



ANHIDROTIC

ECTODERMAL

DYSPLASIA,

Epidemiology

X-linked hypohidrotic ED (X-LHED) occurs in all racial groups and is thought to have an incidence at birth of approximately 1 in 100,000 males.

ECTODERMAL DYSPLASIAS AT

A GLANCE

- A group of inherited disorders characterized by developmental abnormalities in two or more ectodermal structures.
- These include hair, teeth, nails, and sebaceous and sweat glands.
- There may be abnormalities in non-ectodermal structures and functions.
- Distinction is based on clinical features, mode of inheritance, and molecular findings.
- Clinically distinct disorders may be due to different mutations in the same gene (allelic heterogeneity), and clinically similar conditions may be due to mutations in different genes (locus heterogeneity).

Etiology, Pathogenesis, and Genetics

X-LHED results from alterations in the gene ectodysplasin (EDA, EDA1) located at Xq12-13.⁶ It codes for a transmembrane protein, ectodysplasin, which is composed of 391 amino acids and has

alternative splicing forms, the significance of which is not known. A multitude of mutations in this gene causing X-LHED has been identified. There does not appear to be a correlation between the nature of the mutation and the clinical features⁷ (i.e., to date, there have been no phenotype-genotype correlations). Interfamilial and intrafamilial variation occurs to a mild degree.

Ectodysplasin belongs to the tumor necrosis factor family and plays a role in regulation of the formation of ectodermal structures. It forms trimers and is expressed in keratinocytes, the outer root sheath of hair follicles, and sweat glands. It localizes to the lateral and apical surfaces of cells.

As is typical of X-linked recessive disorders, expression is full blown in affected males, and carrier females may express none, some, or all of the features of the disorder, often in a patchy distribution. The disorder can be inherited from a carrier mother or newly occur in an affected individual as the result of a de novo mutation. Approximately 70 percent of affected males inherited the mutation from a carrier mother. Between 60 percent and 80 percent of carrier females express some clinical signs of the disorder; the most frequent are patchy hypotrichosis and hypodontia

Mutations in an autosomal gene, EDAR, mapped to 2q11-q13, have been implicated in an autosomal dominant form of hypohidrotic ectodermal dysplasia (HED; OMIM #129490) and in an autosomal recessive form (OMIM #224900)

that are clinically similar to X-LHED. Both these entities are much rarer. EDAR acts as a receptor for ectodysplasin . Mutations in yet another gene, EDARADD, have been identified recently in autosomal recessive HED.

EDARADD is an intracellular adaptor protein that assists in transmitting the signal from the activated EDA receptor to the nucleus of the cell. Individuals with autosomal dominant HED appear to have a milder defect in the ability to sweat.

Certain mutations in the X-linked NEMO gene, which causes incontinentia pigmenti (IP) in females, have been shown to result in males with HED and immune defects

Clinical Manifestations

DERMATOLOGIC

Affected males may present at birth with a collodion membrane or with marked scaling of the skin, ¹³ similar to congenital ichthyosis. Scalp hair is usually sparse, fine, and blonde. It may thicken and darken at puberty, and secondary sexual hair may be normal. Other body hair is usually sparse or absent.

The ability to sweat is significantly compromised, and most affected males have marked heat intolerance. Sweat pores are usually undetectable on physical examination, and fingerprint ridges are effaced. The inability to sweat adequately in response to environmental heat results in an elevation of core temperature and bouts of unexplained high fevers, usually leading to an extensive workup for infectious disease, malignancy, or autoimmune disease before the correct diagnosis is recognized. In an older series of patients, mental retardation was reported as a feature of X-LHED. Currently, this is believed to have been due to damage from prolonged high fevers and convulsions and not to be an intrinsic feature of the disorder.

The nails are usually normal; reports of thin, fragile nails are not convincing, and nail dystrophy plays little role in the burden of the disorder.¹⁴ Periorbital wrinkling and hyperpigmentation are typical and often present, albeit unappreciated, at birth. Eczema plagues more than two-thirds of affected males and is often difficult to manage. Hyperplasia of sebaceous glands, particularly on the face, can develop over time and appear as small, pearly, flesh-colored to white papules that may resemble milia.

SYSTEMIC ASSOCIATIONS

Hypodontia, oligodontia, or anodontia are invariable features of X-LHED in affected males. Appreciation of hypoplastic gum ridges in an affected infant can be an early clue to the diagnosis of the disorder. Teeth that do erupt are usually peg-shaped and small . The fa
cies
of the disorder are characterized by frontal bossing and a depressed midface with a

saddle nose and full, everted lips. Otolaryngologic manifestations include thick nasal secretions and impaction, ozena, sinusitis, recurrent upper respiratory tract infections and pneumonias, decreased saliva production, hoarse voice, and an increased frequency of asthma.

Gastroesophageal reflux and feeding difficulties may be a problem in infancy. Preliminary studies suggest that there may be failure to thrive in infancy and early childhood in as many as 20 percent to 40 percent of affected boys, with catch-up growth seen later.

Although several reviews have suggested that infant mortality may be increased, unbiased confirmatory data are lacking.

Female carriers for X-LHED may be affected as severely as males or show few, if any, signs of the disorder . Heat intolerance, if present, is usually mild; adult carrier women comment that they do not sweat much or that they do not like very warm weather, but it is unusual for a female to experience fever due to inability to sweat. Typically, a few teeth may be peg-shaped or missing and scalp hair may be patchy or thin. Careful examination of the skin of carrier females often reveals a diminution in or patchy distribution of sweat pores. This sometimes can be appreciated readily just by magnification of fingertip pads or may require more sophisticated sweat testing.

VARIANTS

As noted in Etiology, Pathogenesis, and Genetics, the autosomal dominant and autosomal recessive forms of HED are similar, although the autosomal dominant form may be milder. The X-linked form is by far the most common and always should be the diagnosis of default in a sporadic case.

Histopathology

The epidermis is thinned and flattened. There is a reduction in the number of sebaceous glands and hair follicles. Eccrine glands are absent or incompletely developed. Histologic evaluation of the skin is usually not necessary.

Diagnosis and Differential Diagnosis

The scaling skin at birth may result in a misdiagnosis of congenital ichthyosis. Repeated bouts of fever may be thought to have an infectious source. The diagnosis of HED is recognized readily when expected, such as when an at-risk male is born into a family in which the disorder is known to segregate. Examination for sweat pores and a Panorex view of the jaw leads quickly to the correct diagnosis. In an isolated, fully expressing female, the autosomal dominant and recessive forms of HED need to be considered. Family history, examination of parents, and molecular testing may be helpful. Mothers always should be examined fully to detect mild manifestations of the X-linked form. Molecular testing is not indicated for clinical diagnosis in most instances.

Treatment

Maintenance of cool ambient temperatures is vital to prevent hyperpyrexia. Most children do well with simple measures, such as wet T-shirts, air conditioning in home and school, wet head-bands, etc. Occasionally, cooling vests allow a broader range of participation in sports and vigorous physical activity in warm climates.

Dental restoration is of primary importance, and early implementation of dentures and ultimate use of dental implants are mainstays of treatment.

Management of otolaryngologic complications, asthma, and recurrent infections

needs to be individualized. The eczema may be quite refractory to care.

The National Foundation for Ectodermal Dysplasias (<http://www.nfed.org>) has several pamphlets for individuals and professionals dealing with diagnosis and treatment.

Although infancy and childhood are complicated by many problems, most individuals with HED lead adult lives that allow them to function successfully in society. Heat intolerance seems to decrease due to the development of some ability to sweat in adolescence or to the development of common sense and adaptation of lifestyle, or both.