ANHIDROTIC OR HYPOHIDROTIC ECTODERMAL DYSPLASIA

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Abstract :

Anhidrotic or hypohidrotic ectodermal dysplasia is a rare congenital disease that affects several ectodermal structures and is characterized by anhidrosis or hypohidrosis, dental anomalies, hypotrichosis, prominent frontal bosses, supra orbital ridges and depressed bridge [1]. In this clinical report we describe the characteristics of anhidrotic ectodermal dysplasia (EDA) in six patients. EDA is inherited either as X-linked recessive, autosomal recessive or autosomal dominant. Four of the six reported patients have autosomal recessive mode of inheritance and two autosomal dominant (Clouston's disease).

Case Report :

First patient:

M.A.Y.A. a Qatari female born on 1980 after full term normal vaginal delivery from parents of first cousin relation. As a child she suffered from heat intolerance - no sweating, halitosis, purulent nasal discharge, recurrent attacks of respiratory infections and asthma, flexural eczema and anodontia. She had low growth having had at age of 5 years, the height of 2 years and at the age of 15 years the height of 11 years. Her intelligence is normal. At age of 6 years she had orthodontic treatment with insertion of branemack titanium implants to the mandible to help retain prosthesis and preserve alveolar bone. She was seen in the dermatology clinic at age of 15 years when she showed - sparse wiry scalp hairs, frontal bosses, sparse hairs of eye brows and eye lashes. She had wrinkled dark lower lids, satyr ears, saddle nose, thick everted lips, artificial teeth, very dry nearly hairless skin all over the body, no sweating and her nails were normal (Fig.1-4). Her growth was below normal and was still suffering from halitosis and recurrent attack of respiratory infection. She has been diagnosed as a case of autosomal recessive anhidrotic ectodermal dysplasia.

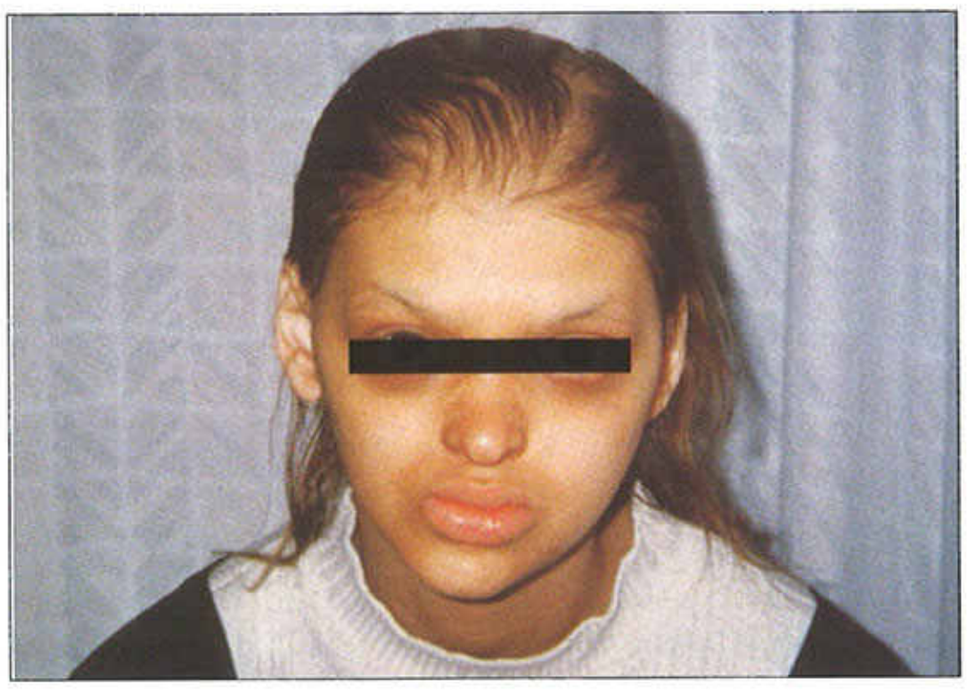

Fig. 1

Second Patient :

Moh. A.Y.A. a brother of the first case - born on 26.9.1985 after normal pregnancy and delivery . He was seen by us at the age of 10 years. He gave the same history as his sister. On examination he had stunted growth, he had sparse hairs of scalp eyebrows and eye lashes ñ he had receding maxilla and protruding lower jaw. He had complete anodontia, - skin was dry, no sweating and hairless skin all over the body (Fig.5-8).

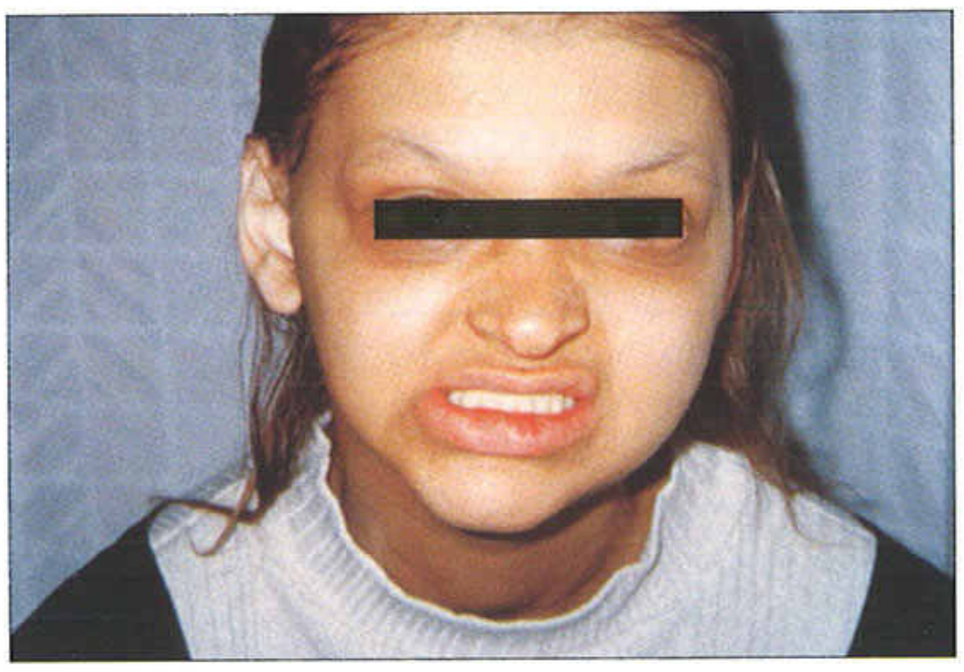

Fig. 2

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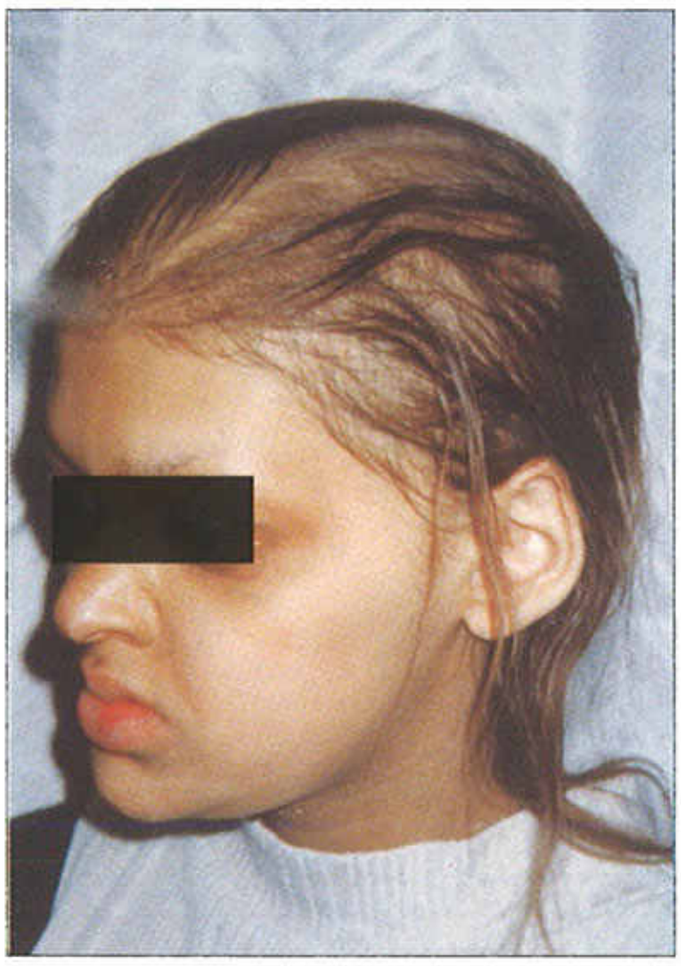

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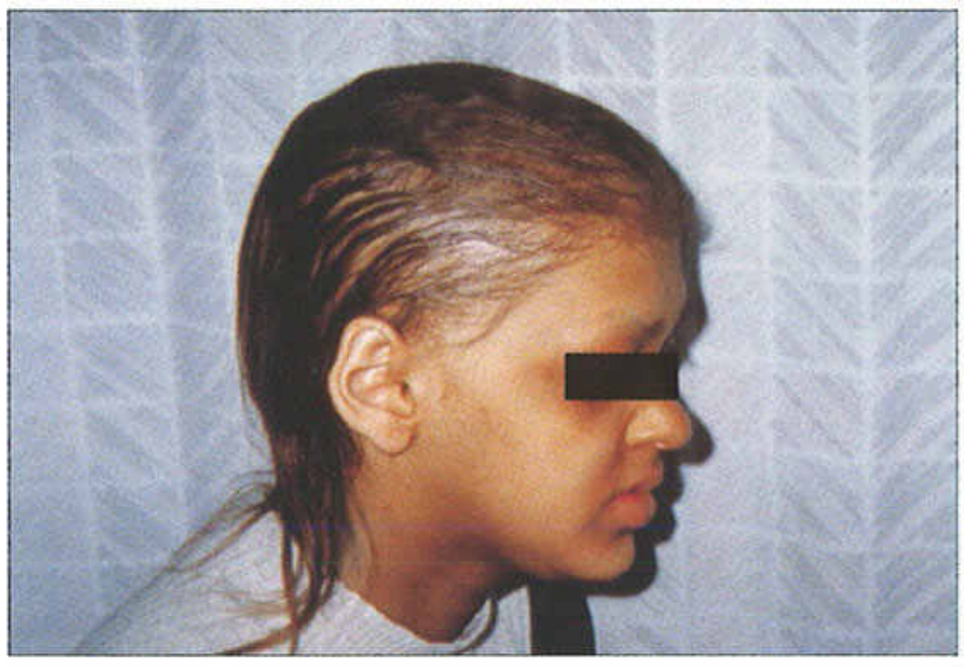

