Ectodermal dysplasia: important role of complex dental care in its interdisciplinary management

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Abstract

Aim Despite the fact that ectodermal dysplasia (ED) is a rare disease, it is often seen in a tertiary clinic. ED affects ectodermal tissues such as skin, hair, teeth, nails, and sweat glands. Patients usually have sparse light hair, deformed nails, and dry skin. They suffer from dental abnormalities such as oligodontia (absence of 6 or more teeth) or complete anodontia; salivation can also be affected. The absence of teeth can be the overriding problem for both patients and their parents, and lead to substantial social ostracisation. This study aims to summarise the facts about the disease, especially dental treatment options based on data drawn from a representative Czech cohort.

Materials and methods The present article summarises the facts about ectodermal dysplasia (ED) in a cohort of 13 patients, where the following were evaluated: clinical manifestations of ED, pathogenic variants detected in selected candidate genes and dental treatment options from child removable dentures to fixed crowns and implants insertion. Three cases are described in detail and demonstrate approaches for different age groups.

Results Our study highlights the need for awareness of the early signs of ED in dental and medical genetic practice. The ideal dental treatment plan includes interim removable dentures at a young age, orthodontic treatment in children and adolescents, and fixed restoration, including implants at a later date. With correct dental treatment, normal development of the patient's jaw, as well as their self-esteem, is markedly improved.

Conclusion Early diagnosis and active cooperation between the geneticist and dentist will facilitate cooperation with parents and patients and assure secondary prevention. It is preferable that the geneticist understands dental treatment options and can discuss these with patients/parents.

KEYWORDS Ectodermal dysplasia; Dental abnormalities; Dental treatment.

Introduction

Ectodermal dysplasia (ED) comprises a group of rare genetic disorders affecting ectodermal tissues such as skin, hair, teeth, nails, and sweat glands. Patients usually have sparse light hair, deformed nails, and dry skin. They suffer from dental abnormalities such as oligodontia (i.e. absence of 6 or more teeth) or complete anodontia, accompanied by problems with salivation [Reyes-Reali et al., 2018; Sfeir et al., 2014]. Additional health issues can include visual impairment and hearing problems. Patients with ED have a characteristic facial gestalt, which negatively impacts self-esteem and overall quality of life [Hashem et al., 2013]. The most frequent forms of ED are the X-linked hypohidrotic or anhidrotic forms (OMIM 305100), which are characterised by the complete absence of sweat glands. Pathogenic variants either occur de novo in the parental germline or are inherited from one parent. Thus far, the genetic variants in EDA (MIM:300451), EDAR (MIM:604095), EDARADD (MIM:606603), TP63 (MIM: 603273) and WNT10A (MIM: 606268) have been associated with more severe forms of ED [Cluzeau et al., 2011]. Importantly, pathogenic variants of the aforementioned genes are responsible for over 90% of ED's hypohidrotic and anhidrotic forms [Prashanth and Deshmukh, 2012]. ED manifests as both isolated and syndromic forms, which include ectrodactyly-ectodermal dysplasia-clefting (EEC; MIM: 129900), Rapp-Hodgkin (HED; MIM: 129400) and ankyloblepharon ectodermal-defects, cleft lip/palate (AEC; MIM: 102260) [Prashanth and Deshmukh, 2012; Itin, 2014], and ADULT (acro-dermato-ungual-lacrimal-tooth (MIM: 103285) syndromes [Whittington et al., 2016]. Females often have a minimal expression or patchy distribution (e.g., concerning abnormalities of sweat glands or hair), while in males, ED is fully expressed.

The current strategy for classifying various types of ED with different manifestations is based on the clustering of phenotypes. In order to introduce a systematic classification of ED, the presence or absence of the four main "ectodermal defects" in different subgroups were established as follows.

- ED1: trichodysplasia or hypotrichosis (hair dysplasia) associated with sparse, fragile hair, usually with extremely low levels of pigmentation. The distribution of body hair can vary, but scalp, pubic, and axillary hair is usually sparse. Eyebrows and eyelashes can be completely absent. The skin is usually pale, dry, and exfoliative.
- ED2: Dental dysplasia, in the form of anodontia or hypodontia (discussed below) leading to poor facial aesthetics, speech problems, and decreased function of the masticatory system.
- ED3: Onychodysplasia (nail dysplasia) is based on a spoon-

shaped appearance of the nails.
- ED4: Dyshidrosis (sweat gland dysplasia) is sweat gland dysplasia leading to hypohidrosis. It is associated with a reduced ability to produce sweat. As a result, patients are prone to hyperthermia, especially during warmer months; it is also associated with early childhood mortality [GHR, 2019].

Different types of ED are allocated to the subgroups based on the presence of the primary defect(s). The most commonly observed forms are in subgroups ED1-ED2-ED3-ED4 (e.g., hypohidrotic or anhidrotic, HED and AED, respectively) and subgroups ED1-ED2-ED3 (e.g., hidrotic ED), with monosymptomatic forms being rare [Clauss et al., 2014].

