Ectodermal dysplasia anhidrotic

Authors: Doctor Kathleen Mortier[1,2], Professor Georges Wackens[1]
Creation date: September 2004

Scientific Editor: Professor Antonella Tosti

[1]Department of stomatology and maxillofacial surgery, AZ VUB Brussels, Belgium. [2]kathleen.mortier@tiscali.be

Abstract
Ectodermal dysplasias (EDs) are a heterogeneous group of disorders characterized by developmental dystrophies of ectodermal structures. The X-linked recessive ED (Christ-Siemens-Touraine syndrome) is the most common disordere (80%of EDs); it affects males and is inherited through female carriers. It is characterized by the triad of signs comprising sparse hair (atrichosis or hypotrichosis), abnormal or missing teeth (anodontia or hypodontia) and inability to sweat due to lack of sweat glands (anhidrosis or hypohidrosis). The lack of teeth and the special appearance were reported to be major concerns. The incidence in male is estimated at 1 in 100,000 births, the carriers-incidence is probably around 17.3 in 100,000 women
Most patients with EDA have a normal life expectancy and normal intelligence. However, the lack of sweat glands may lead to hyperthermia, followed by brain damage or death in early infancy, if unrecognized. Thus an early diagnosis is important. Families with EDA should therefore be offered genetic counseling. Currently the genes and gene products are defined, but the function of the proteins is not fully known. Once the exact function is known, we can understand the embryogenesis and morphogenesis of the ectodermal structures. It is quite possible that these kinds of observations of gene function and interaction may form the basis of new therapeutic methods in the future.
For the patients as well as the dentists tooth agenesis and its secondary effects on growth and development of the jaws is often the most significant clinical and therapeutical problem. The course of the treatment is to restore the function and the aesthetics of the teeth, normalise the vertical dimension and support the facial soft tissues.

Keywords
Ectodermal dysplasia; tooth agenesis; Christ-Siemens-Touraine syndrome, atrichosis, hypotrichosis, anodontia, hypodontia, anhidrosis, hypohidrosis

Disease name and synonyms
Ectodermal dysplasia anhidrotic (EDA)
Anhidrotic ectodermal dysplasia
Hypohidrotic ectodermal dysplasia (HED)
Christ-Siemens-Touraine syndrome

Definition

Ectodermal dysplasias (EDs) are a heterogeneous group of disorders characterized by developmental dystrophies of ectodermal structures, such as

hypohidrosis, hypotrichosis, onychodysplasia and hypodontia or anodontia.

About 160 clinically and genetically distinct hereditery ectodermal dysplasias have been catalogued (Pinheiro and Freire-Maia, 1994). Anhidrotic (hypohidrotic) ectodermal dysplasia (EDA) is the most common ED (80%); it is characterized by hypoplasia of hair, teeth and sweat glands. (Mc Kusick, 1994). In this overview the major medical problems and genetic aspects of the EDA will be presented. Since there is not a complete lack of sweat glands the term hypohidrotic is more adequate than anhidrotic. The anhidrotic (hypohidrotic) ectodermal dysplasia is often inherited as an X-linked disorder (XLEDA).

Diagnosis criteria

This X-linked recessive disorder affects males and is inherited through female carriers. The diagnostic tool is the typical clinical physionomy.

The most characteristic findings in man are the reduced number and abnormal shape of teeth. The delay in teethening is often the first step in the diagnosis. The men have an easily recognizable facies, also referred to as an 'old man' facies. Some infants have a premature look with scaling of the skin. This can also form a clue to the diagnosis. The number of sweat glands is reduced and both scalp and body hair are sparse, with lack of eyebrows and eyelashes. The carrier female has some phenotypic expressions. The clinical findings in carrier females are the same as those in affected males. One third of the carriers appears healthy, another third of them is showing mild symptoms, and the last third exhibits significant symptoms, but often milder than the affected males (Sofaer et al. 1981).

Differential Diagnosis

The differential diagnostic problem is the distinction of the autosomal recessive form of HED (AR-HED) from X-linked HED. AR-HED is considerably less common than XLHED. The clinical features are quite similar in both conditions but due to the different mode of inheritance AR-HED affects both males and females and the heterozygotes have no signs at all. For adequate genetic counseling it is thus important to recognize XLHED heterozygotes by dental examination and sweat tests. To distinguish between AR- and XL-forms, the HED diagnosis should be followed by careful family history for ectodermal manifestations both in male and female and by tests for heterozygote identification. The findings of equally affected males and females in single sibships, as well as the presence of consanguinity, support an autosomal recessive mode of inheritance (Munoz et al 1997).

