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## Ophthalmic Manifestations in Patients with Ectodermal Dysplasia Syndromes

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### Abstract

**Background.** Ectodermal dysplasia (ED) is a disorder that results from abnormal formation of at least two of the four major ectodermal derivatives in the developing embryo. The ectoderm of the embryo forms the skin, teeth, hair and nails, sweat glands and part of the eyes.

**Objectives.** The aim of this article is to reveal ophthalmologic symptoms and signs as multidisciplinary, reliable criteria for ectodermal dysplasia.

**Material and Methods.** In this retrospective study, 24 patients with ED were analyzed from the recorded data. Ophthalmological examination of the patients, who had previously received the diagnosis of ED in the dental department, was done. During the examination, ocular symptoms related to tear film, corneal changes, lacrimal duct, periorbital hyperpigmentation, alteration lashes and eyebrows were evaluated.

**Results.** The age ranged between 3–45, and the mean and standard deviation (Mean  $\pm$  SD) was  $15.8 \pm 7.4$  years. The number of males was 13 (54.2%) and females, 11 (45.8%). Eighteen patients (75.0%) suffered from ocular complaints related to the ocular surface. In 11 of the patients with ED, there were dry eye symptoms. While the mean age of cases with eye involvement was 17.5, it was 23.1 in cases with dry eye symptoms.

**Conclusions.** In the study, it was observed that, in patients with ED, ocular complaints, particularly dry eye symptoms, may increase as age advances (*Adv Clin Exp Med* 2014, 23, 4, 605–610).

**Key words:** dry eye, ectodermal dysplasia, ocular involvement.

Ectodermal dysplasia (ED) is a disorder that results from abnormal formation of no less than two of the four major ectodermal derivatives in the developing embryo. The ectoderm of the embryo forms the skin, teeth, hair and nails, sweat glands and part of the eyes [1]. As it has earlier been reported, the first recorded ED cases seem to have been described in 1792 [2]. However, over 200 differing pathologic clinical conditions have been determined and defined ever since; these conditions are relatively rare, as being between 1 in 10,000 and 1 in 100,000 births [3–5]. Hypohidrotic ectodermal dysplasia (HED), ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome ankyloblepharon-

ectodermal dysplasia-clefting (AEC) syndrome and hidrotic ectodermal dysplasia are the most frequently encountered syndromes [6].

In general, the clinical findings detected in patients with HED are as follows: hypotrichosis, hypohidrosis and cranial abnormalities. These patients' faces are smaller with respect to normal individuals because of frontal bossing, a depressed nasal bridge, absence of sweat glands resulting in smooth, dry skin and/or hyperkeratosis of hands and feet, as well as immunodeficiency. Oral characteristics may present with anodontia, hypodontia and conical teeth [7, 8]. Ocular anomalies are less frequently observed. Eye problems are known

to occur in ED, but how common and the specific ways the eyes are involved is not fully understood. Eye problems do seem to differ between the different types of ED and may vary in severity. As already discussed, the structures of the eye formed from the ectoderm are affected by ED. The function and comfort of the eye is therefore disturbed. Alterations of the eyebrows and lashes are mentioned in combination with several ectodermal dysplasia syndromes [6, 9]. Most recently, Callea et al. [10] have reported infantile bilateral glaucoma in a child with ectodermal dysplasia.

EEC syndrome is a rare autosomal-dominant disease which has a penetrance of 95% and variable expression within one family. It has been mapped to the gene locus 7q11.2-q21.3 [11, 12]. The syndrome is characterized by a clefting deformity of the hands and/or feet (ectrodactyly-lobster claw deformity), ectodermal dysplasia, and cleft lip and palate [13]. The etiology of ocular surface disease in EEC syndrome still remains unclear. The reported ophthalmologic manifestations are strabismus, telecanthus, fused lids at birth, blepharophimosis, entropion, absence of eyelashes, bilateral eyelid cysts, agenesis of lacrimal puncta, dacryocystitis, blepharitis, conjunctivitis, deficient meibomian gland function, and corneal limbal deficiency [13]. Disorders of the tear film and deformities of the meibomian glands are described for the EEC syndrome. Anomalies of the lacrimal system are seen in patients with EEC syndrome. Meibomian gland deformities have so far only been described in patients with EEC syndrome. There is evidence that, on the basis of the similar pathology, other ectodermal dysplasias should also be combined [6, 14, 15].