From the perspective of dentistry, the existing teeth are characterised by disturbances in crown morphology, i.e., smaller or conical shaped (especially the front teeth), mineralisation defects, taurodontism, and root fusion [Reyes-Reali et al., 2018]. The most affected teeth include the maxillary and mandibular canines, first molars, and the mandibular central incisors [Wright et al., 2017; Lexner et al., 2008]. Incorrect timing and order of teeth eruption together with incorrect or wide spacing is also present. Furthermore, deciduous teeth, without successors, can persist. Insufficient mandibular growth and the absence of alveolar processes at teeth agenesis sites lead to smaller lower jaw length, leading to a negative overjet (i.e. underbite). In addition, other facial and skull dimensions are also affected, leaving children with HED approximately two years behind their peers in most of the other facial biometric measurements. This feature is most apparent during early childhood, that is before dental treatments are started. Later, following prosthetic treatment, facial features usually normalise [Preedy, 2012; Sonnesen et al., 2018].

Other dysmorphic features, such as a prominent forehead or frontal bossing, high-set orbits, hypertelorism, and smaller nose and ears, can also be seen [Reyes-Reali et al., 2018; Preedy, 2012]; in females, mammary glands can be hypo/aplastic [Prashanth and Deshmukh, 2012]. Problems related to hyposalivation and gland hyposecretion can lead to eye, ear, and respiratory issues. Hyposalivation can be due to insufficient saliva production or the complete absence of salivary glands [Bergendal, 2014]. Dryness of the mouth and throat can lead to a hoarse voice or a lisp and subsequently impaired dental prostheses retention. Xerophthalmia is often present as well and contributes to visual impairment linked to ED.

The pathogenesis of ED is due to impaired ectodermal development, which is directed by the mesoderm through a complex set of intercellular and intracellular signaling pathways between the ectoderm and mesoderm layers. The mesoderm serves as the initiator of differentiation of adnexa during embryonic development, i.e., when the ectoderm gradually transitions into the epidermis. The genesis of tooth germ (the embryonic tooth) is also a product of an interaction between the mesoderm and ectoderm layers [Reyes-Reali et al., 2018]. The EDA, EDAR, and EDARADD genes are responsible for creating the ectodysplasin A protein (MIM: 300451). This transmembrane protein is part of the TNFα signaling pathway and is critical for interactions between the ectoderm and mesoderm layers [Trzeciak and Koczorowski, 2016]. Disturbed developmental interactions between the two layers lead to disturbances in the formation and function of teeth, hair, nails, skin, and sweat glands, with each tissue being affected by different degrees of malformation or malfunction. Molecular genetic testing in ED involves candidate gene sequencing and deletion/duplication analyses. Moreover, different inheritance patterns have been described [GHR, 2019]. EDA is the only gene responsible for the X-linked HED syndrome, and direct sequencing of this gene can identify up to 95% of the causative variants in males. For the EDAR and EDARADD genes, sequence analysis of the gene's coding and flanking intron regions are also available but provides lower yields. The sequence analysis is not robust because it requires analysis of dosage and specific methods to detect copy number variants (CNVs) [Prashanth and Deshmukh, 2012]. Massive parallel sequencing allows for the analysis of multiple candidate gene panels and often includes CNV detection, which significantly simplifies the entire diagnostic process.

This study aimed to provide an update on dental treatment options for ED in a representative cohort of 13 Czech ED cases. Our study highlights the need for increased awareness of the early signs of ED in clinical dentistry and within clinical genetic examinations. The cohort under study has been been comprehensively evaluated from a dental and genetics perspective. Three cases are described in detail as examples of age-specific approaches to diagnosis and treatment.

Materials and methods

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Patients

A cohort of 13 Czech paediatric patients with ED (10 males and 3 females; age range 1-15 years) was followed longitudinally at the Department of Stomatology. Symptoms of each case are summarised in Table 1; all suffer from oligodontia. Our prospective study was carried out following the recommendations of the American Dental Association (ADA). The patients signed informed consent to take part in our study in accordance with the Declaration of Helsinki.

The study's approval was obtained from the affiliated Ethics Committees of Motol University Hospital and the 2nd Faculty of Medicine, Charles University (reg. n. EK-973IGA 1.12/11).

Confidentiality and legal provisions followed Czech law (details available upon request).

Genetic testing

Pre- and post-test genetic counselling was provided to all studied ED cases and their families where applicable according to provisions stipulated in Art. 28-29 of Act. 373/2011 Coll. Peripheral blood leukocyte DNA was isolated

Patient n.	1	2	3	4	5	6	7	8	9	10	11	12	13
Affected tissues, organs:													
Hair	✔	✔	✔	✔	✔		✔	✔		✔	✔	✔	✔
Nails		✔	✔			✔						✔	
Skin	✔	✔			✔	✔	✔	✔		✔	✔	✔	
Sweat glands		✔	✔		✔		✔	✔		✔	✔		✔
Salivation							✔						
Teeth	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Eyes	✔	✔											
Ears	✔	✔											
Respiratory diseases					✔		✔		✔				
Others	✔			✔							✔		

TABLE 1 Clinical manifestations of the ED patients in the study.

by standard automated extraction procedures according to manufacturer´s protocols (Autogen; USA). Due to the longitudinal ascertainment of the patient cohort within the last decade patient DNA was initially analysed by direct Sanger sequencing and later by massive parallel sequencing (MPS) on sequencing platforms MiSeq or HighSeq2000 (Illumina; USA; data available upon request). Candidate gene panels comprising EDA, EDAR, EDARADD, TP63and WNT10A were Sanger sequenced (oligonucleotide primers are available upon request) or SeqCap EZ choice probes (Roche) were utilised in massively parallel approaches for respective sequence selection and enrichment. Identified Class 4-5 variants (according to the ACMG.net classification) were verified by Sanger sequencing and their segregation was confirmed in affected families, where applicable. Examined genes and detected pathogenic/likely pathogenic variants are summarised in Table 2.