Etiology and Genetics

All the ectodermal dysplasias appear to be genetic in etiology. However, only a small number of ED genes has been genetically mapped or cloned. A little less than a hundred years after Darwin's discussion, the gene for EDA was the first X-chromosomal gene whose map position was suggested, based on the occurrence of an X; autosome translocation in a female patient ("Anly") with the disease phenotype. Later linkage studies confirmed the suggested position of the gene at Xq12-q13.1 (*XLHED*-gene) (Kere et al 1996). The localisation of the gene has permitted more accurate diagnostics of the disorder, both in carrier females and in prenatal screening. The discoveries of disease genes and the identification of mutations in patients represent great progress in biomedical science. In order to help patients suffering from the diseases it is obviously not enough that the gene defects are known. It is necessary to understand the context in which genes function and the details of the biological processes where they are involved.

The recent cloning of the gene has led to the identification of a novel transmembrane protein "ectodysplasin" (TNF family ligand) and receptor "edar" (TNF receptor). This TNF ligand and receptor have a developmental regulatory role and are tightly associated with epithelial-mesenchymal interactions and signaling pathways that regulate ectodermal appendage formation and organogenesis during the initiation of development (Laurikkala et al. 2001).

The next step in research, the analysis of the function of the genes and the effects of gene mutations will be a challenge for researchers for many decades to come, and this can be expected to result in the development of new therapeutic methods. It is quite possible that these kinds of observations of gene function and interaction may form the basis of new therapeutic methods in the future.

Clinical Features

EDA is characterized by the triad of signs comprising sparse hair (atrichosis or hypotrichosis), abnormal or missing teeth (anodontia or hypodontia) and inability to sweat due to lack of sweat glands (anhidrosis or hypohidrosis). The lack of teeth and the special appearance were reported to be major concerns.

Most patients with EDA have a normal life expectancy and normal intelligence. However, the lack of sweat glands may lead to hyperthermia,

followed by brain damage or death in early infancy, if unrecognized. Thus an early diagnosis is important. Families with EDA should therefore be offered genetic counseling.

Craniofacial structures

Considering how much osseous and dental tissue is missing, these patients have surprisingly normal facial structures.

Already in 1936, Tannhauser stated that the characteristic deformity of the cranial bones of all affected patients is such that the resemblance among the patients is bigger than when compared with their own unaffected sib (Bergendal et al. 1998).

Clinically, the forehead appears square, with frontal bossing, and there is a prominent supra-orbital ridge. The nose has a depressed nasal bridge and is called a saddle nose. The midface is depressed and hypoplastic, giving it a “dished-in” appearance. The cheekbones are high and broad, although they appear flat and depressed as well. The chin may be pointed and the lips everted and protuberant (Johnson et al. 2002).

In non-treated patients with EDA, craniofacial deviations from the norm increased with advancing age (Clarke et al. 1991) with a tendency toward a Class III pattern with anterior growth rotation (Bondarets et al., 1998). Cephalometric analysis and anthropometry studies have been performed. The quantitative findings show reduced facial dimensions, decreased lower facial height, variable pattern in facial widths, the maxilla has been relatively more retruded than the mandible, the nasal alar width and mouth width were significantly smaller (Sforza et al. 2003).

This remarkable variability in facial dimensions and harmony found in patients with ED probably corresponds to the different kinds of dysplasia, with different expression of the interested genes (Ruhin et al. 2001).

Oral structures

Missing teeth or the delay in teething often starts to worry the parents and leads to the diagnosis of EDA in the second year of life (Pirinen et al. 1996). A dentist should not hesitate to radiographically examine a patient whose teeth have not erupted by the appropriate age in order to exclude EDA. The screening limit for the first tooth to erupt is 15 months ((Pirinen et al. 1996).

Besides the delay in teething, the teeth appear radiagraphically abnormal in shape and structure. The enamel layer is thin and the cervical area of the tooth is constricted. Enamel is rarely hypoplastic (Bergendal et al. 1998). If at that stage aplasia of several teeth is seen, the patient should be referred to a geneticist in a paediatric unit with a suspescion of EDA diagnosis.

Tooth crowns are small and abnormal in shape. Upper incisors and cuspids are always conical or pointed.

Taurodontism, frequently on the second deciduous molars, is a common feature .Not only the shape is abnormal, but also the number. A severe hypodontia is a universal feature amongst affected individuals. All lacked some deciduous teeth and permanent teeth. The number varies from four to twenty. A few patients have congenital anodontia. There are generally more teeth in the maxilla than in the mandibula, although both jaws can be toothless (Aswegan et al. 1997). Most often the lower incisors and premolars are missing, followed by the upper premolars and incisors. The upper cuspids and first upper and lower molars are formed.