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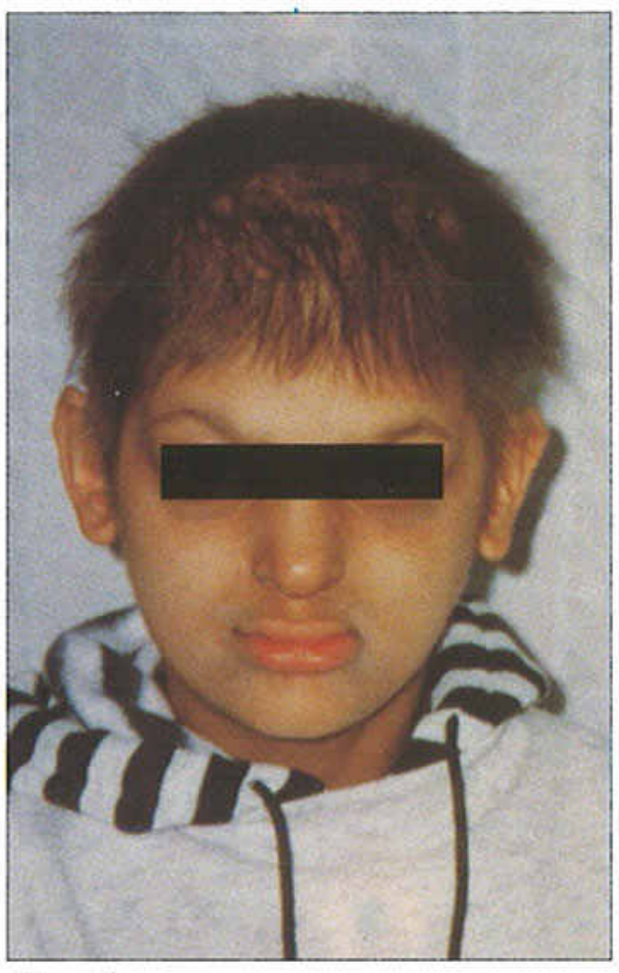

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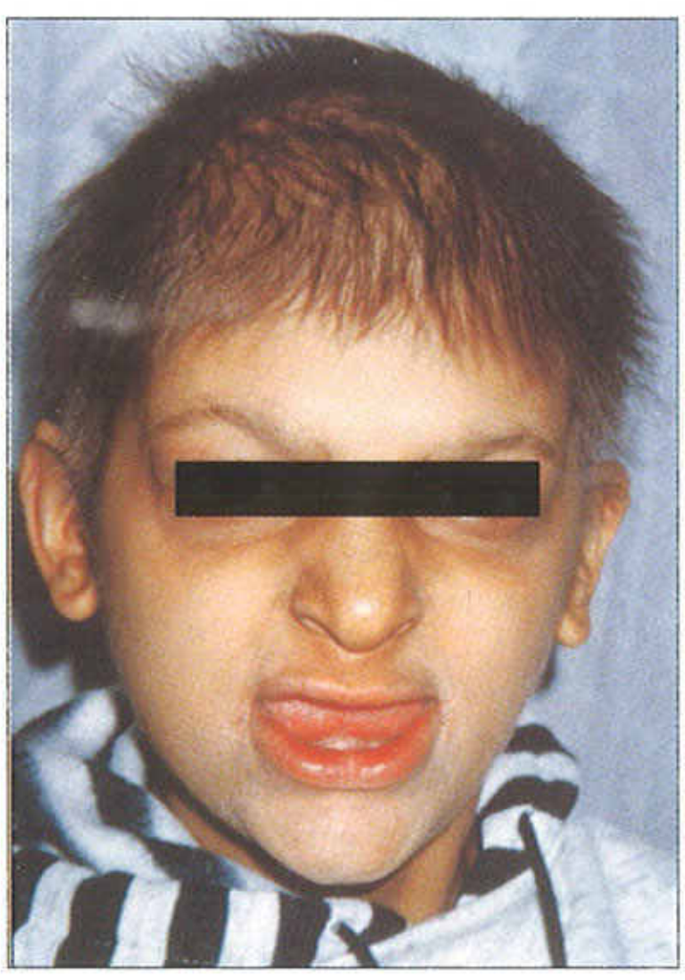

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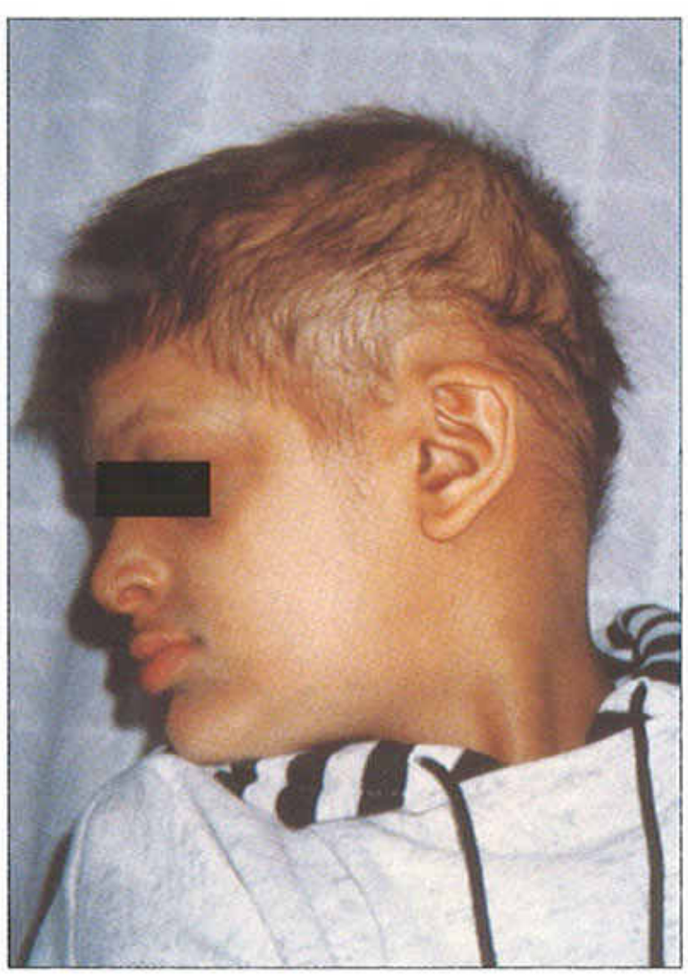

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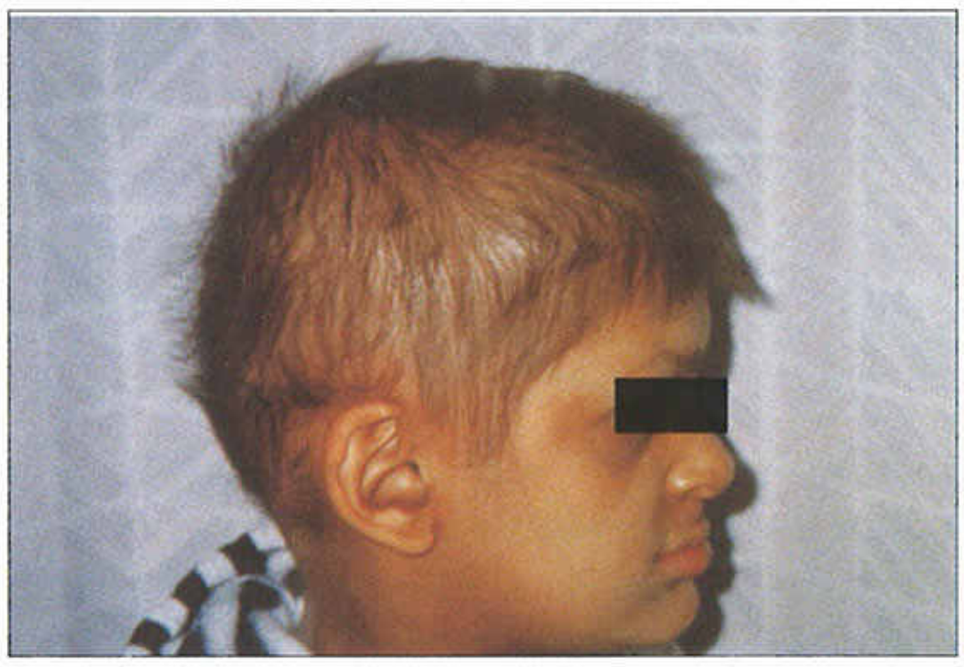


Fig. 8

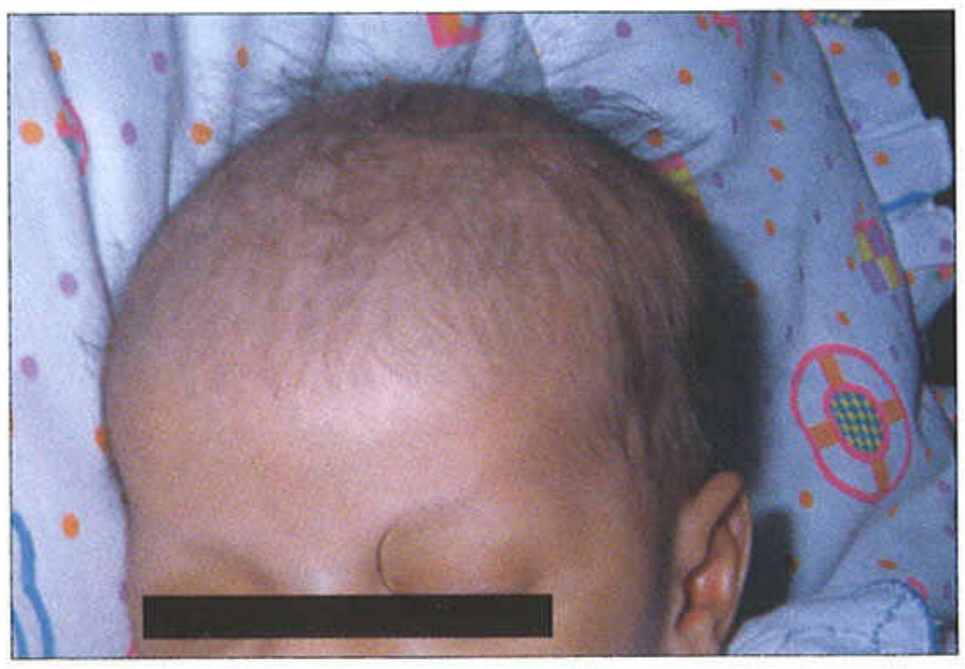
Skin biopsy was done on 6.1.1986 with the report H/21/86 describing no pilosebaceous follicles and occasional sweat glands which show severe atrophy.