3D facial gestalt analysis

We used the 3dMDface System, Ultra-Fast Capture Speed: ≈ 1.5 milliseconds, Geometry Accuracy: < 0.2 mm RMS or better (3dMDS, 2020). Facial scanning used a non-invasive 3D morphometric imaging method to monitor the patient's facial dimensions or growth without any additional radiation exposure. Superimpositions of various facial scans allow a comparison of the patient's growth pattern or comparison of the patient with a control group of non-syndromic individuals. In our case, the control groups included both males and females, and each age group had 30–50 individuals. The scans are superimposed based on the correspondences, and the color "heat map" represents differences in the degree of protrusion/retrusion.

Results

Clinical findings

The most common clinical features include sparse, pale hair (11 out of 13 patients) and skin issues (9 out of 13 patients). Except for two cases, all patients were referred to our clinic forthe first time at or under 6 years of age. The main reason for the for their referral was eruption delay, hypo/anodontia, and/or conical tooth shape of existing teeth detected at regional dentistry offices (Table 3).

Patient n.	Gene	Variant (cDNA level, protein level, reference sequence)	Inheritance pattern	Variant Class
1.	TP63	c.727C>T p.(Arg243Trp) NM_003722.4	AD, de novo	5 – pathogenic
2.	EDA	c.575G>A p.(Gly192Glu) NM_009809.1	X-linked, maternally inherited	5 – pathogenic
3.	EDA	c.583G>A p.(Gly195Arg) NM_009809.1	X-linked, de novo	4 – likely pathogenic
4.	EDA	c.659delC p.(Pro220Glnfs*60) NM_001399.4	X-linked, maternally inherited	4 – likely pathogenic
5.	EDA	c.463C>T p.(Arg155Cys) NM_009809.1	X-linked, maternally inherited	5 – pathogenic
6.	WNT10A	c.321C>A p.(Cys107Ter) NM_025216.2	AD, maternally inherited	4 – likely pathogenic
7.	EDA	c.557G>A p.(Gly186Asp) NM_001399.5	X-linked, maternally inherited	5 – pathogenic
8.	EDA	c.802G>T p.(Gly268Cys) NM_001399.5	X-linked Parents declined further testing	4 – likely pathogenic
9.	EDA	c.1133C>T p.(Thr378Met) NM_001399.4	X-linked, maternally inherited	5 – pathogenic
10.	EDA	c.463C>T p.(Arg155Cys) NM_009809.1	X-linked, maternally inherited	5 – pathogenic
11.	EDA	c.1028_1078del151insTG,p.(Tyr343Leufs*15) NM_001399.5	X-linked, de novo	5 – pathogenic
12.	WNT10A	c.321C>A p.(Cys107Ter) NM_025216.3 (homozygous)	AR	5 – pathogenic
13.	EDAR	c.126del p.(Leu43Cysfs*60) and c.444T>G p.(Cys148Trp) NM_022336.3	AR	c.126del: 5 - pathogenic c.444T>G: 4 – likely pathogenic

Legend AD- autosomal dominant; variant Classes are denoted according to the ACMG.net classification system

TABLE 2 Pathogenic variants detected in selected candidate genes.

Patient:	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at dg. (y /m)	13/0	2/1	1/7	1/2	5/9	2/2	1/7	1/4	4/8	0/4	3/7	5/0	15/0
Sex	M	M	M	F	M	M	M	M	M	M	M	F	F
OPG *	✔	✔	✔	-	✔	-	-	-	✔	✔	✔	✔	✔
N. deciduous teeth	N/A	6	2	7	4	6	8	3+	4	8	2	10	5+
N. of permanent teeth	13	2	0	NA	7	NA	NA	NA	4	2	0	14	9
Conical teeth		✔		✔	✔		✔	✔	✔	✔	✔	✔	✔
Diastema		✔		✔	✔		✔	✔	✔	✔	✔	✔	✔
Taurodontism (larger pulp chamber)	✔									✔		✔	✔

Legend OPG: Since majority of the patients under investigation are minors, not all of them had orthopantomograms performed. (OPG). N- in deciduous and permanent teeth refers to developed / developing teeth; NA- not applicable due to patient age; M-male, F-female

TABLE 3 Dental manifestations in the examined cohort.

Genetic findings

Pathogenic variants in the EDA gene were found in nine patients; two patients had variants in the WNT10A gene, one has a variant in the TP63 gene and EDAR genes each. Nine patients suffered from X-linked ED, of whom three have the hypohidrotic form (Table 2).