The edentulous EDA patients do not have any alveolar processes either (Söderholm and Kaitila, 1985). In those patients with some natural teeth, there is a striking difference in the intra-oral height and breadth of the bone.

In areas where no teeth have developed, the alveolar bone is missing and the bone ridge is very thin in contrast to the normal alveolus surrounding an occasional tooth.

Many patients complain of dry mucous membranes in mouth and nose. Reduced salivary secretion has been spotted in some EDA patients (Söderholm and Kaitila, 1985). The oral mucous glands should be missing in the lips. Autopsy has also shown absence of mucous glands in the pharynx, larynx, trachea and bronchi. This is in agreement with the susceptibility to respiratory infections. The other salivary glands are not described in literature. Analysis of the saliva has revealed a reduced buffer capacity and an increased number of bacterial cultures. Most affected individuals were susceptible to dental caries (Aswegan et al. 1997).

Hair, nails, skin and skintags

Abnormalities of hair are present in all affected individuals. Most individuals have sparse, fine, slowly growing scalp hair. Some individuals are completely bald by their middle teens, whereas other individuals have normal amounts of scalp hair, though it may exhibit an abnormal texture. Sparse eyebrows and eyelashes were always found. Most individuals show decreased body hair, pubic hair,

and/or axillary hair, but these features are more variable. However, beard and moustache hair are normal. Electron microscopy of hairs from affected and unaffected individuals showed no abnormalitites.

About half of the affected individuals exhibit mild fingernail abnormalities and nail dystrophy. Slow nail growth and split nails are most often reported. A few individuals had a longitudinal ridging, thinning and superficial peeling. Nail problems occur more frequently in older individuals. This suggests that the nail beds are more susceptible to progressive injury with age. Toenails were generally normal.

Most individuals report dry skin. Affected individuals have a smooth, almost velvety skin texture. The skin of patients also seems to be “thinner” than expected for age. Some infants may have a premature look because of the thin skin. Scaling in the neonate may form a clue to diagnosis.

Almost all affected relatives have decreased sweating, and many show heat intolerance. Some individuals only sweat in certain areas on their body. Common sites of sweating include palms, soles and axillae (Aswegan et al. 1997). Because of the reduced number of sweat glands, there is a danger of hyperthermia. In this way EDA has been associated with sudden infant death. The hyperthermia may also lead to brain damage, and is probably the cause of the rare cases of EDA reported with mental retardation. Subcutanuous fat is often diminished and over one third of the boys have abnormalities of the breast, including absent or accessory nipples (Goodship et al., 1990).

Episodes of hyperpyrexia and severe respiratory infections are life-threatening components in EDA. The delay in teething often leads to the diagnosis in childhood. After the first critical years of life the patients experience a general improvement in health. The lack of teeth is the most important factor in determining the quality of life in these patients, particularly in later life. They all suffer greatly from their abnormal facial and dental appearance.

Epidemiology

The prevalence of EDA is unknown; however, the incidence in male is estimated at 1 in 100,000 births although the condition is usually overlooked in infants (Bergendal et al. 1998). This X-linked recessive disorder affects males and is inherited through female carriers. This carriers-incidence is probably 17.3 in 100,000 women (Sofaer 1981) -. The autosomal dominant and autosomal recessive inheritance EDA is an extremely rare condition.

Genetic Counseling

Because of the importance of an early diagnosis, families with X-linked EDA should be offered genetic counseling. This implies a calculation of the risk of having an affected child. For genetic counseling the diagnosis of female carriers is very important. The advantage of diagnosing female carriers of EDA includes the optimisation of neonatal and paediatric care for affected male infants, who may be at substantial risk of death in infancy. There is substantial mortality and morbidity in male infants, with about 30% dying in the first two years of life, because of fever or a chest infection (Clarke and Burn, 1991). So it is important for carrier females to be aware of their 1/4 risk of having an affected child , for the sake of their child’s health. For the calculation of the risk for a particular female to be a carrier, both clinical and pedigree information are necessary.

Phenotypic tests, however, are still of practical importance in genetic counseling. Signs of EDA are found in about 70% of obligate carriers. In most cases, it is difficult to place much weight upon subjective assessments of scalp hair density, heat intolerance, breast feeding difficulties or the appearance of the eyebrows. So the most significant finding is hypodontia, which is easily recognized. There is also a greater tendency for abnormal crown form and smaller tooth size in carrier females. Without accurate information regarding past extractions, it is impossible to be certain which teeth were congenitally absent. Dental radiographs can provide useful additional information and can be a simple screening test for the carrier status. Certainly, in cases of uncertain diagnosis there is a correlation between the hypodontia and the result of the sweat tests.