The aim of this study is to establish easily detectable ophthalmologic symptoms and signs as reliable criteria for ectodermal dysplasia syndromes.

## Material and Methods

In this retrospective study, 24 patients with ED, evaluated between January 1997 and January 2012 at the Department of Ophthalmology Clinic, were analyzed from the recorded data. The diagnosis of the patients had previously been made in the dental department. For ophthalmologic evaluation, however, the patients were referred to our clinic. During the examination, ocular symptoms related to tear film, corneal changes, lacrimal duct, periorbital hyperpigmentation, alteration lashes and eyebrows were evaluated.

The photographs of those patients who had agreed that images of the face, teeth, hands and eyelids could be included into the study were documented.

The study was performed according to the guidelines of the Declaration of Helsinki.

## Statistical Analysis

Mean and standard deviation ( $\bar{x} \pm SD$ ) were calculated for continuous variables. All categorical variables were presented as number of patients and percentages. Statistical evaluations were analyzed through use of the statistical package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

In the whole series of 24 patients with ED, the age ranged between 3–45, and the mean and standard deviation (Mean  $\pm$  SD) was  $15.8 \pm 7.4$  years. The number of males was 13 (54.2%) and females, 11 (45.8%). The mean age of the cases with ocular complaints was 17.5, while it was 23.1 in those who had dry eye symptoms.

Twenty-two patients included in this study were suffering from HED. There were 2 patients with EEC syndrome. All of the cases had dental aspects of different degrees, conically shaped teeth, and dental agenesis presenting maxillary retrusion, maxillary hypotrophy and forward-upward-displaced-protused mandible (Fig. 1).

Eighteen patients (75.0%) were suffering from ocular complaints related to the ocular surface. They reported irritation, tearing, epiphora, photophobia, redness and recurrent inflammations of the lids. The ocular findings of the patients are shown in Table 1. Periorbital hyperpigmentation and eyebrow anomalies were detected in 88.9% of cases, and lashes anomalies in 83.3% (Fig. 2).

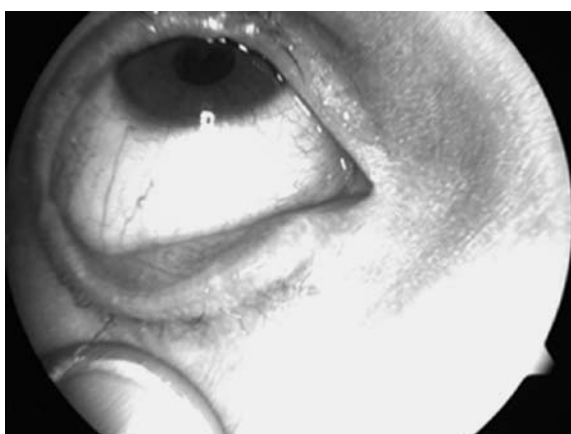
There were ocular symptoms in 18 of those with ED. Dry eye complaints in 9 of these patients were moderate, a Schirmer I test was over 10 mm, and the tear film break-up time (BUT) was between 8–12 s. In 2 cases, there were severe dry eye findings, the Schirmer I test was below 5 mm in both eyes, and BUT was short by 5 s. There was



Fig. 1. Dental aspect of a case



**Fig. 2.** Trichodysplasia and Protuberant lip seems



**Fig. 3.** Upper and lower puncta are inexistent in EEC case



**Fig. 4.** Early DCR was performed on the patient with lacrimal duct hypoplasia, cleft lip and palate of 3 years case

**Table 1.** Ocular findings of ocular involvement with ED patients (18 cases)

|                               |                  |
|-------------------------------|------------------|
| Periorbital hyperpigmentation | 16 cases (88.9%) |
| Eyebrows anomaly              | 16 cases (88.9%) |
| Lashes anomaly                | 15 cases (83.3%) |
| Dry eye symptoms              | 11 cases (61.1%) |
| Lacrimal duct anomaly         | 4 cases (22.2%)  |
| Corneal Opacity               | 2 cases (11.1%)  |



a)



b)

**Fig. 5.** Ectrodactyly in hands (a); Ectrodactyly in feet (b)

positive fluorescein staining. In both eyes of these patients, there was corneal opacity, and the mean age of these patients was 37.5 years.