Dental treatment

The stomatology treatment in young patients can be problematic for multiple reasons. To illustrate the treatment process of young patients at different ages, we present three cases where we could improve their dentition and facial features. All of them suffered from X-linked form of ED.

Patient with primary dentition

Patient no. 3 (Table 1-3) was referred to our clinic at the age of one year and seven months due to delayed tooth eruption. His dysmorphic appearance led to a subsequent referral to the collaborating genetics department. He has sparse hair, minimally developed eyelashes and eyebrows, dry skin, and suffers from hyperthermia due to lack of sweat glands. Genetic testing revealed a de novo X-linked hypohidrotic form of ED (Table 2). The patient's cooperation only allowed for intraoral photos (Fig. 1a, 1b).

The first attempt at making a temporary removable prosthesis was at the age of 3. Even though there was an attempt to make a prosthesis as early as possible, postponement until the age of 4 or older is often needed. This patient was able to cooperate starting at the age of five when the first orthopantomogram (OPG) (Fig. 1c) was performed; the upper partial denture and lower denture were created; 3D facial scans were performed at this time.

Figure 1e compares the facial scan of a 3-year-old patient with a non-syndromic control group of the same age. The lagging area around the mouth is well illustrated, while the chin is more prominent. This phenomenon is not surprising considering normal or increased skeletal jaw growth usually seen in ED patients. The less pronounced lips could be explained by the absence of support by the teeth. This same growth pattern remains present at the age of 5 (Fig. 1f).

Figure 1h and 1i represent the superimposition of two facial scans made at the age of 5 years, one without dentures and one with dentures. The improved lip support is visible in both profile and en face representations.

Figure 1g compares the patient wearing dentures with non-syndromic peers. The area of the mouths is grayer, which means fewer differences compared to non-syndromic peers. Nonetheless, the cheeks are around 4 mm retruded, and the chin is still prominent by about 3 mm, but the overall differences between the two are minor.

At this stage, preserving existing teeth and alveolar bone is crucial since aesthetic considerations have become more important. Further treatment will include fabrication of permanent prosthetics, ideally implant-supported.

Patient at the age of early permanent dentition

Patient no. 12 (Table 1–3) is a 5-year-old girl with conical shaped teeth with temporary dentition and agenesis of the secondary lateral incisors. She was referred by her dentist to the Pediatric Dentistry Department at the Institute of Dentistry and Oral Sciences in Olomouc (Czech Republic) (Fig. 2b). The patient showed typical signs of ED, i.e. sparse, light hair, deformed nails (Fig. 2c, 2f), and dry skin. Ortopantomograms showed multiple tooth agenesis and taurodontism of the first permanent molars (Fig. 2a). However, the distribution of teeth in the jaws was sufficient to provide acceptable mastication, so her situation did not require a removable denture at that time. For this, as well as for psychological reasons (i.e. bullying in kindergarten), we chose to proceed with a fixed restoration. The main goal was to improve tooth shape and, in so doing, also improve the aesthetics of the teeth, both of which were achieved (Fig. 2e). Genetic testing

