported by Rinne et al.[26] in a patient with ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC). These findings are consistent with the AEC syndrome diagnosis, and the patient was managed in accordance, with the pediatrician, odontostomatologist, and dermatologist follow-up.

AEC Syndrome is particularly rare, with about 100 patients reported to date[23]. The most common features, namely skin erosions, orofacial cleft, and ankyloblepharon were missing in our patient, underlining the great interindividual variability. In addition, the latter is missing in Rapp Hodkgin syndrome, regarded as part of the AEC spectrum. These particularities highlight the importance of combined clinical suspicion and genetic analysis.

Concluding remarks

EDs form a diverse group of inherited disorders with variable complications. Molecular findings have helped to elucidate physiopathology and categorize such a heterogenous class, explaining its clinical signs, variability in severity, associated malformations and overlap seen in some ED patients. Equally, such comprehension will lead to future genetically targeted therapeutic approaches. Meanwhile, treatment is symptom-directed, and a multidisciplinary approach is therefore crucial. When achieved, the general prognosis is good with a normal life expectancy, underlining the relevance of an early and careful clinical evaluation.

Ethical responsibilities

Protection of people and animals. The authors declare that for this research no experiments on humans and/or animals were performed.

Confidentiality of data. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and written consent. The authors declare that they have received written consent from the patients and/or subjects mentioned in the article. The author of the correspondence must be in possession of this document.

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