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A Case Report and Review

Ectodermal Dysplasia

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Synonyms of Ectodermal Dysplasia

Anhidrotic Ectodermal Dysplasia, CST syndrome, HED, Christ-Siemens-Touraine Syndrome,

ABSTRACT

Background and Setting: Hypohidrotic (anhidrotic) ectodermal dysplasia (HED) is a congenital syndrome that exhibits features of oligodontia/anodontia, scant hair and reduced sweating. It has an estimated prevalence of 1/17000, worldwide. Presented here is a case of HED in a 22-year-old male patient who had congenitally missing teeth. He had heat intolerance and other discomforts, especially in the summer season. Intraoral examination revealed partial anodontia, with a generalised spacing of teeth, peg-shaped or conical upper anterior teeth and smaller sized single molar tooth that caused an underdeveloped alveolar ridge; a reduced facial height and everted lips.

INTRODUCTION

In 1875, Mr W. Weddenburn communicated to Charles Darwin about a condition that affected 10 men of four generations of a Hindu family. [1]

History

The first description of the clinical case of HED was obtained in 1792. [2] The HED comprised of a complex and large nosological group of diseases, first described by Thurnam in 1848. [3] But the term 'ectodermal dysplasia' was coined by Weech in 1929.

Epidemiology: There are about 150 types of ectodermal dysplasias with Hypohidrotic Ectodermal Dysplasia being one of them. EDs affect at least 1 in 17,000 people worldwide. [4] HED has a prevalence of approximately 1/15,000. Christ-Siemens-Touraine Syndrome (CST) syndrome is the most common sub-type (80% of cases) affecting males of 1/50,000 to 1/100,000 births. [5]

Classification: Freire-Maia and Pinheiro proposed the first classification system of the ectodermal dysplasias in 1982; with additional updates in 1994 and 2001. Their original classification system stratified the ectodermal dysplasia into 10 different subgroups according to the presence or absence of:

ED1: Trichodysplasia (hair dysplasia)

ED2: Dental dysplasia

ED3: Onychodysplasia (nail dysplasia)

ED4: Dyshidrosis (sweat gland dysplasia). [6]

The defects of ectodermal dysplasias can be observed as early as 3 weeks of gestation, and it may present either as a true or a syndromic pattern; together with the involvement of other systems. Pure hair and nail affecting ectodermal dysplasias are exceedingly rare and have been known to be associated with multiple abnormalities such as skeletal and hematological abnormalities, keratoderma or ichthyosis, mental or psychomotor retardation, cardiac irregularities and cataracts. [7]

Overall, the ectodermal dysplasias are classified into either

- Group A disorders, which were manifested by defects in at least 2 of the 4 classical ectodermal structures as stated above, with or without other defects, and
- Group B disorders, which were manifested by a single defect in one characteristic ectodermal structure (1 to 4) in combination with (5) a defect in one other ectodermal structure (for e.g.,. ears, lips, dermatoglyphics).

Felsher in 1944 altered the word anhydrotic to hypohydrotic because the persons with hypohydrotic form were not truly devoid of all sweat glands.

In the Hidrotic form/Clouston syndrome, hair and nails are affected. The sweat glands are usually spared. It is commonly inherited as an autosomal dominant trait. [1]

Currently there are about 150 different types of ectodermal dysplasias. Different sub-groups have been made in an attempt to classify ED based on the presence or absence of the 4 primary ectodermal dysplasia (ED) defects:

Based on the above, the 150 different types of ectodermal dysplasias are divided into subgroups:

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 most common ectodermal dysplasias are hypohidrotic (anhidrotic) ED which falls under subgroup 1-2-3-4 and hydrotic ED which comes under subgroup 1-2-3.

Other features include:

Lightly pigmented skin, which may be red or brown in color with the skin cracking, bleeding or getting infected; and these may be dry and prone to infections and rashes.

The absence of tears causes dry eyes. Cataracts and visual defects may be seen.

Hearing problems may be common. Cleft palate/lip may be seen.

There may be missing fingers or toes.