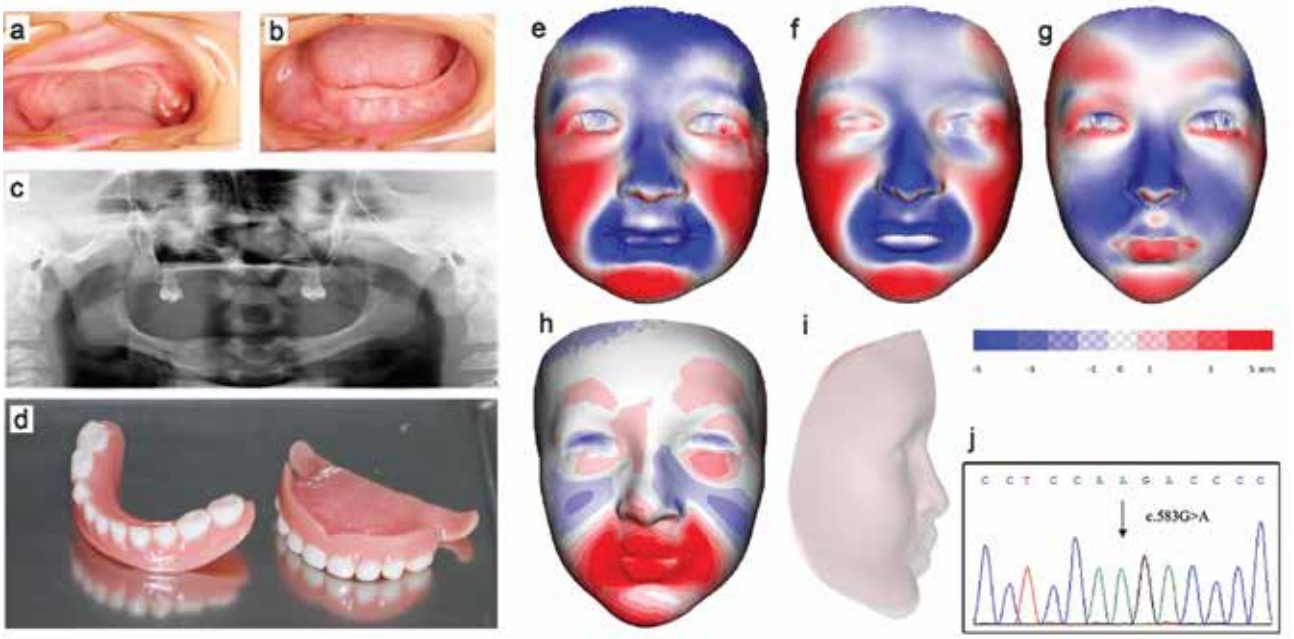

FIG. 1 Case 1: Intraoral photograph of the upper and lower jaw at the age of 3 years (a, b); OPG X-ray at the age of 5 years (c); Upper and lower partial dentures at the age of 5 years (d). 3D Facial scans (e–i): 3-year old vs. normal (e); 5 years old vs. normal (red protrusion/blue retrusion according to color intensity) (f); 5-year old with dentures vs. normal (g); 5 years old with and without dentures (h) 5-yearsold with and without dentures (profile), and j) Single nucleotide substitution in the EDA gene leading to X-linked hypohidrotic ED.

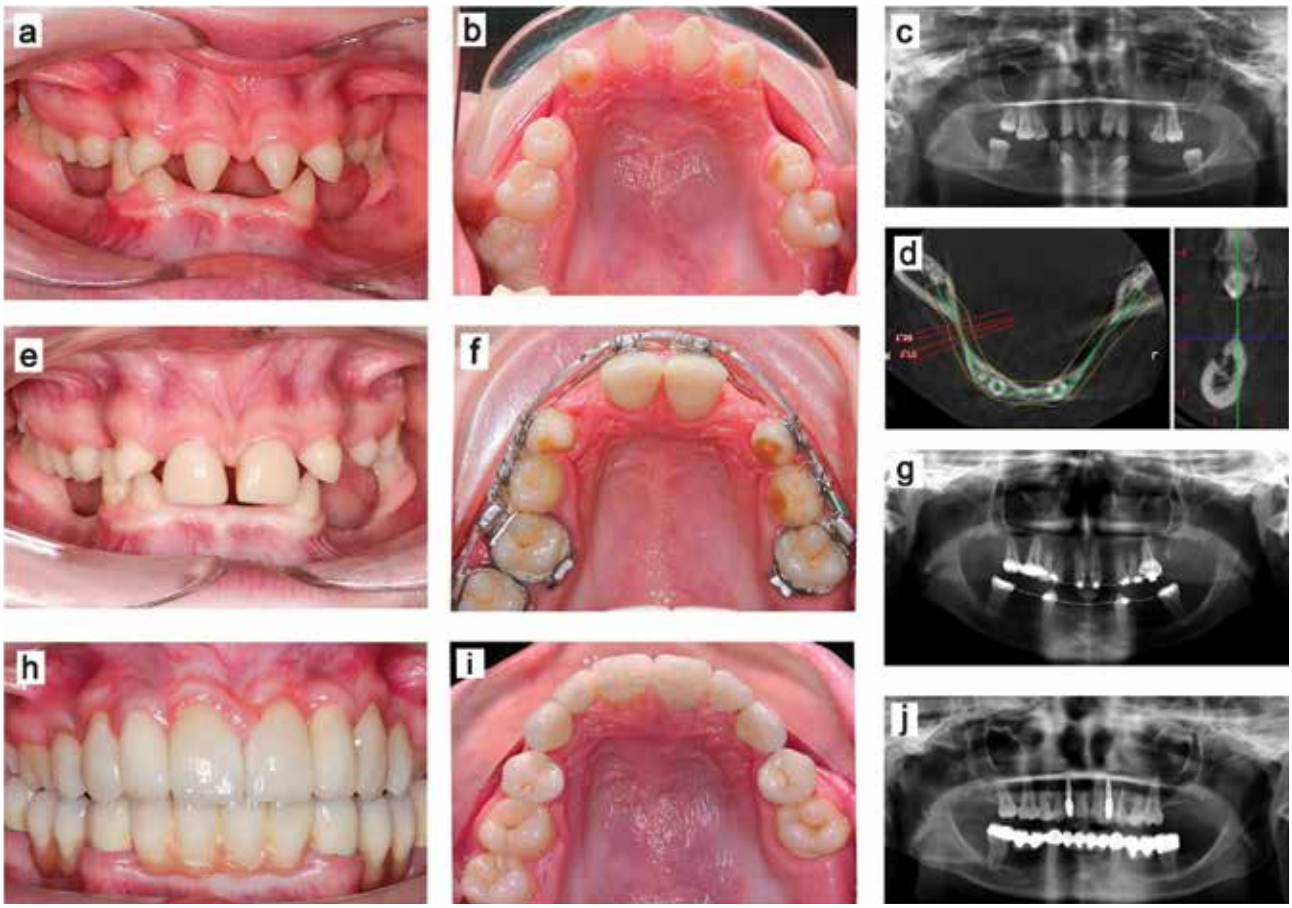

FIG. 2 Case 2: OPG at the age of 5 years (a); Intraoral photograph at the age of 5 years (b); Affected nails (c and f); OPG at the age of 14 years (d); intraoral photograph at the age of 14 yrs (e).

revealed a pathogenic variant in the WNTA10 gene.

