Genodermatoses / Dermatology
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**Genodermatoses :-** Are skin disorders caused by genetic (chromosomal) defects i.e. inherited.

*Familial* – refers to the clustering of a disorder, with more close relatives affected than predicted by the population prevalence of the condition.

*Inherited* – are disorders require the transmission of genetic variants from one generation to the next.

*Congenital* – means the character or disorder was present at or detectable before birth, such abnormalities may not be genetically determined and include developmental defects due to environmental agents e.g. infectious (rubella), physical insults (amniotic bands, radiation). Only a proportion of inherited disorders reveal them self at birth, i.e. are congenital.

**Principles of medical genetics :-**

Inherited characteristics are transmitted from one generation to the next by **chromosomes**, which composed of double helix strands of **DNA**.

*Gene* - is a sequence of bases in DNA, encoding a polypeptide.

*Locus* - is the precise position of the gene on a genetic map (chromosome).

*Meiosis* - is the process of cell division by which **male** and **female** gametes (germ cells) are produced.

*Alleles* - are alternative genes at a single locus.

*Heterozygous* - is an individual with two different alleles at a particular locus.

*Homozygous* - is an individual with two identical alleles at a particular locus.

*Hemizygous* - is an abnormal gene on the X-chromosome in a male.

*Homologous pairs* – are pairs of chromosomes (46 chromosomes - 44 are somatic and 2 are sexual), found in most of somatic cells, hence two copies of every gene exist, one maternal and the other paternal in origin. In males the Y-chromosome only pairs with X-chromosome at pseudo-autosomal region.

*Dominant* - is an allele manifested as a phenotype, when present only on one member of the chromosome pair (heterozygous stat), before it can exert its full effect.

*Recessive* - is an allele manifested as a phenotype, when present on both corresponding loci (homozygous stat), i.e. the terms dominant and recessive are referred to a phenotype characteristic rather than a gene.

*Autosomal* – are genes borne on chromosomes other than the sex chromosomes (X and Y), called somatic chromosomes, it's number in normal cells are 44 chromosomes.

*Sex-linked* - are genes borne on the X or Y chromosomes, the great majority of this disorders are exclusive to the X-chromosome, because Y-chromosome is smaller than X,
for this traits the term recessive applies to males who carry only one (mutant) allele (hemizygous).

**Histocompatibility antigens and disease association** :-

*Human leukocyte antigens (HLA)*- are glycoproteins on the cell surface of most nucleated human cells. These differ in subtle ways from person to person and uniquely fingerprint each person's cells. **The importance** of HLA system has been highlighted by the need to match donors and recipients in the transplantation of human tissues. The HLA region is located on the short arm of chromosome 6, referred to as the **major histocompatibility complex (MHC)**, a person inherits HLA as a set, one set (haplotype) from each parent. There are at least 4 or 5 genetic loci that produce HLA, termed A, B, C, D and DR, and their gene products are called HLA-A, HLA-B, HLA-C, HLA-D, and HLA-DR. The association of an HLA with a given disease, means that there is a higher incidence of that antigen in a group of patients with that disease than in a group of people without that disease.

The ways in which the presence of a particular HLA might be involved in the pathogenesis of a disease are :-

1. **Molecular mimicry** – i.e. an infective agent may have a similar configuration to HLA, so the agent is then not attacked by the body's defense system.
2. **Receptor effects** – many chemicals, including drugs and toxins bind to the cell surface before they are taken into the cytoplasm, since HLAs are presented on the cell surface, could modify the binding of these potentially toxic substances.
3. **Genetic linkage** – the HLA may be close to another gene on the same chromosome that produces a disease, either directly (e.g. due to an enzyme deficiency), or indirectly due to an effect on the immune response, leading to autoimmunity, or abnormally decreased leading to infection.

The association between an HLA and a particular disease is rarely absolute. Some skin diseases known to be associated with particular HLA, e.g. dermatitis herpetiformis with B8, Dw3, DRw3, pemphigus with DRw4, Reiter's disease with B27, Behcet's disease with B5, psoriasis with B13, B17, B37, Cw6, Dw7, psoriatic arthropathy (central-B27, and peripheral Bw38).

**Chromosomal disorders** :-

**Genetic counseling**- is advice to parents for an accurate diagnosis and a detailed family history to reduce the risk of chromosomal disorders, by termination of pregnancy, a risk greater than 10% is high, weather a risk of less than 5% is considered low.