Two methods of assessment of sweating have been developed to identify possible female carriers. The first sweat test is performed on the backs of the carrier female and gives a V-shaped pattern of streaks that refers to the lines of Blaschk (Clarke and Burn, 1991).

The other method of assessing sweat pores in female carriers is to make counts of the sweat pores along ridges on the fingertips or palms, but there are methodological difficulties.

The size of the patches is variable and to count sweat pores where they are clearly visible will bias the results obtained. Patches of skin where the ridges appear flattened and the pores reduced may be caused by domestic labour or by pure quality application (12. Such considerations have led us to favour the first method of assessing sweating, by performing sweat tests on the whole back of the

subjects in search of patchiness that might follow the lines of Blaschko. The test is regarded as positive if several areas of at least 1 cm diameter are clear of active sweat glands, by an asymmetry between the two sides or if a complete absence of sweating is found. If it gives a clearly abnormal result, then one can be fully confident of its accuracy. The results seem clear cut, but unfortunately the interpretation of the sweat test is inherently subjective. The value of the test is limited due to temporary functional differences of sweat glands (a patchy pattern may also be present in normal individuals). Secondly, the density of sweat pores may vary among normal individuals and a low mean number may lead to false results. Combination of both dental examination and sweat testing enhances clearly the chances of making a correct diagnosis, namely of identifying female carriers of XLHED. In a substantial number of carriers no signs of EDA are found. The calculation of the risk of being a carrier may then be based on the family history and pedigree information. The mapping of a gene for X-linked EDA has given new possibilities for the detection of carriers of XLHED by molecular genetics (Zonana et al., 1992). The gene locus of EDA has been mapped to proximal Xq and close flanking markers are available. This often allows female carriers in a family to be identified with a high degree of accuracy. Even if DNA diagnosis is feasible, it is not yet available as a service in most centres and will continue to be expensive and thus unattractive for the foreseeable future.

Prenatal Diagnosis

Prenatal diagnosis of EDA has occasionally been reported. The diagnosis has been made on fetal skin biopsy, obtained by fetoscopy by 20 weeks gestation after determination of the sex of the fetus (Bergendal et al., 1998). By histological analysis they demonstrate of either complete lack of, or reduction in, the number of pilosebaceous follicles and by the lack of sweat glands primordia in multiple skin biopsis (Pirinen, 1996). The interpretation of the biopsis can be difficult if one does not appreciate the normal regional variability of the distribution of skin appendages of fetal skin, and that sweat gland primordia only begin to develop at around 20 week gestation. This procedure is complicated and implies a considerable risk to the pregnancy.

The use of linked markers on DNA from chorionic villi has greatly improved the safety of prenatal diagnosis of X-linked EDA. This new method of prenatal diagnosis has major advantages as well as disadvantages. It permits the diagnosis to be made in the first trimester of pregnancy prior to the development of the affected structures, thereby allowing an early determination of an affected pregnancy. It is technically simpler and may present a lower risk to the pregnancy than the fetoscopy and multiple skin biopsies. Disadvantages to a linkage based indirect analysis include the need for the sampling of previously affected individuals. The counseling of families is more complex since one is dealing with the probabilities of an affected fetus, rather than a more definitive diagnosis based on direct observation. However, these statistical concepts are difficult for many families to comprehend fully.

The identification of mutations in the family will further improve the accuracy of prenatal diagnosis (Kere et al. 1996). However, EDA is a disorder which in most cases is associated with a normal life expectancy and a normal intelligence. Prenatal diagnosis will therefore probably not be an option in most families with EDA.

Treatment

Children with ectodermal dysplasia present many and different clinical problems from early childhood through adolescence and also present a life-long need for maintenance care and revisions. For the patients as well as the dentists tooth agenesis and its secondary effects on growth and development of the jaws is often the most significant clinical problem. The course of the treatment is to restore the function and the aesthetics of the teeth, normalise the vertical dimension and support the facial soft tissues. As long as there are no physical, psychological or social burdens, no treatment is necessary. Early placement of partial or full dentures is commonly recommended from the age of two or three years onwards. The denture must be periodically modified as alveolar growth, erupting teeth and rotational jaw growth change both the alveolar, occlusal and basal dimensions. In children, breakage and even loss of removable protheses is quite common. They have also a limited retention and stability, a fastened bone destruction of an already hypoplastic alveolar process and the middle of the upper jaw is covered and so it blocks the sutural growth. For this reason, in young children we prefer a treatment with crowns and bridges.