TABLE 1: Salient features of Ectodermal Dysplasias

Hair
Hair- coarse, brittle, curly or twisted
Scalp and hair on body- thin, sparse, light-colored
Nails
Fingernails and toenails- thick, abnormal in shape, discoloured, ridged, slow growing or brittle
Nails may be absent
Cuticles may be prone to infection
Sweat glands
Eccrine sweat glands may be absent or sparse and may function abnormally or may not function at all
Body cannot regulate temperature due to absence of sweat glands
Children may experience pyrexia leading to seizures and neurological problems
Overheating may be experienced in patients living in warmer places
Teeth
Abnormal tooth development- missing teeth, peg-shaped or pointed teeth
Tooth enamel defective
Dental treatment is mandatory and young children may need dentures

Respiratory infections may occur due to lack of saliva and mucus.

Chronic nasal infections may occur that may cause foul smelling discharge.

Breast development may be absent. [6]

There is another classification for the ED in which the lesions have been classified into three groups

- Pure,
- Complex, and
- Related.

Pure ectodermal dysplasia syndrome involves the hair, nails, and sweat glands only.

Complex syndromes comprise of these findings together with others.

Syndromes in which other factors are primary as compared to the effects on the hair, nails, sweat glands, or teeth are considered to be related conditions. [1]

Etiology:

Ectodermal Dysplasias comprise of approximately 150 related diseases that arise due to defective ectodermal germ cell layers during embryogenesis. Since this germ layer is under the inductive influence of other layers, they may also be affected. The precise genetic and biochemical defects are indefinite and are thought to differ from one form of the disorder to another.

• HED is due to a genetic mutation in the ectodysplasin (TNF Family ligand/NF-κB pathway that may be essential for the proper development of several ectodermal structures.

• On the other hand, the mutations in EDA (Xq12-q13.1), that encodes the epithelial morphogen ectodysplasin-A of the tumor necrosis factor family, causes the CST syndrome. The tumor necrosis factor (TNF) family ligand ectodysplasin An (EDA) shows 2 full-length splice variants: EDA1 and EDA2; that attaches to EDA receptor (EDAR) and X-linked EDA receptor (XEDAR/EDA2R), respectively. [8]

• Mutations in EDAR or TNF receptor (2q13) that encodes the Ectodysplasin-A receptor, or EDARADD (1q42.3), encode the EDAR-associated death domain (EDARADD) protein, to cause both AR and AD HED.

• A combination with immunodeficiency may occur due to the IKBKG (Xq28) mutations. NFKBIA, WNT10A, EDA2R or TRAF6 mutations may be responsible for some HED cases. [5]

Genetics: ED is primarily caused by mutations in the EDA, EDAR, and EDARADD genes.

The EDA, EDAR, and EDARADD genes guides in making proteins that work together during embryonic development [4] as early as the placode stage and may play a role in adult appendage function. [9] These proteins participate in the signaling pathway that is vital for the communication between the 2 cell layers, the ectoderm and the mesoderm; responsible for the formation of a large number of the body's tissues and organs such as the skin, teeth, hair, nails and sweat glands; which if defective, may lead to the characteristic features of hypohidrotic ectodermal dysplasia.

Mutations in the EDA gene are inherited in an X-linked recessive pattern. (An X-linked condition occurs when the mutated gene that results in this disorder is present on the X chromosome. In males (one X and one Y chromosome), one transformed copy of the gene in each cell is adequate to cause the condition. In females (who have X+X chromosomes, the mutated gene is called as the carrier), a mutation must affect both copies of the gene to cause the disorder. X-linked disorders affect males more frequently than females and fathers cannot pass X-linked traits to their sons. Carriers in 70% cases may exhibit mild features of the condition.

Autosomal dominant or recessive mutations in the EDAR or EDARADD gene may also cause hypohidrotic ectodermal dysplasia. [4]

Mutations in GJB6, GJB2 and GJA1 are also found related to HED. [8]

Clinical Features:

The Ectodermal Dysplasias are a group of hereditary, non-progressive syndromes in which the affected tissues are derived primarily from the ectodermal germ layer. There may be a predisposition to respiratory infections, mainly due to an immune system that is depressed and defective mucous glands in parts of the respiratory tract; which may prove fatal.