The chromosomal disorders may be due to :-

a. **Abnormalities of number** – somatic cells are diploid (46 chromosomes), wear as gametes (ova and sperm) are haploid (23 chromosomes), in this abnormalities there are either a gain or loss of one or more chromosomes and rare known as aneuploidies.
b. **Structural abnormalities** – are due to breakage with subsequent reunion in a different configuration.

**The largest group of inherited skin abnormalities is the single gene disorders**, these are:

1. **Autosomal dominant (AD) inheritance** – their features are:
   a. Affect both males and females.
   b. Affected individuals are heterozygous for the abnormal allele.
   c. Affected person will usually have an affected parent.
   d. On average 50% of the children of an affected parent will be affected.
   e. The age of onset and severity of disorder may be variable and the affected individual may remain without signs or symptoms i.e. remain well into adult life.
   f. Some AD disorders show reduced penetrance i.e. person who inherits the gene dose not develop the disorder.
   E.g. acute intermittent porphyria, epidermolysis bullosa, ichthyosis.

2. **Autosomal recessive (AR) inheritance** – their features are:
   a. Affect both males and females.
   b. Affected individuals are homozygous for an abnormal allele and typically are born to unaffected parents.
   c. On average, 1 in 4 of the children of heterozygous parents will be affected.
   d. Typically no family history is seen.
   e. Consanguinity increases the risk of an AR disorder because both parents are more likely to carry the same mutant allele.
   f. The offspring of an affected person will be healthy heterozygote and can be affected only if the other parent is also a gene carrier.
   g. Are often severe disorders e.g. inborn errors of metabolism.
   E.g. epidermolysis bullosa, ichthyosis, acrodermatitis enteropathica.

3. **X-linked recessive (XLR) inheritance** – their features are:
   a. Usually only males are affected.
   b. The disorders are transmitted through healthy female carriers, occasionally a heterozygous female may show some features of the condition.
   c. A female carrier will transmit the disorder to half of her sons, and half of her daughters will be carriers.
   d. When a male is affected, all his daughters will be a carrier heterozygote.
   e. The trait can not transmitted from father to sons.
   f. An XLR condition should be considered when the family history indicates affected males in different generations of the same family.
   E.g. anhidrotic ectodermal dysplasia, Fabry's disease.

4. **X-linked dominant (XLD) inheritance** – their features are:
   a. Will give rise to a disorder in both hemizygous males and heterozygous females.
b. Affected males will transmit the disorder to their daughters, but not to their sons.

c. Affected females will transmit the disorder to half of their sons and half of their daughters.

d. In some disorders the condition is lethal in hemizygous males, so only female patients are encountered in clinical practice. E.g. Incontinentia pigmenti.

**Down's syndrome:**
Is AD disorder, frequency 1/700 of live birth.
*caused by* (in 95% of patients) trisomy of chromosome 21, i.e. extra chromosome is derived by non-disjunction at meiosis, usually from the mother.

*pathological and clinical features are*: congenital heart diseases, small brain with flat convolutions, renal tract anomalies, immunological defects including autoimmune diseases and impairment of T-cell functions, atopic state and increased risk of developing acute leukemia usually under the age of 5 years.

The patient can be presented with:
*Mongoloid face.*

*Stumpy limbs, lax joint ligaments, short fingers and cone-shaped some times webbed.*

*Mental retardation IQ<50.*

*Congenital heart malformations in 40% of cases.*

*duodenal atresia.*

*Skin* – at birth is normal, early childhood is soft and velvety, between 5-10 years become increasingly dry and less elastic, 15 years and over 70% shows generalized xerosis, accelerated skin ageing, patchy lichenification on upper arms, wrists, fronts of thighs, back of ankles and back of neck. Chronic follicular popular eruption on presternal and interscapular regions, due to malassezia folliculitis, responded well to itraconazol capsules, hyperkeratotic psoriasis, red checks, dermatoglyphic abnormalities, skin infections and lentiginous melanoma.

*Hairs* – is often fine and may be hypopigmented, with high prevalence of alopecia areata.

*Mouth* – teeth are hypoplastic and late to erupt, fissuring and thickening of the lips which increase in prevalence and severity with age, scrotal tongue.

Confirm the diagnosis by chromosomal study, no treatment is available.