The patient is currently 14-years old, and all the permanent teeth have erupted; therefore, she is now ready for specialised orthodontic treatment (Fig. 2d). Definitive prosthetic rehabilitation is planned for completion by the age of 18 years.

Young adult patient

Patient no. 13, a 15-year-old patient (Table 1–3) who came to our clinic with her parents but without GP recomendation with a request for prompt treatment of her teeth due to social ostracisation. She also had partial alopecia and did not sweat at all. Genetic testing found autosomal recessive hypohidrotic ED.

Intraoral examination revealed agenesis of 9 teeth and a conical shape of the front teeth (Fig. 3a-c). A panoramic image using cone-beam computed tomography (CBCT) revealed that the alveolar processes were not established at all, and only the body of the mandible was apparent at some parts of the jaws (Fig. 3d).

Temporary crowns were fitted on teeth 11 and 22 in the shape of the central upper incisors (Fig. 3e). An upper fixed appliance was also fitted (Fig. 3f and 3g): the diastema between 11 and 21 was closed, the deciduous canines were distalised into Angle Class I, the space in region 12 and 22 were opened to 6 mm, and the second deciduous molars and first permanent molars were medialised. The first deciduous molars were left in the dental arch. A lower fixed appliance was fitted at the same time as the upper: the roots of the mandibular canines were straightened; the canines were then distalised, and the second molars were medialised into the position of the first molars in order to decrease the space between the teeth serving as pillars and to create spaces for the future replacement at the site of the premolars and incisors. The distance between canines and molars was decreased from 40 mm to 20 mm. Implantations in the sites of 12 and 22 were performed according to a surgical template. Impladent 2.9 x 14 mm implants (Lasak, Czech Republic) were placed and, to replace bone tissue, a mixture consisting of autogenous bone obtained during preparation (bone chips) and collagen material (BioOss; Geistlich, Switzerland) was used. Once the bone graft formed, the augmented area was covered with a membrane (BioGide; Geistlich, Switzerland). The prosthesis was planned to harmonise the dentogingival-facial aesthetics. The permanent prostheses for the upper jaw consisted of ceramic crowns on the teeth and crowns on the implants (region 12 and 22). For the mandible, a fixed bridge was fabricated (Fig. 3h and 3i).

The final aesthetics was very satisfactory, both in terms of the macro-aesthetics and micro-aesthetics. An OPG image two years after treatment showed no pathological changes (Fig. 3j).

Discussion and conclusions

ED patient management requires the cooperation of multiple specialists. For dental treatment alone, the team should consist of a general dentist, a prosthetist, an oral and maxillofacial surgeon, an implantologist, and an orthodontist. The role of

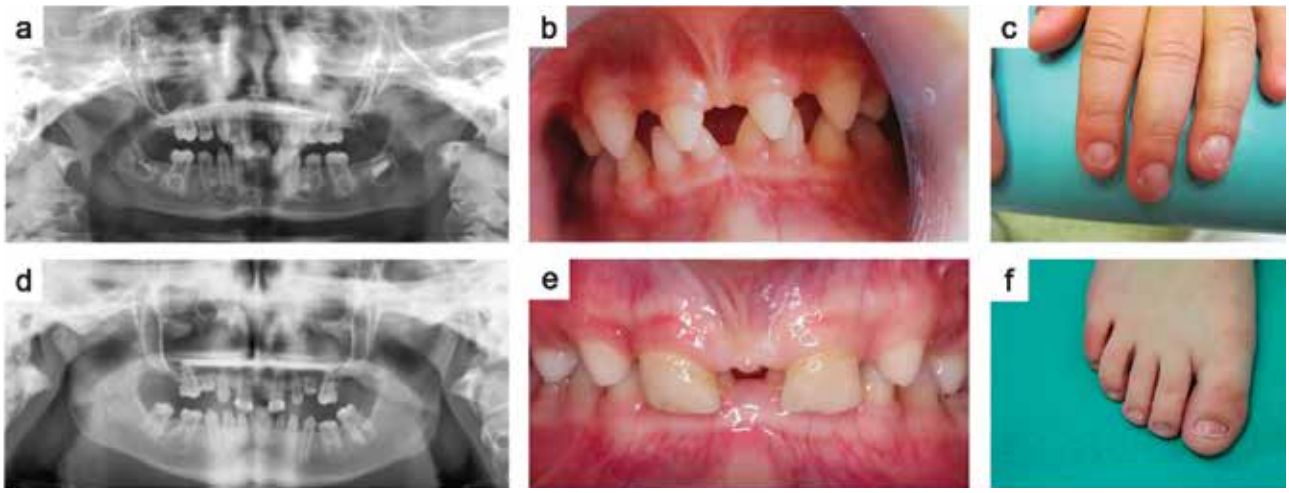

FIG. 3 Case 3: Intraoral image before treatment (a and b), OPG image before treatment (c): extreme disto-inclination of mandibular canines, a section from the CBCT (d) shows the huge insufficiency of the alveolar ridge, temporary crowns on 11 and 21 before fitting the fixed appliance (e), space openings in area of 12 and 22 to 6 mm for future implantation (f), OPG image before removing the fixed appliance (g), with straightened canines, final prosthetic reconstruction (h and i), and panorex (X-ray) 2 years following treatment (j).

dermatologists and medical geneticists is clearly substantiated as well.