Third case :

A Qatari girl who was admitted in the pediatric department because of fever of unknown aetiology. Anhidrotic ectodermal dysplasia was suspected and a dermatologist saw the infant who showed sparse hairs of scalp, broad forehead, saddle nose, dark haloes around eyes, protruding everted lips and there were no nail changes (Fig. 9-12). Skin biopsy confirmed the diagnosis of congenital anhidrotic ectodermal dysplasia.

Fourth Case :

M.B. a female Sudani was admitted in pediatric department at the age of four months because of fever of unknown cause. She is a product of consanguineous marriage and was born on April 1994 af-



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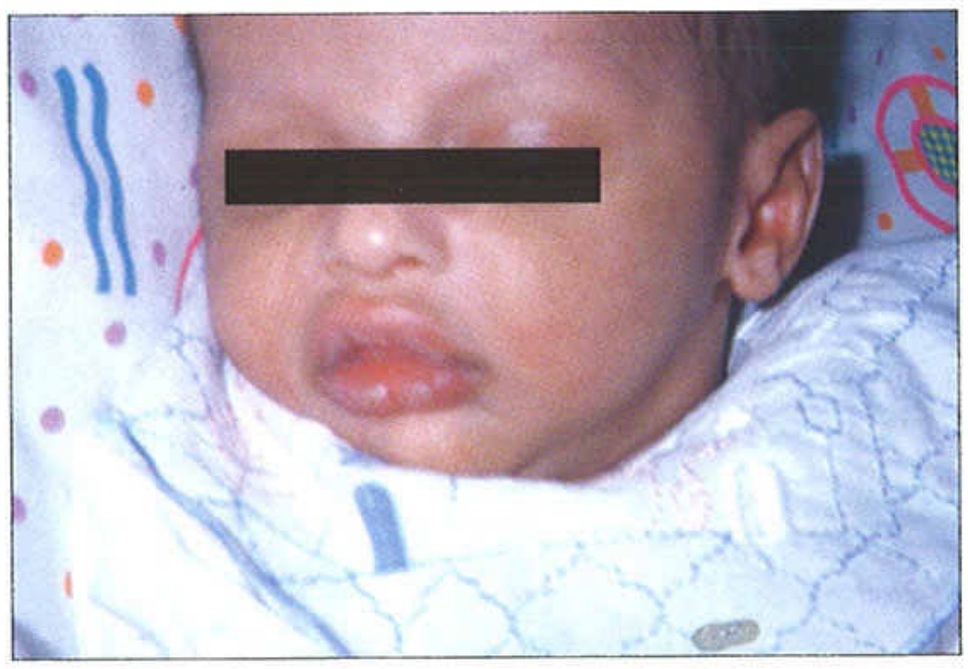

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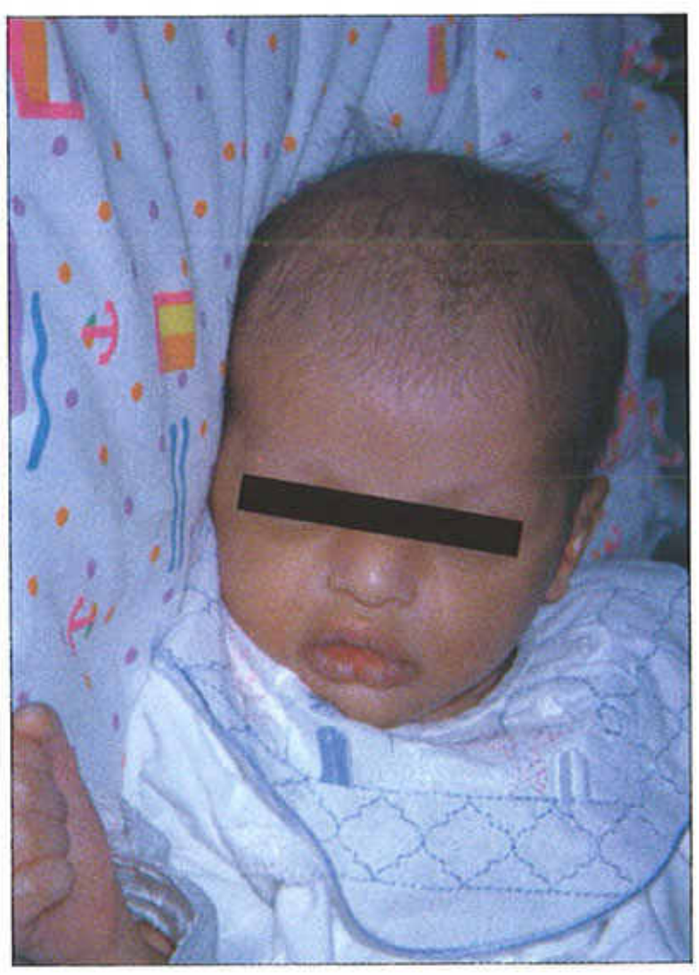

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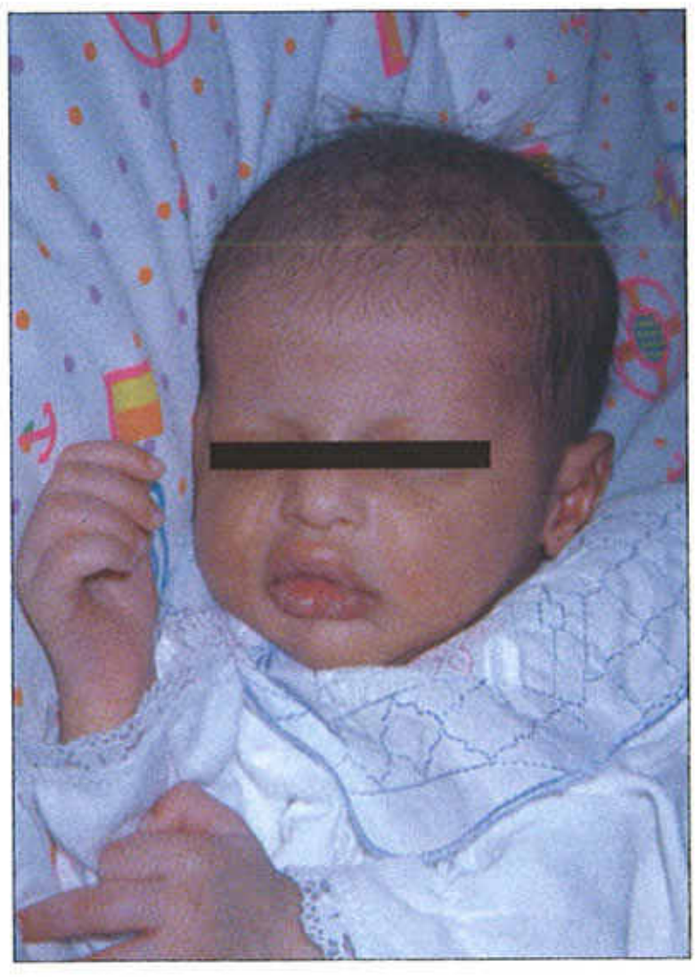


Fig. 12

ter a normal delivery. She was seen by a dermatologist who suggested the diagnosis of anhidrotic ectodermal dysplasia. She had frontal bosses and was suffering from hypotonia (Fig. 13, 14). Two skin biopsies were taken from right and left scapular region. She was admitted again at the age of 17 months because of fever, hypotonia and chest infection.

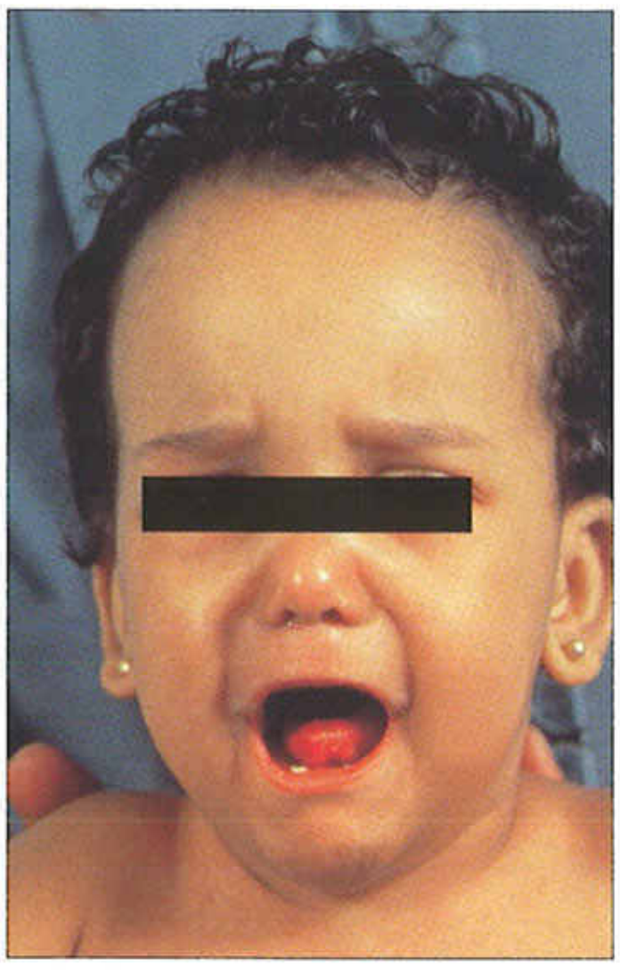
Fifth Case :

RSS is a Qatari female born on 1993, file # 89917040. She presented with hypotrichosis, loss of eye brows and eye lashes of both eyes. The skin was generally smooth and the nails of both hands and feet were thickened and short and her teeth were normal. Scalp hairs were rough wiry and easily broken (Fig.15, 16, 17, 18, 19, 20).