**Turner's syndrome:**
Is defined as a gonadal dysgenesis due to missing or structurally defective X-chromosome, is XLD, frequency 1/2500 female births, 80% of cases there are 45 chromosomes with an X0 sex chromosome complement, and most of the remaining 20% of cases are chromatin positive in buccal smears.
Clinical features:
* Over 95% of cases there is early loss of the fetus (abortion).
* At birth, growth failure is consistent finding, redundant neck skin and peripheral lymphangiectic oedema.
* Small stature and primary amenorrhea.
* Increased number of melanocytic naevi, with increased risk for melanomas.
* Skeletal abnormalities.
* Cardiovascular abnormalities in 25% especially coarctation of aorta.
* Intelligence is usually normal.
* Failure of development of secondary sexual characters.

Diagnosis: prenatally by amniocentesis and postnatally by clinical features, supported by increased serum FSH and LH by fifth day of age, and low serum estrogen, and confirmed by buccal smear examination for chromosomal studies.

Treatment – estrogen and human growth hormone replacement.

Klinefelter's syndrome: -
Is XLR disorder, frequency 1/600 male births, buccal smears are chromatin positive, and indistinguishable from those of normal female, but in cultures there are 47 chromosomes with a XXY sex-chromosome complement.

Clinical features:
* Before puberty there are no clinical manifestations.
* At puberty, the testes are small and fail to produce adult levels of testosterone, poorly developed secondary sexual characteristics and infertility.
* High growth on the trunk and limbs (tall, obese), the face tend to be blow average.
* Psychiatric disorders, but with out mental deficiency.
* Risk of development of SLE and leg ulcers.

Diagnosis – is by clinical features, supported by increasing urinary excretion of gonadotrophin, and confirmed by chromosomal studies.

Treatment – replacement therapy by testosterone to improve the secondary sexual features, but infertility is the rule.

Noonan's syndrome: - Occurs in both sexes, phenotypically resembles Turner's syndrome, but the karyotype is usually normal (46XY or 46XX), many cases appear to be sporadic, although Autosomal dominant inheritance has been frequently reported, and only few cases had chromosomal abnormalities. Clinical features are: short stature, broad short neck, hypertelorism of the face, blepheroptosis, epicanthic folds, small chin, skeletal defects, congenital heart defects, normal intelligence, mental retardation, lymphoedema of feet and legs, leukokeratosis of lips, coarse hair.

Familial multiple tumor syndromes: -
1. Neurofibromatosis (NF): Comprise several distinct genetic disorders, that lead to the formation of tumors surrounding nerves and a variety of other pathological features, the two main forms are NF1 and NF2.

a. Neurofibromatosis 1 (NF1) — SYN. VON-RECKLINGHAUSEN’S NF.
NF1 is an inherited neuroectodermal abnormality, characterized by the presence of six or more café-au-lait spots, axillary freckles, multiple neurofibromas and lish nodules.

Aetiology — it is inherited as Autosomal dominant, with 100% penetrance by the age of 5 years, sporadic cases result from a high gene mutation rate. The prevalence is about 1/2500-3300 births, incomplete or monosymptomatic forms are frequent, the gene for NF1 is located on chromosome 17.

Clinical features:
A diagnosis of NF1, according to the National Institutes of Health Consensus Development Conference Statement (NIHCDCS) is based on two or more of the following criteria:

* Six or more café'-au-lait macules of over 5cm in greatest diameter in prepubertal individuals and over 15cm in greatest diameter in post pubertal individuals.

* Two or more neurofibromas of any type or one plexiform neurofibroma.

* Freckling in the axillary or inguinal regions.

* Optic glioma.

* Two or more lish nodules.

* A distinctive osseous lesion, such as sphenoid dysphasia, or thinning of the long bone cortex with or without pseudoarthrosis.

* A first degree relative (parent, sibling, off sibling) with NF1, by the above criteria.

Café'-au-lait macules — are sharply defined, light-brown patches that vary in size from 0.5-50cm, although the majority are 10cm or less in size. It is the first feature of the disease to appear in all children by the age of 4 years, 82% of children have the lesions by the age of one year.