Removable (partial) dentures are usually a well-accepted treatment offering good aesthetic outcomes and functional mastication even though they have to be replaced every 3.5–4 years [Filius et al., 2016]. However, Hsieh et al. [2018] suggest different treatment options for different age groups. On average, treatment starts at the age of 4 years. For children up to 6 years of age (i.e. during primary dentition phase), interim denture prostheses are the best choice, mostly with clamps. Restoration of hypoplastic or malformed molars can be done using stainless steel crows when needed [Ou-Yang et al., 2019]; by this age, the ED diagnosis should be confirmed. At ages of up to 12 years (i.e. within the phase of mixed dentition), it is important to adjust or replace existing prostheses as necessary. At this age, implants in the mandible's anterior area can be considered, especially for edentulous patients. For patients between the ages of 13 and 18 years (i.e., early phase of permanent dentition) it is possible to consider orthodontic treatments and reshaping of existing teeth; orthodontic treatment can function as supportive therapy as well.

Levander E. et al. [1998] showed that orthodontic pre-treatment does not improve the dental status due to a higher tendency for apical root resorption. Still, it is important to adjust removable prostheses to protect the existing teeth and alveolar bone. In edentulous patients, complete dentures are used, both removable and implant supported. In patients with at least one tooth, a tooth-supported denture can be considered. For adult patients, the creation of permanent prostheses with bone augmentation, as needed, and implant insertion is the standard course. Bone augmentation has the same success rate in patients regardless of ED status [Hsieh et al., 2018]. Use of existing teeth as an abutment for crowns is not recommended for non-adult ages due to the large pulp cavities of teeth at younger ages. Edentulous patients usually receive fixed implant-supported prostheses containing eight implants in the upper jaw and 6 in the lower jaw [Kutkut et al., 2015].

When comparing implant treatments in patients with ED and non-syndromic hypo/oligodontia, we found that the annual failure rate of implants in ED patients was higher than in non-syndromic oligodontia patients. However, once the implant is in place for more than six months, the success/survival rate was about the same, and the failure rates were similar to those without ED [Terheyden and Wüsthoff, 2015]. One of the main reasons for implantation failure seems to be the absence of the alveolar bone [Wang et al., 2016]. Implant survival rates vary between 88.5% and 97.6%, with higher risks of failure in children [Yap and Klienberg, 2009]. Implants failure rates in children are significantly higher (25.8%) than in juveniles (7.0%) or adults (2.6%) [Terheyden and Wüsthoff, 2015].

Chewing improvement after implant treatment was very important to the patients, and most of them reported being satisfied with bite and chew improvements [Finnema et al., 2005]. After skeletal growth concludes in HED patients, orthognathic surgery may be required, especially if no treatments were undertaken earlier [Preedy, 2012]. Our group of patients had similar outcomesin appearance, diagnostics, and treatment as other ED patients. The ideal dental treatment plan includes interim removable dentures, starting at a young age, orthodontic treatment before adulthood, followed by permanent prostheses. With proper dental treatment, the normal development of the patient's jaw and their self-esteem is ensured. It is not always possible to achieve all desired steps. An early diagnosis and teamwork between the geneticist and dentist will improve the relationship with parents and patients. It is preferable that the geneticist be familiar with dental treatment options and be able to discuss them.

We observed significant improvements in face proportions after dental treatment. Assessments using a comparison of patient facial scans with those of their peers is possible without any additional X-ray examination or other forms of radiation.

Conflicts of interest

All the authors declare no conflicts of interest.

References

› Bergendal B. Orodental manifestations in ectodermal dysplasia-A review. Part A. Am J Med Genet 2014;164:2465–2471. https://doi.org/10.1002/