This condition dates back to birth. Family history is positive for similar affection of her elder sister, mother and maternal grandmother. None of the males in the family is affected. The patient is diagnosed as a case of autosomal dominant EDA (Cloustonís disease).

Sixth Case :

(NR) a 24 years old Palestinian male whose parents are first cousins. He began to loose scalp hair at age of 8-9 years, he has partial alopecia with steel wiry hairs, loss of eye brows, madarosis. He has smooth hairless skin with hypotrichosis of axillae, supra pubic region and hypotrichosis of beard and moustache. Nails of hands and feet show furrows, pitting, irregularity, roughness



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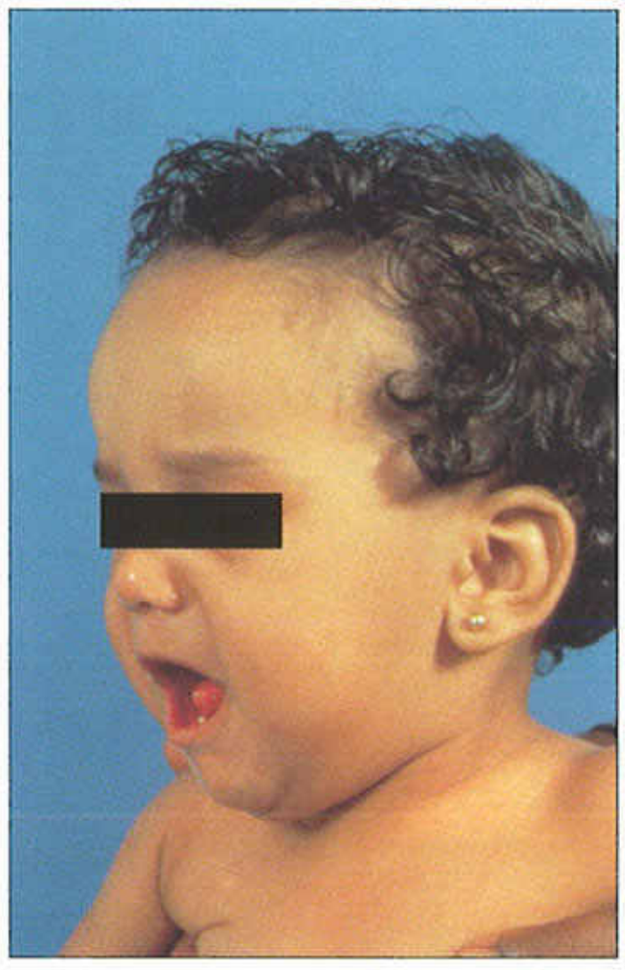

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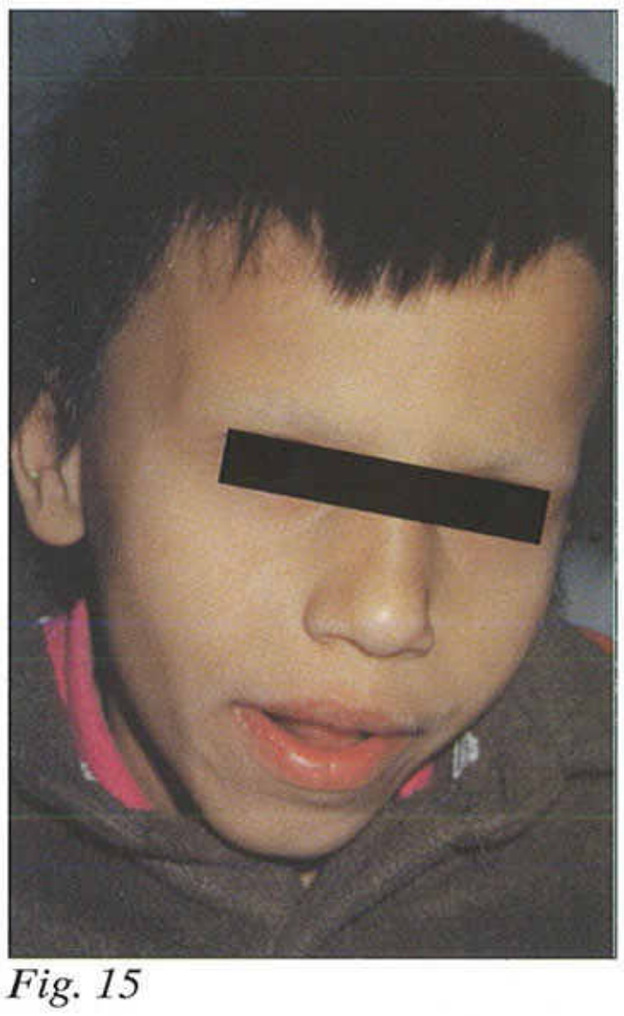

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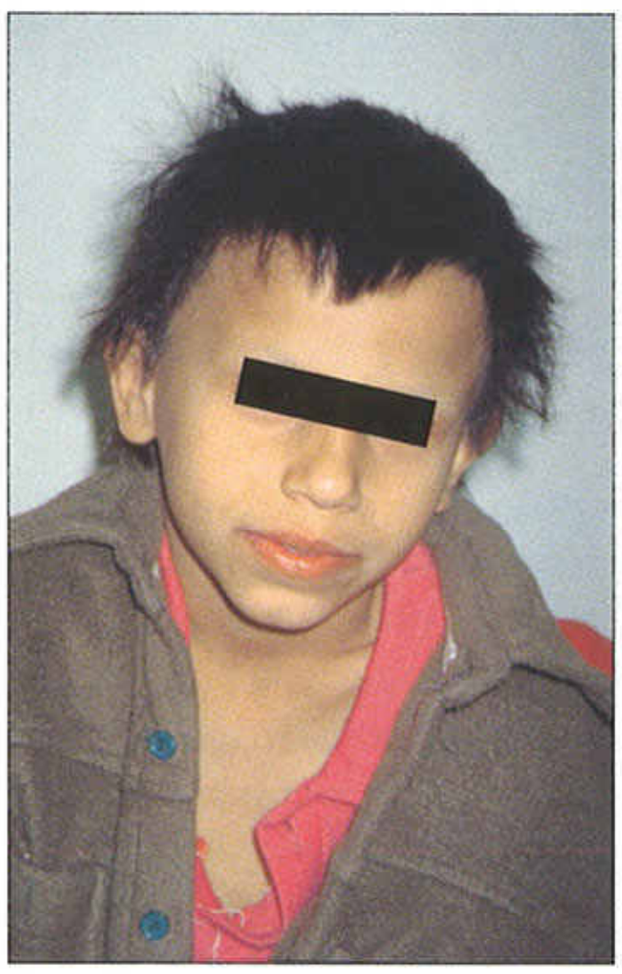

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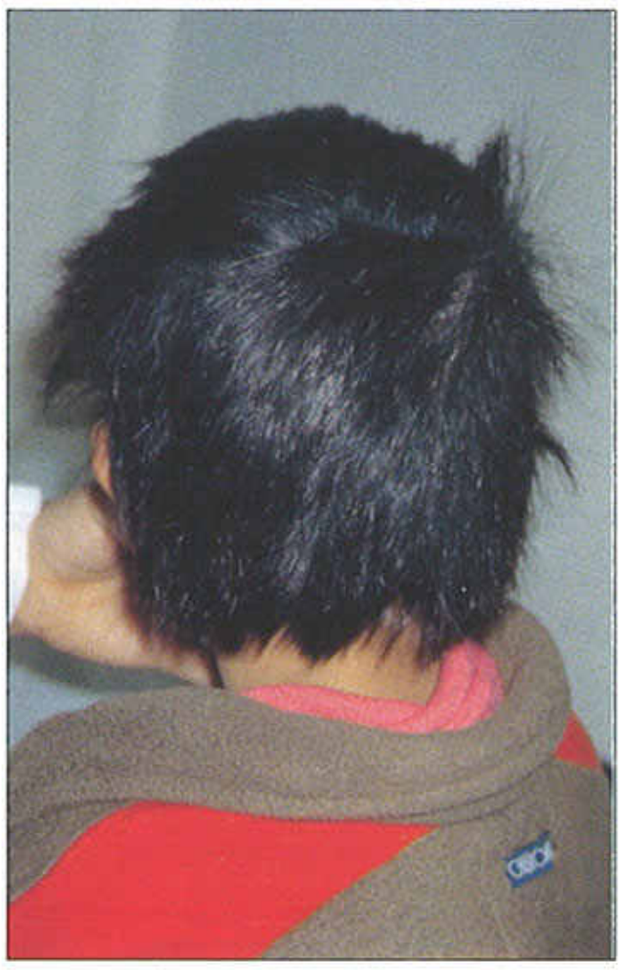