Two patients with EEC had lacrimal duct anomaly. In a female patient of 3.5 years old, there was lacrimal system agenesis, and upper and lower puncta were nonexistent (Figure 3). In a male patient of 3 years old, however, the upper punctum was nonexistent, and there was lacrimal system hypoplasia (Fig. 4). In both patients, there were cleft lip and palate, as well as ectrodactyly in hands and feet (Fig. 5a, b).

## Discussion

It is now explicitly known that HED is mostly inherited as an X-linked recessive trait. In these cases, only in male patients can the disorder be fully expressed. Female cases who carry only a copy of the disease gene (heterozygote carriers) are likely to present with some signs and findings associated with the disorder. There are also reports that have been documented in literature suggesting that HED seems to have been inherited as an autosomal recessive genetic trait, in which the disorder is fully expressed in both male and female cases [9, 16, 17]. In the current study, the number of female cases (11) is seen to be lower than that of males (13 cases).

In his study, Kaercher [6] reported that 94.4% of the patients suffered from dry eye symptoms, reduction of eyebrows was seen in 94.4%, and the lashes were altered in 91.6%. In our study, however, ocular symptoms were detected in 18 cases (75.0%). In cases with ocular symptoms, periorbital hyperpigmentation (88.9%), eyebrow anomalies (88.9%), lashes anomalies (83.3%) and dry eye symptoms (61.1%) were observed. Dry eye symptoms were observed to exist in 11 patients in our study; in 9 of these, a Schirmer I test was found to be within normal limits and BUT was shorter than normal (8–12 s). The values obtained in our study were found to be partly lower with respect to those by Kaercher [6]. Patients in our study (mean age 15.8 years) were younger than those in Kaercher's (mean age 21.9 years) [6]. We observed that ocular complaints increased together with age. The mean age of patients with ocular complaints was 17.5, whereas it was 23.1 in the group having dry eye symptoms, suggesting that ocular complaints and dry eye symptoms increase together with age. In the literature, severe ocular symptoms are described for adult patients with ectodermal dysplasia [6, 11].

Kaercher [6] reported corneal opacity as 19.4%. We determined keratopathy in two patients (11.1%). The mean age of these patients was higher (37.5 years) with respect to the other patients (15.8 years). Therefore, we are of the opinion that the development of keratopathy would be seen in older ages. Some earlier studies have reported that keratopathy is seen in advanced ages [6, 11]. In both patients, the Schirmer I test was below 5 mm, and BUT was short by 5 s in both eyes. Although the Schirmer I test was 5/6 mm and BUT 6/6 s in one patient, he had no dry eye complaints. The authors attributed the corneal abnormalities to an unstable tear film due to a lack of lipid secondary to absence of meibomian glands and goblet cell abnormalities [15, 18–20].