Prior to that it is generally advantageous to modify the crowns of the existing teeth with direct or indirect composite crowns. When conical anterior teeth are crowned the appearance of the child is very much normalised. Restauration of facial height improves both facial aesthetics and speech.

Impaired salivary secretion rates constitute an increased risk for dental diseases, namely caries. The fragile oral mucosa may affect the clinical situation as well as the possibilities to wear removable protheses.

It is commonly agreed that osseo-integrated implants should be not placed before cessation of growth. Even in young adults, alveolar growth can be remarkable. In EDA boys, the situation is different as no alveolar growth takes place in the totally edentulous areas of the mouth. There are several published cases of early implant placement in toothless EDA patients; the success, however, has been variable (Bergendal et al. 1998).

References

Aswegan A.L., Josephson K.D., Mowbray R., Pauli R.M., Spritz R.A., Williams M.S.: Autosomal dominant hypohydrotic ectodermal dysplasia in a large family. Am. J. Med. Genet. (1997) 72: 462-467

Bergendal B., Koch G., Kurol J., Wänndahl G.: Consensus conference on ectodermal dysplasia with special reference to dental treatment. The Institute for Postgraduate Dental Education, Jönköping, Sweden (1998)

Bondarets N., Jones R.M., McDonald F.: Analysis of facial growth in subjects with syndromic ectodermal dysplasia: a longitudinal analysis. Orthod. Craniofac. Res. (2002) 5: 71-84

Clarke A., Burn J.: Sweat testing to identify female carriers of X-linked hypohidrotic ectodermal dysplasia. J. Med. Gen. (1991) 28: 330-333

Goodship J., Malcolm S., Clarke A., Pembrey M.E.: Possible genetic heterogeneity in X-linked hypohidrotic ectodermal dysplasia. J. Med. Genet. (1990) 27: 422-425

Johnson E.R., Roberts M.W., Guckes A.D., Bailey L.J., Phillips C.L., Wright J.T.: Analysis of craniofacial development in children with hypohidrotic ectodermal dysplasia. Am. J. Med. Genet. (2002) 112: 327-34

Kere J., Srivastava A.K., Montonen O., *et al*.: X-Linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein. Nature Genetics (1996) 13: 409-416

Laurikkala J., Mikkola M., Mustonen T., *et al*.: TNF signaling via the ligand-receptor pair ectodysplasin and edar controls the function of epithelial signaling centers and is regulated by Wnt and Activin during tooth organogenesis. Dev. Biol. (2001) 229: 443-455

McKusick V.A.: Mendelian inheritance in man. The John Hopkins University Press, Baltimore, 11th edition (1994)

Munoz F., Lestringant G., Sybert V., *et al*.: Definitive evidence for an autosomal recessive form of hypohidrotic ectodermal dysplasia clinically indistinguishable from the more common X-linked disorder. Am. J. Hum. Genet. (1997) 61: 94-100

Pinheiro M., Freire-Maia N.: Ectodermal dysplasias: a clinical classification and a causal review. Am. J. of Medicinal Genet. (1994) 53: 153-162

Pirinen S. In: Meurman, Murtomaa, LeBell, Autti, Luukkanen (eds): Therapia Odontologica. Academica Kustannus Oy, Helsinki (1996) p. 414

Ruhin B., Martinot V., Lafforgue P., Catteau B., Manouvrier-Hanu S., Ferri J.: Pure ectodermal dysplasia: retrospective study of 16 cases and literature review. Cleft Palate Craniofac. J. (2001) 38: 504-18

Sforza C., Dellavia C., Vizzotto L., Ferrario V.F.: Variations in facial soft tissues of Italian individuals with ectodermal dysplasia. Cleft Palate Craniofac. J. (2003) 41(3): 62-67

Söderholm A.L., Kaitila I.: Expression of X-linked hypohidrotic ectodermal dysplasia in six males and in their mothers. Clin. Gen. (1985) 28: 136-144

Sofaer J.A.: A dental approach to carrier screening in X-linked hypohidrotic ectodermal dysplasia. J. Med. Genet. (1981) 18: 459-460

Zonana J., Jones M., Browne D., *et al*.: High-resolution mapping of the X-linked hypohidrotic ectodermal dysplasia (EDA) locus. Am. J. Hum. Gent. (1992) 51: 1036-1046