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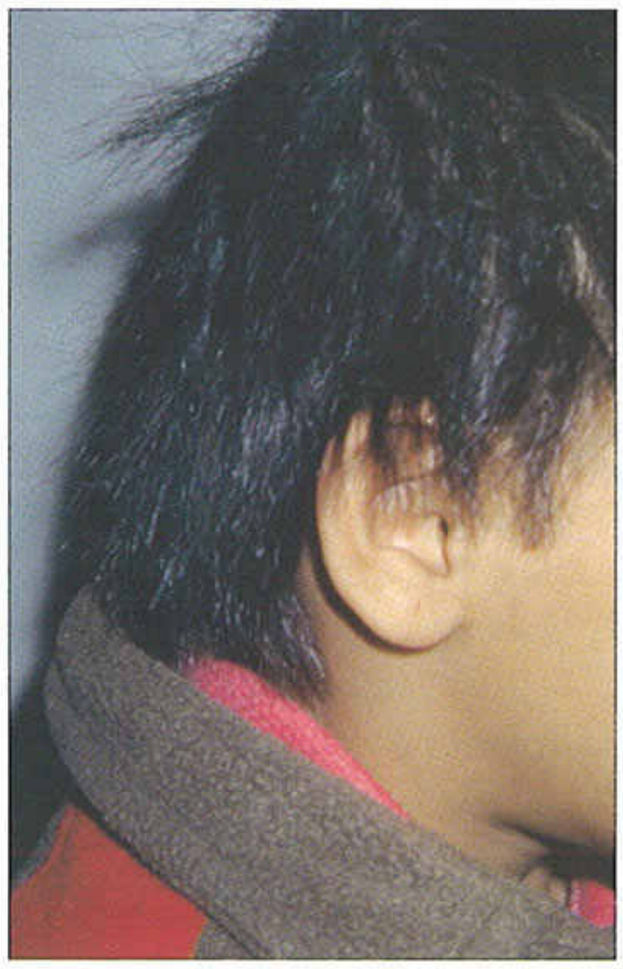

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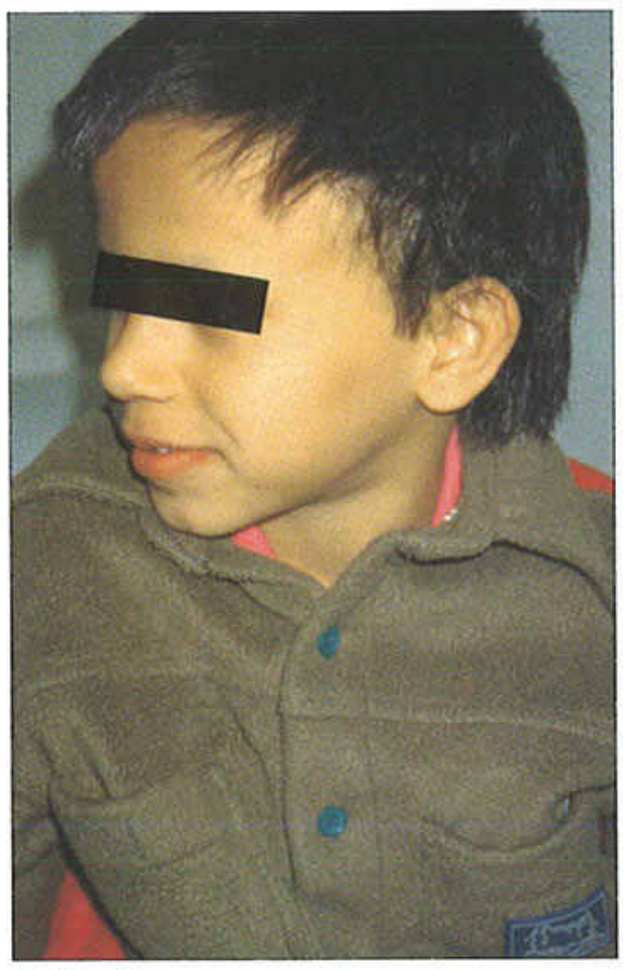

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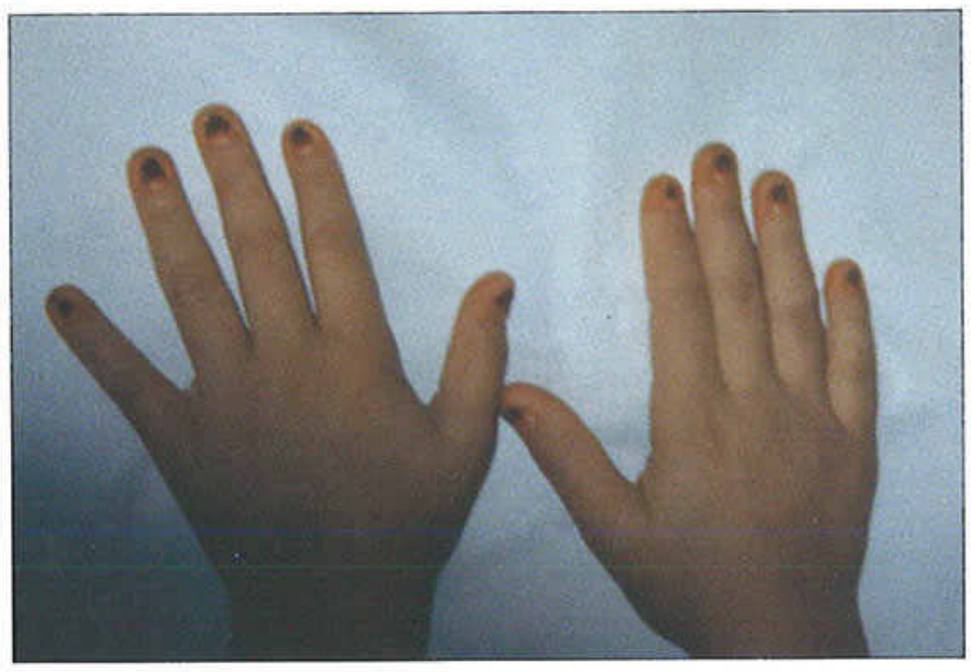

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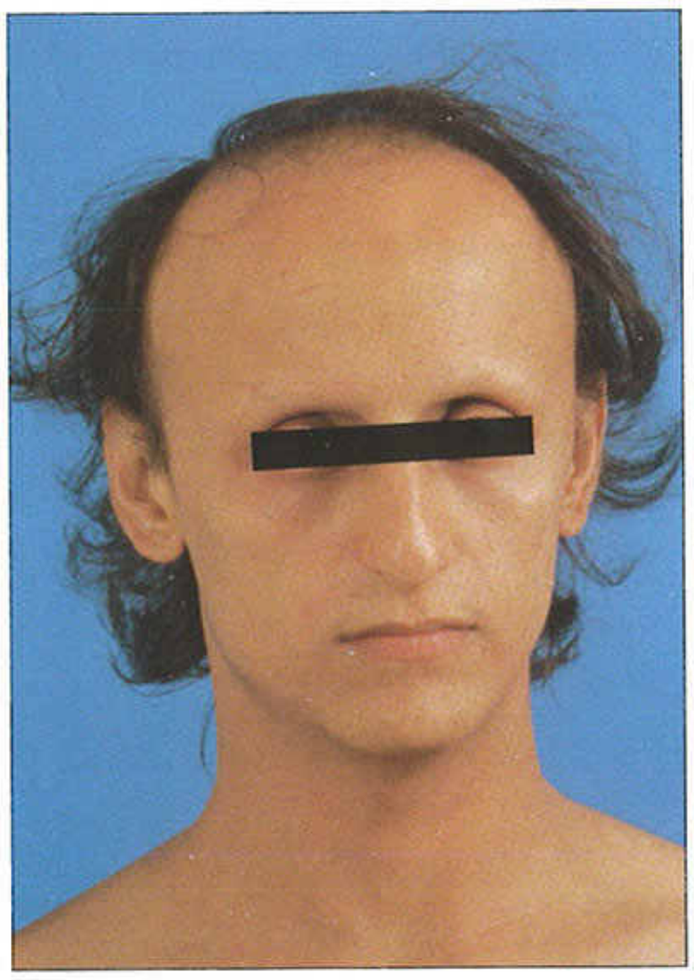

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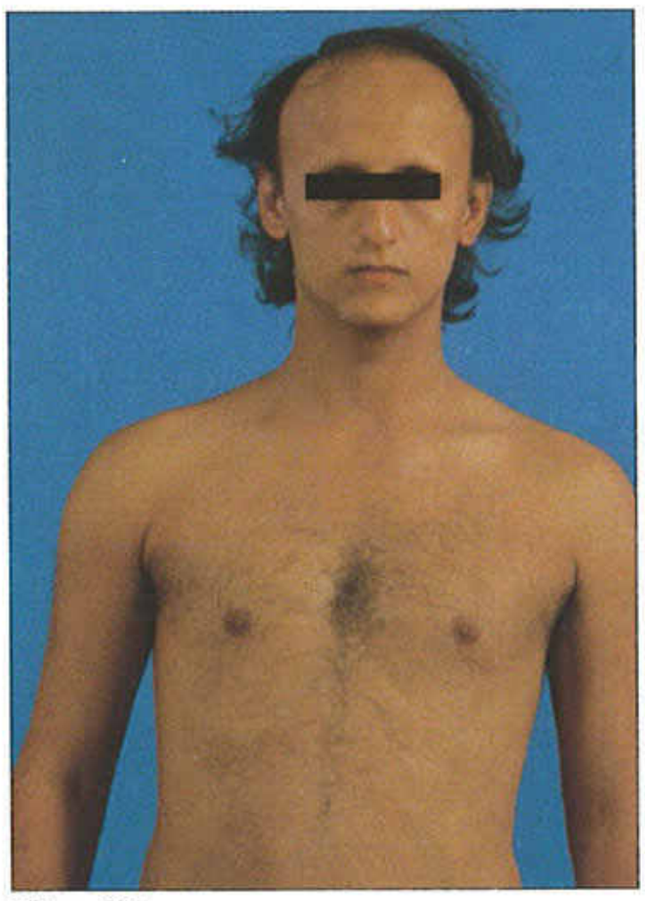