Case Report

22- year- old male patient of normal intelligence reported to the clinic with a chief complaint of difficulty in chewing

due to the absence of some teeth. The patient stated that the teeth were congenitally missing. The patient also complained of heat intolerance and discomfort during the summer season but reiterated that his visit to the clinic was purely due to his missing teeth. Past medical and treatment history was insignificant. His growth and developmental history were normal with no history suggestive of neural, aural, ocular deficits. No positive family history was observed. On general physical examination, the hair on his scalp was found to be stunted, fine and brittle; with a sparseness that was predominant in the temporal and occipital areas; eyebrows showed generalised hypotrichosis and few fine vellus hair over the eyebrows. Eyelashes appeared short and sparse too. Hair pull test was negative. The patient showed frontal bossing with sunken cheeks and thick everted lips. The skin was dry and light colored and scaly. (Figures-1 and 2) The nails exhibited deformities with longitudinal ridges; with peri-orbital hyperpigmentation; saddle nose; soft, dry skin with an increased pigmentation; as well as thin, linear wrinkles in the peri-oral region. (Figures 1 and2)

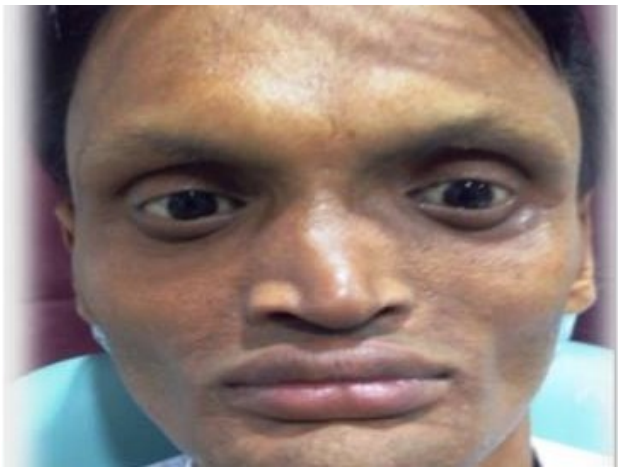


FIGURE 1: *Sparse hair and eyebrows with everted lips, saddle nose, frontal bossing*

Routine blood investigations and blood biochemistry results were insignificant.
On intraoral examination partial anodontia with generalized spacing, and no history of exfoliation or extraction of deciduous or permanent teeth was given. A history of delayed eruption of teeth; peg shaped or conical upper anterior teeth and underdeveloped molars; only one mandibular

FIGURE 2: *Nails are short, thick and shows longitudinal ridges.*

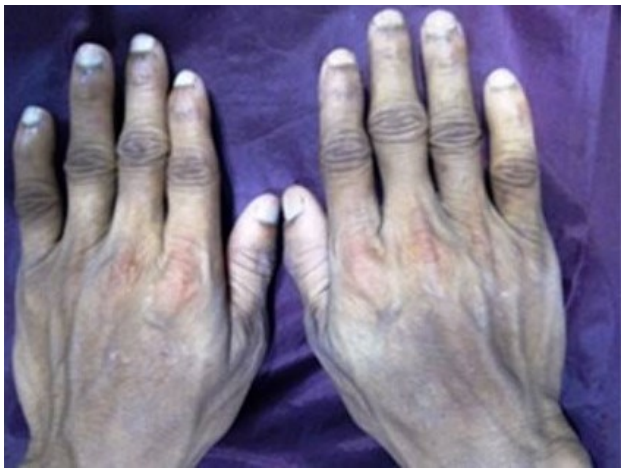
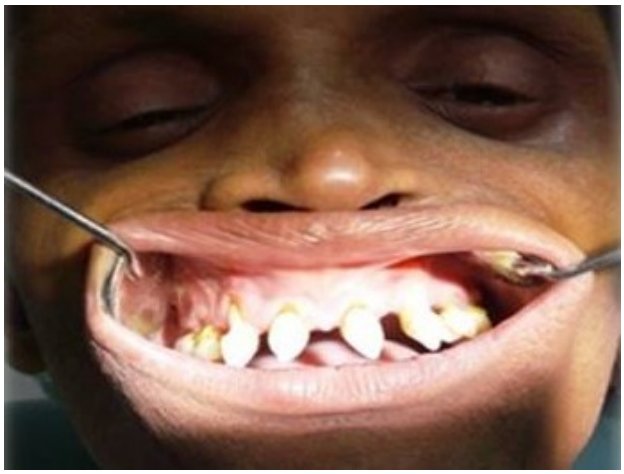


