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Review article

Ear nose throat manifestations in hypoidrotic ectodermal dysplasia

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ABSTRACT

The ectodermal dysplasias (EDs) are a large and complex group of inherited disorders. In various combinations, they all share anomalies in ectodermal derived structures: hair, teeth, nails and sweat gland function. Clinical overlap is present among EDs. Few causative genes have been identified, to date. Altered gene expression is not limited to the ectoderm but a concomitant effect on developing mesenchymal structures, with modification of ectodermal–mesenchymal signaling, takes place. The two major categories of ED include the hidrotic and hypohidrotic form, the latter more frequent; they differentiate each other for the presence or absence of sweat glands.

We report Ear Nose Throat manifestations of ED, linked to the reduction of mucous glands in the nasal fossae with reduced ciliar function, and decrease salivary glands function.

Often patients report an increased rate of infections of the upper respiratory tract and of the ear. Nasal obstruction due to the presence of nasal crusting, hearing loss and throat hoarseness are the most represented symptoms.

Environmental measures, including a correct air temperature and humidification, is mandatory above all in subjects affected by hypohidrotic form.

Contents

1. Introduction

Ectodermal dysplasias (EDs) refer to a rare group of heritable disorders affecting ectodermal derived tissues. The skin and at least two of the appendages (teeth nails, hair and sweat glands) are involved [1–3].

More than 100 different forms of ED have been described, in many cases subjects present dysplasia also of mesodermal derivates [3]. The reported incidence is of 1 on 100,000 live births [4,5].

The two major categories of ED are the hidrotic (Clouston syndrome) and, the most frequent, hypohidrotic (Christ–Siemens–Touraine syndrome) form. They mainly differentiate by the presence or absence of eccrine sweat glands; although, they have

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a different mode of inheritance and may present different associated anomalies [6].

The hidrotic form (MIM 129500) is characterized by autosomal dominant inheritance and is caused by mutations in connexin 30 (MIM 604418). Affected patients present normal sweating, normal or conical shape teeth, nail dystrophy (onychodysplasia), alopecia or hypotrichosis (scanty, fine hair on the scalp and eyebrows) that is, in some cases, associated with sensorineural hearing loss [3].

The hypohidrotic anhidrotic form of ectodermal dysplasia has been attributed to at least 3 genes (EDA1 [ectodysplasin]; EDAR [the EDA-A1 isoform receptor]; and EDARADD [EDAR-associated death domain]). With three corresponding modes of inheritance: X-linked recessive (OMIM 305100), autosomal dominant (OMIM 129490), and autosomal recessive (OMIM 224900). Recently, WNT10A gene was identified as responsible for various autosomal recessive forms of ectodermal dysplasia [3].

The most frequent form is inherited as X-linked recessive trait. Males are usually more severely affected, while carrier females show a variable severity from mild to severe presentation because of X-chromosome inactivation. Recently, EDA1, EDAR, EDARADD, and WNT10A genes have been studied in a large cohort of 65 unrelated patients. These four genes accounted for 92% (56/61 patients) of HED/EDA cases: (1) the EDA1 gene was the most common disease-causing gene (58% of cases), (2) WNT10A and EDAR were each responsible for 16% of cases. Although no clinical differences between patients carrying EDA1, EDAR, or EDARADD mutations could be identified, patients harboring WNT10A mutations displayed distinctive clinical features (marked dental phenotype, no facial dysmorphism) helping to decide which gene should be first investigated in HED/EDA [3]. The affected always present a triad of clinical signs: deficient sweating (hypohidrosis), partial or complete absence of the primary and/or permanent dentition with conical shaped crowns and sometimes microdontia and sparse hair [7,8]. Other physical findings include saddle-shaped nose or depressed nasal bridge, thick and protruding lips, sparse or absent eyebrows, dry skin with eczematous changes and periorbital pigmentation [9].

Since abnormalities are present at birth, the diagnosis of the majority of ED cases is possible within the first year of life with the identification of recurrent episodes of unexplained hyperthermia, dry and scaly skin, delayed teething, ceruminal clots and recurrent airway infections, and other characteristics (thin, lightly pigmented scalp hair, and decreased sweating); the syndrome is usually non-progressive and life expectancy is similar to general population [10].