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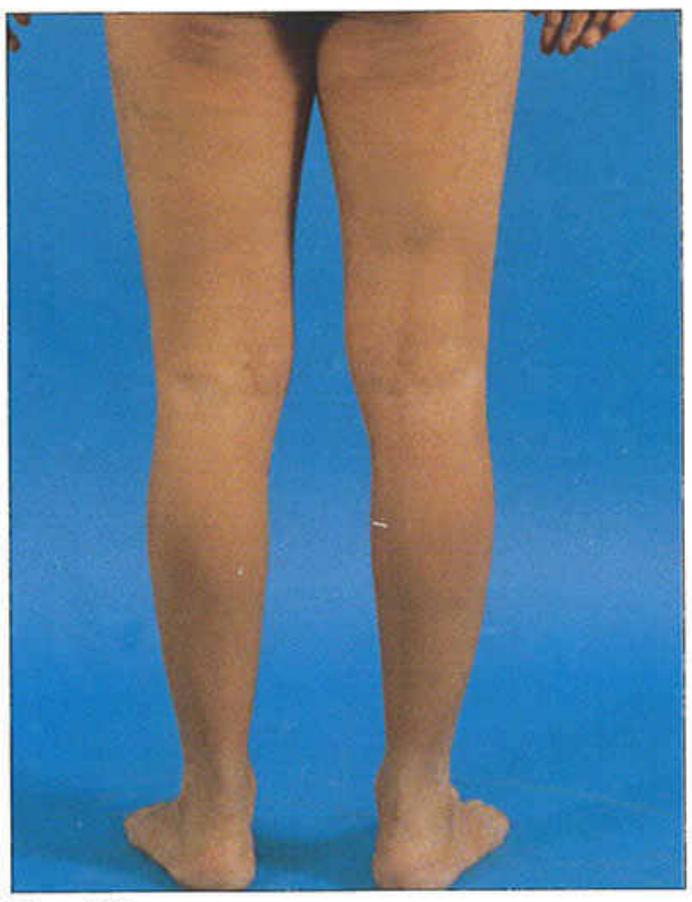

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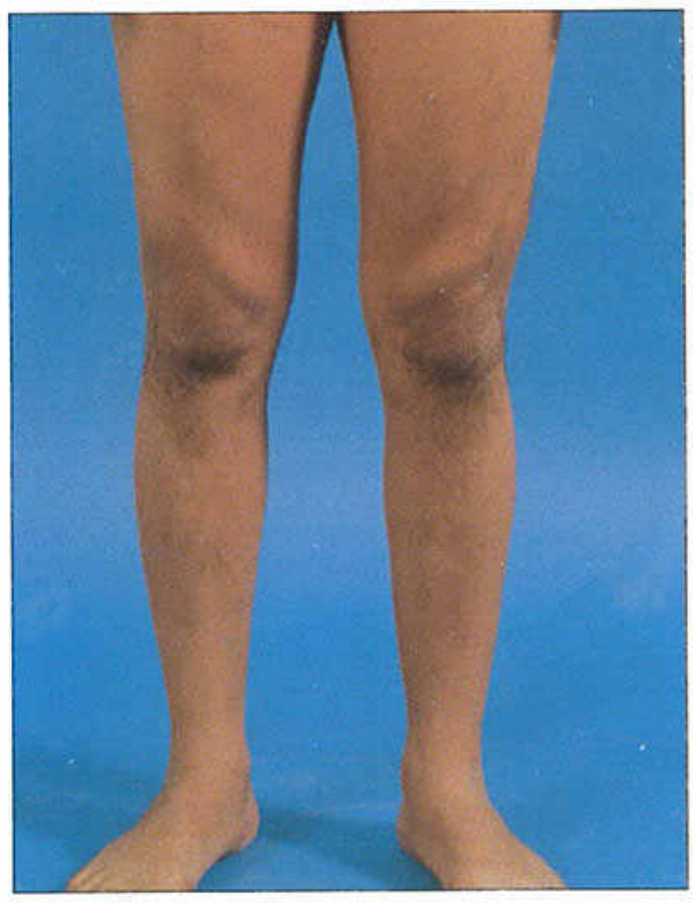


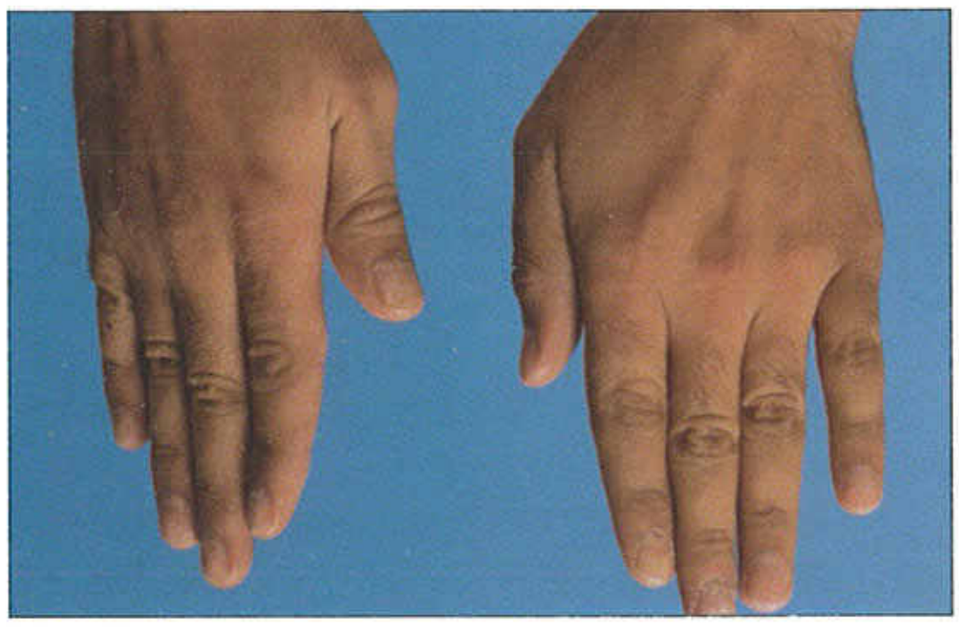
Fig. 24

with loss of luster and slow growth. Many of his teeth are carious (Fig.21, 22, 23, 24, 25, 26, 27). No other members of the family were similarly affected. A younger brother died immediately after birth and a second younger brother has stunted growth and glycogen storage disease. Skin biopsy was done on 19.12.1995 with a report H/8819/95 suggesting hypohidrotic ectodermal dysplasia (Fig. 28, 29, 30).

Discussion :

We present in this paper 6 cases with ectodermal dysplasia. The first four have typical clinical, histopathological and family history suggestive of autosomal anhidrotic or hypohidrotic ectodermal dysplasia which cannot be clinically differentiated from the x-linked recessive type known as Christ Siemens Touraire syndrome. The fifth case is typical of autosomal dominant hidrotic or hypohidrotic ectodermal dysplasia known as Clouston's disease. Case number six shows the clinical and histopathological characteristic of Clouston's disease yet the family history is not clear and cannot prove or rule out the diagnosis because some of the family members might have shown mild manifestations that were unnoticed.

Hypohidrotic or anhidrotic ectodermal dysplasia (EDA) is a rare hereditary congenital disease that



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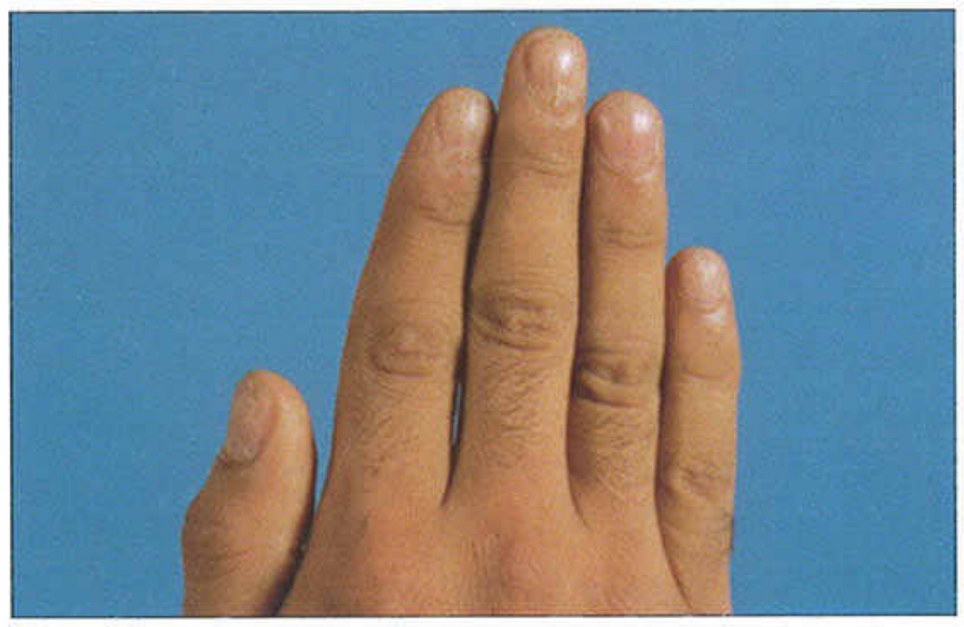