FIGURE 3: *Maxillary hypoplastic peg shaped conical anterior teeth with spacing*



molar present, leading to the underdeveloped mandibular alveolar ridge and a reduced facial height; (Figures-3 and 4) with a high arched palate. The loss of sulcus depth in the posterior regions of maxillary and mandibular jaws (Figures 3 and 4) was also observed. Salivary flow was normal. OPG (Orthopantomogram) (Figure-5) supported the diagnosis of hypohidrotic ectodermal dysplasia. The treatment plan included a removable partial denture for the maxillary missing teeth and an Implant supported denture was suggested for the mandibular arch. Due to the financial constraints, the patient opted for an acrylic based complete denture for the mandibular arch and a partial denture for the maxillary jaw.

DISCUSSION

HED comprises of a triad of signs made up of abnormal (e.g. conical or peg shaped) or missing teeth (anodontia/hypodontia),

FIGURE 4: *A Mandibular arch with just one molar present.*

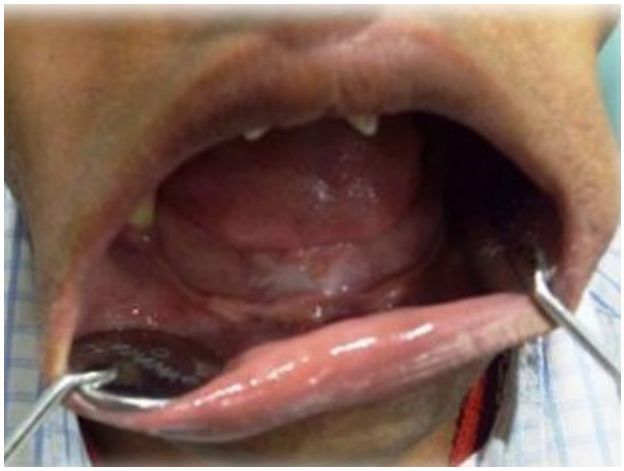
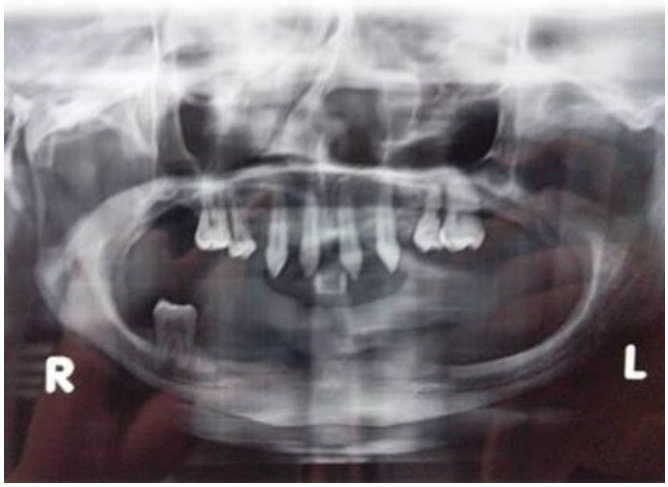