ajmg.a.36571
› Clauss F, Waltmann E, Barriere P, Hadj-Rabia S, Manière MC, Schmittbuhl M. Dento-maxillo-facial phenotype and implants-based oral rehabilitation in Ectodermal Dysplasia with WNT10A gene mutation: Report of a case and literature review. J Cranio-Maxillofacial Surg 2014;42: e346–e351. https://doi.org/10.1016/j.jcms.2014.01.037
› Cluzeau C, Hadj-Rabia S, Jambou M, Mansour S, Guigue P, Masmoudi S, Bal E, Chassaing N, Vincent MC, Viot G, Clauss F, Manière MC, Toupenay S, Le Merrer M, Lyonnet S, Cormier-Daire V, Amiel J, Faivre L, De Prost Y, Munnich A, Bonnefont JP, Bodemer C, Smahi A. Only four genes (EDA1, EDAR, EDARADD, and WNT10A) account for 90% of hypohidrotic/anhidrotic ectodermal dysplasia cases. Hum Mutat 2011;32:70–72. https://doi.org/10.1002/humu.21384
› Filius MA, Cune MS, Raghoebar GM, Vissink A, Visser A. Prosthetic treatment outcome in patients with severe hypodontia: A systematic review. J Oral Rehabil 2016;43:373–387. https://doi.org/10.1111/joor.12384
› Finnema KJ, Raghoebar GM, Meijer HJA, Vissink A. Oral rehabilitation with dental implants in oligodontia patients. Int J Prosthodont 2005;18:203–9.
› Genetics Home Reference. Hypohidrotic ectodermal dysplasia - Genetics Home Reference - NIH. Natl. Libr. Med. 2019.
› Hashem A, Kelly A, O'Connell B, O'Sullivan M. Impact of moderate and severe hypodontia and amelogenesis imperfecta on quality of life and self-esteem of adult patients. J Dent 2013;41:689–694. https://doi.org/10.1016/j.jdent.2013.06.004
› Hsieh YL, Razzoog M, Hammaker SG. Oral care program for successful long-term full mouth habilitation of patients with hypohidrotic ectodermal dysplasia. Case Rep Dent 2018; 2018. https://doi.org/10.1155/2018/4736495
› Itin PH. Etiology and pathogenesis of ectodermal dysplasias. Part A. Am J Med Genet 2014;164:2472–2477. https://doi.org/10.1002/ajmg.a.36550
› Kutkut A, Abu-Eid R, Sharab L, Abadi B, Van Sickels J. Full mouth implant-supported rehabilitation of a patient with Ectodermal Dysplasia: Clinical report and literature review. J Int Acad Periodontol 2015;17:34–41.
› Levander E, Malmgren O, Stenback K. Apical root resorption during orthodontic treatment of patients with multiple aplasia: A study of maxillary incisors. Eur J Orthod 1998;20:427–434. https://doi.org/10.1093/ejo/20.4.427
› Lexner MO, Bardow A, Juncker I, Jensen LG, Almer L, Kreiborg S, Hertz JM. X-linked hypohidrotic ectodermal dysplasia. Genetic and dental findings in 67 Danish patients from 19 families. Clin. Genet 2008;74:252–259. https://doi.org/10.1111/j.1399-0004.2008.01037.x
› Ou-Yang LW, Li TY, Tsai AI. Early prosthodontic intervention on two three-year-old twin girls with ectodermal dysplasia. Eur J Paediatr Dent 2019;20:139–142. https://doi.org/10.23804/ejpd.2019.20.02.11
› Prashanth S, Deshmukh S. Ectodermal Dysplasia: A genetic review. Int J Clin Pediatr Dent 2012;5:197–202. https://doi.org/10.5005/jp-journals-10005-1165
› Preedy VR. Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease, Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease. Springer: New York; 2012. https://doi.org/10.1007/978-1-4419-1788-1
› Reyes-Reali J, Mendoza-Ramos MI, Garrido-Guerrero E, Méndez-Catalá CF, Méndez-Cruz AR, Pozo-Molina G. Hypohidrotic ectodermal dysplasia: clinical and molecular review. Int. J Dermatol 2018;57:965–972. https://doi.org/10.1111/ijd.14048
› Sfeir E, Nassif N, Moukarzel C. Use of mini dental implants in ectodermal dysplasia children: follow-up of three cases. Eur J Paediatr Dent 2014 Jul;15(2 Suppl):207-12.
› Sonnesen L, Jasemi A, Gjørup H, Daugaard-Jensen J. Upper cervical spine and craniofacial morphology in hypohidrotic ectodermal dysplasia. Eur Arch Paediatr Dent 2018;19:331–336. https://doi.org/10.1007/s40368-018-0362-8
› Static-3dMD Systems | 3dMD [WWW Document], n.d. URL http://www.3dmd.com/static-3dmd_systems/ (accessed 6.29.20).
› Terheyden H, Wüsthoff F. Occlusal rehabilitation in patients with congenitally missing teeth—dental implants, conventional prosthetics, tooth autotransplants, and preservation of deciduous teeth—a systematic review. Int J Implant Dent 2015;1. https://doi.org/10.1186/s40729-015-0025-z
› Trzeciak WH, Koczorowski R. Molecular basis of hypohidrotic ectodermal dysplasia: an update. J Appl Genet 2016;57:51–61. https://doi.org/10.1007/s13353-015-0307-4
› Wang Y, He J, Decker AM, Hu JC, Zou D. Clinical outcomes of implant therapy in ectodermal dysplasia patients: a systematic review. Int J Oral Maxillofac Surg 2016;45:1035–1043. https://doi.org/10.1016/j.ijom.2016.03.011
› Whittington A, Stein S, Kenner-Bell B. Acro-dermato-ungual-lacrimal-tooth syndrome: an uncommon member of the ectodermal dysplasias. Pediatr Dermatol 2016;33:e322–e326. https://doi.org/10.1111/pde.12938
› Wright JT, Grange DK, Fete M. Hypohidrotic Ectodermal Dysplasia. 2017; 2003 Apr 28 [Updated 2017 Jun 1], in: Adam MP, Ardinger HH, Pagon RA, et al. Editors. GeneReviews® [Internet]. University of Washington, Seattle; 1993-2018.
› Yap AKW, Klienberg I. Dental Implants in patients with ectodermal dysplasia and tooth agenesis: A critical review of literature. Int J Prosthodont 2009;22:268-76. https://doi.org/10.1016/s0022-3913(10)60099-6