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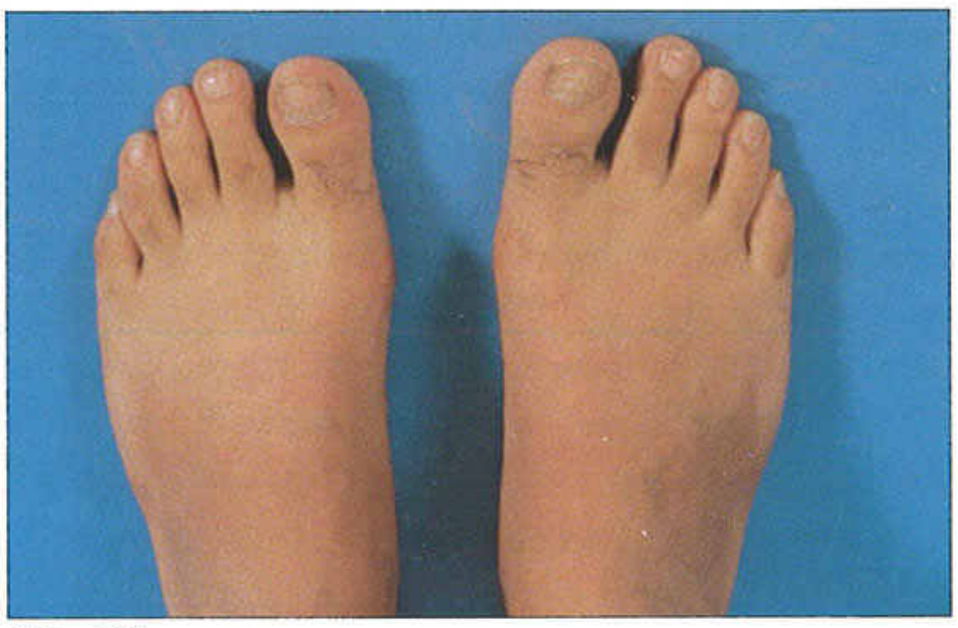

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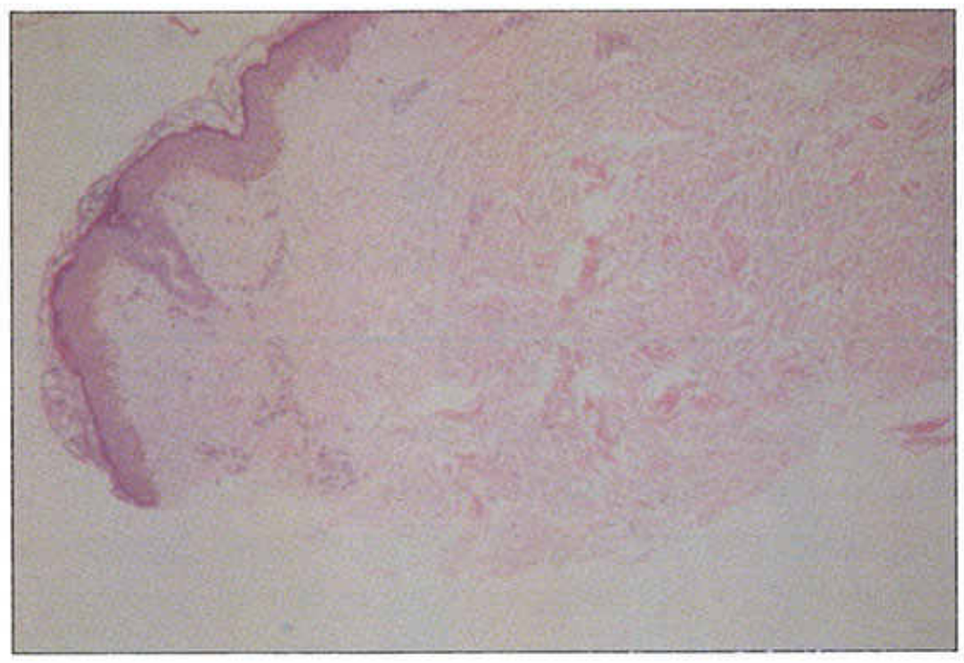

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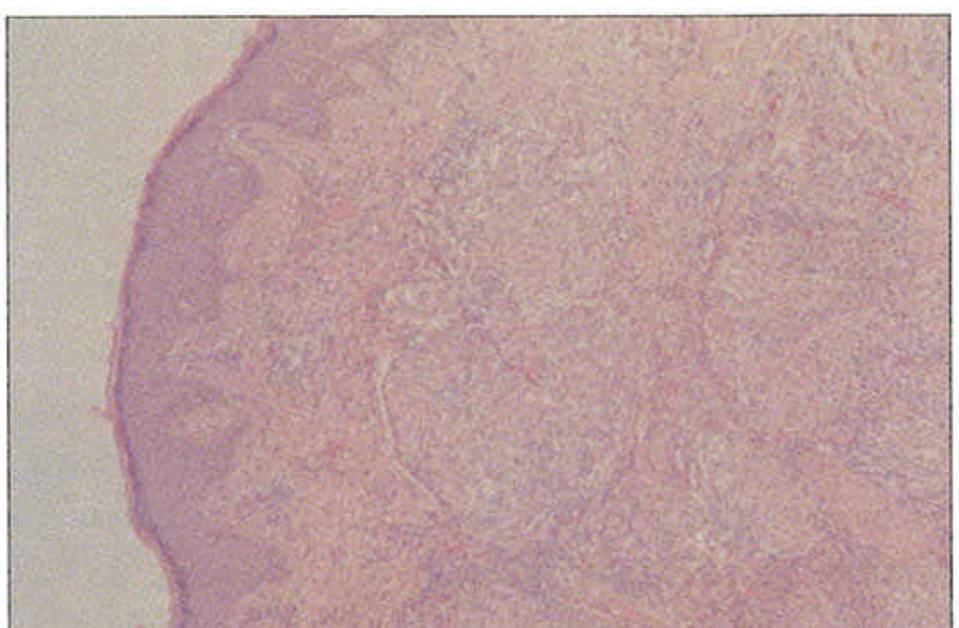

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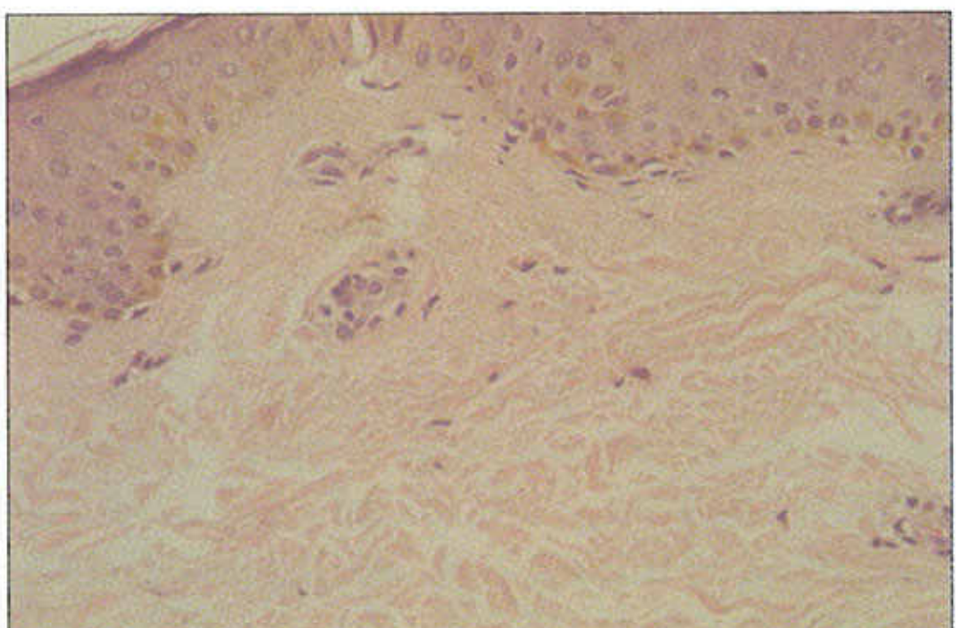

Fig. 30

affects several ectodermal structures [1]. Nonectodermal tissue with mesodermal origin may be affected as well [2]. The commonest or most frequently seen form of EDA is inherited as x-linked recessive. This form is also known as Christ Siemens Touraine Syndrome [3,4], and is mainly seen in males. It is inherited as x-linked recessive with significant morbidity and mortality in affected males but with little or no clinical expression in many carrier females [5]. The x-linked EDA is mapped to the xq12-q13.1 region of the x-chromosome. A gene from this region has been cloned and encodes a predicted transmembrane protein of 135 aminoacid which was found to be expressed in keratinocytes, hair follicles and sweat glands [6,7].

The occurrence of the same disorder in 2 siblings with unaffected parents and similarly affected females suggested an autosomal recessive inheritance.[8, 9] Hidrotic or hypohidrotic ectodermal dysplasia (Clouston's Syndrome) is autosomal dominant and affects males and females.[10] Both recessive and dominant forms of anhidrotic, hidrotic or hypohidrotic ectodermal dysplasia map on chromosome 2q11-q13. [11, 12] In all sporadic cases of females with classic EDA x-linked recessive as well as autosomal recessive inheritance has to be investigated. [8 EDA is a developmental defect that involves incomplete formation of hairs, sweat glands, disordered follicular keratinization with disturbed cytokeratin pattern and pathological aminoacid composition of terminal hairs. [13] Autosomal recessive EDA cannot be differentiated clinically from x-linked recessive EDA.[14] EDA compose over 150 syndromes of unknown pathogenesis.[15]

EDA is characterized by anhidrosis or hypohidrosis, dental anomalies, hypotrichosis and characteristic facies.[1] The pathognomonic features among affected males and females are heavy frontal supraorbital ridges, frontal bossing, prominent chin, saddle nose or depressed bridge, everted thick lips, large ears, thin sparse slow growing hairs on scalp, alopecia is prominent and rarely total and hairs are fine dry and short and may show pili-torti. More than half of the affected males show precocious baldness and some show dyskeratosis. [1,16]

They also show sparse eyebrows, short eye lashes, wrinkles around eyes, smooth dry hairless skin in most affected persons or hairs of the body are sparse and hairs of the beard and moustache are rather vellus than terminal. Total or partial absence of the teeth [1, 17] or deformed peg shaped teeth.[2] Articulation problems of speech arise because of the dental defects.