FIGURE 5*: OPG showing oligodontia with the absence of alveolus and conical anterior maxillary teeth in bony crypts*



sparse hair (atrichosis/hypotrichosis) and decreased or absent or lack of sweat glands (anhidrosis/hypohidrosis); that may result in heat intolerance and cause repeated, potentially grave hyperthermic episodes. The skin is dry, scaly thin and eczematous with regional hyperkeratosis. Most of the patients have “dry eyes” in the form of chronic conjunctivitis and blepharitis, dryness of the nasopharynx and bronchitis-like symptoms. It is seen together with characteristic facial features such as a bossing forehead, thin, sparse and fine eyebrows and eyelashes, creases under the eyes and nd typical periorbital hyperpigmentation; a saddle nose, and hypoplastic mandible. Hair pigmentation is often absent or light. The patient is frail. In the X-linked type, the females may be asymptomatic or have a milder affliction that may include conical incisors, oligodontia, moderate hypohidrosis and hypotrichosis. [5]

Signs & Symptoms

The most common forms of ED are the

- X-linked hypohidrotic (Christ-Siemens-Touraine syndrome) and
- Hidrotic (Clouston syndrome) types.

The former shows anodontia or hypodontia, hypohidrosis/ anhidrosis and hypotrichosis, while the latter is more severe, causing palmoplantar keratoderma, nail dystrophy and the hypotrichosis. [10]

Symptoms include

- Abnormal hair,
- Poorly functioning sweat glands,
- Eczema,
- Disfigured nails, and
- Disturbances in the nasal and ear canals.
- The teeth fail to develop properly.
- Skin is smooth, undergoes rashes, which heals slowly.
- Other complications may include loss of sight, hearing deficit, limb abnormalities, mental retardation, cleft lip and palate, and urinary tract anomalies.
- Allergies are common, leading to bronchitis and pneumonia.

The numerous syndromes associated with ED are a combination of these symptoms and include:

- The Rapp-Hodgkin hypohidrotic ectodermal dysplasia: The Rapp-Hodgkin Syndrome, by comparison, is an autosomal dominant disorder
- Ectrodactyly ectodermal dysplasia,
- Ectrodactyly-ectodermal dysplasia-clefting syndrome,
- Trichorhinophalangeal syndrome,
- Oral-facial-digital syndrome,
- Nail dystrophy-deafness syndrome,
- Trichodento-osseous syndrome, and the
- Johanson-Blizzard syndrome. [1]

The ectodermal dysplasias, as a rule, are not pure “one-layer diseases.” Mesodermal and, rarely, endodermal dysplasias coexist.

It is still unclear about what disease should be categorised under the blanket of ectodermal dysplasia, and what should be excluded from it. Many syndromes involve ectodermal structures but are progeroid diseases, i.e. they cause untimely ageing. Others are made up of the congenital absences of a single ectoderm ally derived structure, such as the pituitary. Most researchers do not consider such disorders as ectodermal dysplasias.

Differential Diagnosis

Other types of ectodermal dysplasias need to be considered in the differential diagnosis, and they include the following:

- Witkop tooth and nail syndrome
- Tricho-dento-osseous syndrome
- HED with immunodeficiency caused by pathogenic variants in IKBKG (formerly NEMO), the gene that codes the protein nuclear factor kappa-B (NF-kappa-B) essential modulator
- Ectodermal dysplasia, anhidrotic, with T-cell immunodeficiency caused by pathogenic variants in NFKBIA. [11]

Treatment

Treatment for ED is mainly symptomatic. Over the counter, medicaments may relieve skin discomfort. There is a requirement of dentures, hearing aids, etc. Heat and over- exercising needs to be avoided. Antibiotics and antiseptics are used to reduce infections of the skin and respiratory tract. Cleft palate and lip, limb deformations and syndactyly, are treated by surgery. Genetic counselling is important for Ectodermal Dysplasia patients and their relatives planning to have children. [12]

Patients with ectodermal dysplasias are commonly treated by implants, multiple issues must be considered such as the jaw relationship, the remaining teeth in the arch and their positions, the volume of bone present, and the age of the patient. [13]

CONCLUSION

A multidisciplinary treatment should be given to syndromic patients by professionals, by providing them with a basic and operative treatment. These patients' oral functions need to be completely restored so that they gain confidence to face society.

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