There is evidence that keratopathy in ectodermal dysplasia syndromes is the result of an altered lipid layer of the tear film. It is, in fact, an indirect consequence of the meibomian gland alteration [6, 21]. The age-dependent appearance of keratopathy would favor this hypothesis. Besides that, there are cases with an early onset of keratopathy. Baum reports that ectodermal dysplasia is a possible primary developmental defect in the corneal epithelium during embryogenesis, and that corneal alterations are a primary sign of ectodermal dysplasia syndromes, starting with an epithelial insufficiency and ending with stromal scarring and vascularization [22]. Corneal changes in EEC may have a different presentation. For instance, limbal stem cell deficiency (LSCD) seems to play a role in the etiology of this keratopathy. Among other risk factors for the severity and progression of the disease are recurrent infections from lacrimal drainage obstruction and tear film instability [18]. Most recently, Di Lorio [23] has described the ocular phenotype of 23 cases through EEC syndrome. According to what they reported in their study, EEC results from heterozygous missense mutations in the DNA-binding domain of the p63 gene, which is known to be a crucial element during embryogenesis and stem cell differentiation of stratified epithelia. Fourteen cases (61%) were diagnosed with LSCD as evidenced by the absence of limbal palisades of Vogt on slit-lamp examination. They hypothesized that p63 mutation resulted in LSCD, leading to progressive keratopathy, the major cause of visual morbidity in EEC patients. It is still unclear why, in many cases, the corneal epithelium remains intact, whereas the stroma, which is of non-ectodermal origin, shows opacifications [6].

In our study, lacrimal duct complaints were seen in 4 patients (22.2%); two of them were males and two females. There was epiphora and recurrent infection. Silicone tube was applied to a male patient of 4 years. Dacryocystorhinostomy (DCR) was performed on a female patient of 24 years due to chronic dacryocystitis. The other two patients were those with EEC syndrome.

EEC syndrome is a rare disorder that is inherited as an autosomal dominant trait with low penetrance and variable expression [13]. The ocular findings are atresia of tear ducts in 59% of cases, hypoplasia of tear ducts, frequent dacryocystitis and pathology of the tear duct system overall in 87% of cases, entropion, trichiasis, blepharitis, defective tear film due to absence of the meibomian glands and progressive keratopathy in 62% of cases, recurrent keratitis, progressive vascularized corneal scarring, rare cases of spontaneous corneal perforation and premature cataract formation in rare cases. In the literature, patients with non-

familiar, sporadic EEC syndrome are usually presented as affected more severely [12]. Two cases in our group were sporadic cases, and there were not any siblings in their family.

The shortened BUT assessed on several occasions suggested marked instability of the tear film, assuming that the absence of meibomian glands would lead to a deficiency in the lipid layer. The other is the absence of meibomian glands as first described in 1984 [11]. The absence of the meibomian glands leads to an instability of the tear film, with a normal Schirmer test but pathological BUT. Lemp [24] reported that patients with absent or deficient meibomian gland function should be categorized in the evaporative group of dry eye syndromes [15]. Matsumoto et al. [13] measured the tear evaporation rate to clarify the changes in tear quality. They reported that the tear evaporation rate was still higher compared to that in patients with obstructive meibomian gland dysfunction. In addition, Mathers [25] reported that the tear evaporation rate was three times higher in patients with meibomian gland disease.

Lemp [24] presumed that EEC syndrome belonged to the evaporative type of dry eyes. Matsumoto et al. [13] reported that increased tear evaporation is one of the most important processes in the pathogenesis of dry eye and keratopathy in this rare syndrome. In our patients with EEC,

there was no keratopathy. One of the patients was male (3 years) and the other was female (3.5 years). In both patients, there was a lacrimal duct anomaly. In one patient, the absence of bilateral lower and upper punctus, and in the other patient, the absence of bilateral upper punctus were seen. Although the Schirmer I test was found to be within normal limits in both patients, BUT was 7/8 s. in one patient and 8/8 s. in the other. In both patients, there was recurrent infection, and the meibomian orifices were of normal appearance. There were no dry eye symptoms in the patients. We think that the absence of dry eye symptoms may be related to the nonexistence of tear drainage. Early DCR was performed on the patient of 3 years. The other was followed up. Cleft palate-lip and ectrodactyly were detected in both patients.

Patients who receive a diagnosis of ED should be assessed in terms of ocular findings. In patients with ED, degradation arises in the tear lipid layer due to alterations in the meibomian gland, on the basis of which dry eye and ocular surface symptoms are seen. When ED is diagnosed, ocular symptoms that disturb patients do not exist. However, with increasing age, ocular symptoms, especially dry eye symptoms, increase. As soon as the dry eye symptoms occur, conservative treatment should be initiated and followed up.

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