Recently, a syndromic X-linked ectodermal dysplasia syndrome with immunodeficiency has been reported [11] in patients with hypomorphic mutations in IKBKG (inhibitory B kinase gene), which encodes NEMO (nuclear factor B [NF-B] essential modulator) protein, the regulatory subunit of the IKK (I B kinase) complex. Mutations in the IKBKG gene NEMO can cause an heterogeneous group of disorders, including Incontinentia Pigmenti and Hypohidrotic Ectodermal Dysplasia with immunodeficiency associated withosteopetrosis and lymphoedema.

Among recent clinical works on ED, few of them focused on upper respiratory and ENT manifestations, although a prevalence of 75% is reported [12–15].

2. Report

2.1. Nose

People with ED often have pathognomonic cranial–facial features, often distinctive, including frontal bossing, longer or more pronounced chins and broader nose with depressed nasal bridge [4].

The presence of abnormal cilia and hypo/aplasic serous mucous glands lining the aero-digestive tract is the causal factor for the problems involving the sinonasal tract and Eustachian tube. The most represented finding is an impressive dryness of the mucosa, often causing persistent nasal crusting often with rhinoliths, often increasing with age. Nasal fossae appears wider than in normal subjects and present a feature sometimes resembling ozena. The presences of wider nasal fossae often provoke complaints of nasal obstruction, since a higher difference of pressure is required for nasal flow. As a consequence of it, epistaxis is a common disorder in these subjects. The abnormal mucociliary clearance of the epithelium explains the pooling of secretions in the nasal cavities. Among total ED subjects, nasal dryness and crusting with obstruction have been reported in around 80% of patients [16–18] (Fig. 1).

It is under debate whether patients with ED have a normal olfaction, since subjects with other genetic disorders leading to a perturbation in the function of ciliary microtubules, responsible for the intracellular transport of proteins, present olfactory disorders [19].

Allergic rhinitis, reported in 44% of cases, often worsen nasal symptoms and predispose to sinonasal infections; chronic sinus infections are more common than acute rhinosinusitis with purulence, although 26% of patients requires more than three courses of antibiotics per year for recurrent sinus infections and 18% of subjects need sinonasal surgery [16].

In order to reduce the nasal symptoms and infections, it is necessary to humidify the environment where patients normally live and to periodically and gently remove nasal crusting. Nasal saline solutions and nasal douches with sodium bicarbonate have demonstrated to be helpful for the purpose, as well as topic therapy with vaseline-based ointments while local gentamycin in the treatment of nasal bad smell has been proposed. On the contrary, antibiotics should be proposed when an acute infection occurs [9]. Recently, a case of an ED patient with an history of recurrent sinonasal infections due to a nasal myasis has been reported [20]. In some cases, reduction of the nasal cavity volume by submucosal implantation of allogenic rib cartilage was suggested [21] while in order to improve quality of life, some authors proposed a surgical management of saddle nose deformity; in both cases surgeon has to keep in mind that these patients have a tendency toward respiratory tract infections [22].

In some forms of ED, an association with tumors such as non-Hodgkins lymphoma, hamartoma, keratoakanthoma, Merkel-cell cancer, squamous-cell carcinoma has been described, although it

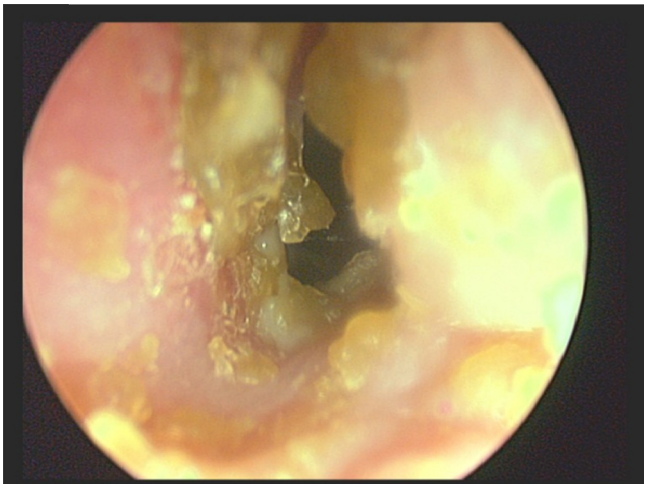

Fig. 1. Left nasal fossa showing wide crusting of mucosa resembling ozena.