EDA is a cause of recurrent hyperthermia and fever of unknown origin in young infants and may induce infant death.[18, 19, 20, 21] Unexplained pyrexia and heat intolerance is usually the earliest presentation of the disease and in adults physical exercise leads to increased temperature and raised blood pressure. [22]

Diagnosis of EDA must be considered in infant boys with recurrent fever and respiratory infection.[23] Early diagnosis of EDA is important to avoid effect of over heating on infant development.[24] Boys with x-linked EDA suffer from severe illness and nearly 30% die.[25] Many has feeding problems, atopic disease, recurrent respiratory infections and some (up-to 50%) fail to thrive. They have normal sexual development but sometimes hypogonadism is seen. EDA is to be suspected in infants with under developed breasts[26]. EDA patients do not show consistent endocrinologic abnormality.[25] Hypothyroidism was reported in two brothers with EDA, both had urticaria pigmentosa like skin pigmentation with increase in mast cells and melanin deposition in the dermis. The association of EDA with primary hypothyroidism gives an insight into the potential extent of structural defects of ectodermal dysplasia during embryogenesis. [27]

EDA patients have scanty mucous glands of oropharynx, trachea and bronchi with deficient cilia. This leads to chronic respiratory tract infection, dysphagia and hoarse voice due to absence of mucosal covering of the folds. [2] Oozena is sometimes the presenting sign of EDA.[28] Some of the reported findings in EDA are persistent fetid smelling nasal discharge with crust formation and loss of sense of smell and taste, hearing problems and atrophic rheinitis [29, 30], mild mental retardation and agenesis of corpus callosum.[31, 32] Retardation may be due to inadequate treatment of episodes of hyperthermia or may be due to social deprivation and rejection due to their appearance and speech defects.

Nails are affected in 50% of cases. Nails become thin brittle or ridged and seldom grossly deformed. Sebaceous glands are few and salivary glands and lacrymal glands are occasionally absent[2] and nasolacrymal ducts are narrow leading to conjunctivitis

and corneal opacities and some patients show cortical opacity of lens.[33] Some of the reported unusual manifestation of EDA include café au-lait spots, depigmentation of lips, buccal cavity& left arm, absent tragii, plantar keratoderma and kyphosis,[34] primary interdigital webbing and contracture of fingers and toes.[35]

Additional findings reported were bilateral syndactyly and polydactyly of the feet and choanal atresia which is a birth defect in which a bone or a membrane blocks the passage-way between the nose and the throat.[36]

Extra medullary hematopoiesis of the cranial dura was associated with EDA.[37] A peculiar finding is the absence of an active cutaneous vasodilatation although the vasculature and sympathetic innervation are apparently normal.[38] EDA patients have no consistant immunological abnormalities although most have abnormal immunoglobulin production.[25] EDA may be possibly associated with a polysaccharide specific humoral immunodeficiency.[39]

Impaired cell mediated immunity and raised IgE may be seen in EDA patients who show atopic dermatitis. Histopathologically, the skin shows absent or rudimentary eccrine glands and ducts.

Autosomal recessive EDA is clinically identical to the x-linked recessive EDA[3] and are sometimes associated with Friedreichs ataxia, Horner syndrome and nystagmus. Histopathologically the epidermis is thin and sweat glands are absent or rudimentary with variable reduction of hair follicles and sebaceous glands. The dermis may show normal connective tissue or fragmented collagen and elastic fibres.

The hereditary autosomal dominant hidrotic or hypohidrotic ectodermal dysplasia (Clouston's disease) is characterized by abnormal alfa proteins in hairs and nails. The ultrastructure of hairs by electron microscopic scanning show disorganization of the hair fibrils with loss of cuticular cortex and this suggests a biochemical defect in keratin of integumentary system.[10] Clouston's disease affects males and females and is clinically characterized by partial or total alopecia, slight coarse fragile hairs, eye brows are absent or partially present, eye lashes are short or sparse or absent and corneal involvement was also reported.[40] Nails are slow growing, thickened, discoloured, longitudinally straited, keratotic accumulations under the nails and increased side to side convexity. Nails are prone to infection (bacterial or fungal) with ultimate partial or complete loss of nails. Carcinoma of nail bed was reported. Dermatoglyphics are reduced and palmo-plantar hyperkeratosis is described. Pebbling over acral area in the distribution of sweat glands is seen. Eccrine poromas are also seen. Eccrinesyringofibro adenoma of Mascaro (ESFA) was reported with Clouston syndrome and appears as keratotic verrucous, soft nodules with cobble stone arrangement on erythematous plaques on soles and thighs.

ESFA has been reported as a neoplasm, hamartoma or nevus[41] or could represent an human papilloma virus induced epithelial proliferation.[42] General body skin is smooth because of fewer follicles and is dry because of less sebaceous glands. Hyperpigmentation over knees, knuckles, elbows and axillae.

Sweat glands may show ductal hyperkeratosis which extends like a pseudohair. Eyes may show, strabismus, conjunctivitis, pterygium or cataract. Buccal, gingival, lingual and palatal leukoplakeas were seen in some cases. Pathology shows hyperkeratotic epidermis on palms and soles, eccrine poromas may be seen. Hairs show irregular configuration or square configuration, hair bulbs are dystrophic. By scanning electron- microscopy autosomal dominant EDA show defective cuticular layer and hair shafts show longitudinal grooving.[43,44] Study of the skin of the finger tips and palms of EDA patients and their families are useful in finding the geneologic back ground . Defects seen by such study include abnormalities of the morphology and pattern of epidermal ridges, reduction of sweat pores varying from 13-87% of normal and changed anatomy of the opening of the sweat glands. The sweat pores were shallow with less whorling compared to normal funnel shaped sweat pores. Micropores were also observed with an average diameter of 5.3 micrometer.[43] The sweat pore count is lower in males and females affected with EDA by 42% and 60% of normal values respectively.[16] It is suggested that examination of finger tips for sweat pores microscopically is a simple non invasive procedure which is even preferable to skin biopsy in diagnosis of EDA.[45]

Detection of Asymptomatic carriers of EDA :

It is important to examine female relatives of x-

linked recessive EDA patients to detect carrier females by various clinical criteria.[46] They show palmar and plantar ridge flattening[47,48] with paucity of pores and characteristic dermatoglyphic pattern.[49] Some carriers of x-linked recessive EDA showed on their back a linear distribution of hypohidrotic areas following lines of Blaschko forming a V shaped area over the spine.

These lines apparently reflect the dorsoventral outgrowth of two functionally different populations of cells during early embryogenesis.[50] Some carriers show lack of more than four permanent teeth.[51] The frequency of carriers of x-linked EDA among females with hypodontia of permanent teeth excluding third molar could be as high as 1 in 500 and among females with deciduous hypodontia as high as 1 in 50.[52]

Carriers among females with hypodontia in general could be detected by virtue of sweat pore count. This could be done by using organic silicum cream to evaluate sweat pores on finger prints.[53] Patchiness of sweat pore distribution on fingers and palms may be useful in descrimination of heterozygotes.[54] When female carriers are recognized their affected sons could be detected early.[25]

Three females with incontinentia pigmenti presented with white hairless streak on the limbs as the predominant skin abnormality with focal absence of sweating in these lesions similar to EDA and suggesting genetic overlap between these two x-linked conditions.[55]

Prenatal diagnosis :

Prenatal diagnosis of EDA is possible by skin biopsy specimen sampled under fetoscopy[56,57,58] at 20 weeks. The skin biopsies show absent skin appendages. The earliest signs of EDA were detected at week 8 in the epidermis and neuroectodermal cells. Starting at 12 weeks osteoblasts and thymus were positive for EDA m RNA. Hair follicles expressed EDAm RNA from the eighteenth week of gestation.[59]

The main differential diagnosis of Anhidrotic or Hypohidrotic Ectodermal Dysplasias includes : [60]

Pachyonychia congenita which is characterized by thick nails, palmoplantar hyperkerratosis, keratosis, pilaris, occasional scalp hair absence, natal teeth and leukoplakia oris.

Basan syndrome (Autosomal dominant ectodermal dysplasia) which is characterized by sparse eyebrows, eyelashes throughout life, hypotrichosis, hypohidrosis, defective teeth, severe early dental caries, aberrant dermatoglyphic and minimal nail changes which are described as being short and thick.

Chondroectodermal dysplasia (Ellis-van-Creveld syndrome) is characterized by abnormal teeth, abnormal hairs, nail dystrophy, bone deformities and congenital heart lesion.

Dyskeratosis congenita is characterized by nail and teeth dystrophy, leukoplakia, bullae on mucous membranes, eye abnormalities and atrophic hyperpigmented changes of skin.

Rapp-Hodgkin hypohidrotic ectodermal dysplasia is an autosomal dominant ectodermal dysplasia characterized by hypohidroses, heat intolerance.[61] The hairs are light in color, sparse with steel wood texture and may show pili torti. Patients have distinctive features with high forehead, narrow nose, small mouth maxillary hyperplasia, cleft lip or palate, oligodontia and conical teeth or anodoma, aplastic lacrimal puncta, hypoplastic nails, small stature, hypospodius and cleft lip or palate.

Schopf-Schulz-Passarge syndrome : is a rare form of congenital ectodermal dysplasia characterized by hypodontia, hypohidrosis, palmo plantar hyperkeratosis, hypoplasia of nails, numerous cysts of eye lid margin and predisposition to skin cancer.

Treatment:

There is a need for continued treratment[62] by stomatologists and orthodontists who deal with problems related to anodontia.[63] Young children with anodontia caused by hypohidrotic ectodermal dysplasia not only have difficulties in eating and speaking but can also sense that their appearance is different than others. The use of well-fitting and functioning dentures with age-appropriate denture teeth enable children with EDA to look and act more like their peers and will greatly assist in their transitioning into the school years. Although denture fabrication requires multiple patient appointments and good cooperation, it is shown that even young children can cooperate for the denture-making process.

The desire to be like others who have teeth can be a motivator for cooperation in even the young child. Children should be given every opportunity to develop to their fullest potential. The dentist can make a significant contribution to the overall development and well being of a child with EDA.[64] Endosseous implants can be successfully placed and can provide support for prosthetic restoration in patients with EDA[65] and tricalcium phosphate is given to preserve alveolar bone in EDA.[66] After repeated application of acetylcholine the hypoplastic eccrine glandular element in EDA may give rise to normal eccrine glands anatomically and functionally.[67]

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