Cutaneous neurofibromas — **ordinary neurofibroma** (molluscafibrosa), are soft lilac-pink, sessile and dome-shaped tumors, some times pedunculated, most numerous on the trunk and limbs, 100 may be present, ranging from few mm to several cm in diameter. In women, they are prominent on the areola of the breast, small firm nodules may develop in relation to the peripheral nerves. **Plexiform neurofibroma** is diffuse elongated fibroma, along the course of a nerve, frequently involving the trigeminal or upper cervical nerves, and usually not seeniceable with in the first 2 years of life. **Elephantiasis** neurofibromatosis is a similar diffuse neurofibromatosis of nerve trunks, associated with overgrowth of the subcutaneous tissue and of the skin, which is wrinkled and pendulous, and may produce gross disfiguring, neurofibromas may also involve the viscera and blood vessels.
Freckling- occurs frequently in the axilla, when it is virtually pathognomonic, present in about 70% of cases and appears a little later than the café-au-lait spots, also may occur in other intertriginous areas.

_Lish nodules (pigmented iris hamartomas) –_ appears as dome-shaped lesions found superficially around the iris on slit lamp examination occur in over 90% of patients and increasing with age, and asymptomatic.

**Oral lesions**- are present in 5-10% of cases as papillomatous lesion of palate, buccal mucosa, tongue and lips or as macroglossia, which is usually unilateral.

**Kyphoscoliosis** (2%), short stature and macrocephaly, learning difficulties (25-30%), impaired physical development, speech disorders, headache, precocious puberty, acromegaly, Addison's disease, hyperparathyroidism, gynaecomastia, phaeochromocytoma, Reno vascular hypertension, osteomalacia, GIT,UT disorders, cardiovascular abnormalities and pulmonary hypertension.

**Neurological manifestations** – are found in 40% of patients, most commonly solitary intracranial tumour, spinal cord and peripheral nerves tumours, epilepsy.

**Sarcomatous changes** with in a neurofibroma varies from 1.5-15% of cases.

**Pruritis** may be a symptom of NF1, due to the large number of mast cells in the skin, and responding to antihistamines.

**Course and prognosis**:
The course of the disease varies considerably in individual patients and the majority will never develop major complications. Early onset and rapid progression before puberty usually indicate a poor prognosis, also involvement of internal organs like UT, GIT, CNS carries a poor prognosis specially if extensive.

**Diagnosis**: By clinical criterias, prenatal and presymptomatic diagnosis is now possible by chromosomal studies of NF1 gene, with greater than 95% accuracy in families with a suitable structure. Prenatal diagnosis is not an option for approximately 50% of cases who represent new mutations.

**Treatment is symptomatic**.
*Disfiguring lesions can be excised, **Co2 laser** for Cutaneous neurofibromas.*
*Painful lesions and those with rapid increase in size, which suggest malignant changes, are removed surgically.*
*Neurosurgery for intracranial tumours with complications.*
*Genetic counseling is important because 50% of children of the patients are likely to be affected and the disease may be sever.*

**b. Neurofibromatosis 2 (NF2):** SYN. BILATERAL ACOUSTIC NEUROFIBROMATOSIS.
This condition was originally considered to be part of the spectrum of VonRecklinghausen's disease, but now is recognized as a separate entity, because of its distinct genetic bases and natural history, the gene for NF2 is located on chromosome 22.

Clinical features — are bilateral vestibular schwannomas (acoustic neuromas) as well as other CNS tumours of meningeal and glial origin, café-au-lait spots and Cutaneous fibromas may be seen, the mean age of first symptoms in UK was 22.6 years (range 2-52 years), cataract were present 81% of cases.

2. Tuberous sclerosis complex (TSC) : SYN. EPILOIA, BOVRNE VILLE'S DISEASE.

*Definition: TSC is a name referred to the condition previously known as Tuberous sclerosis, which represents a genetic disorder of hamartoma formation in many organs, particularly the skin, brain, eye, kidney and the heart. The characteristic skin lesions are angiofibromas, shagreen patch, periungual fibromas and ash-leaf white macules, classically, although not invariably seen in association with epilepsy and mental retardation. The term complex emphasize the multisystem involvement.

*Incidence is 1/10000-27000.

*Aetiology: TSC is one of the more common single-gene disorders, inherited as Autosomal dominant gene on chromosome No.9C, 50% are TSC1 on chromosome 9q34 and 50% are TSC2 link to 16p13 chromosome. Approximately 60-70% of TSC cases are thought to be the result of new mutation.

*Clinical features: The characteristic features of TSC are *skin lesions, *mental retardation, *epilepsy, but these show very wide variation in age of onset and severity. Onset before the age of 5 years with cutaneous changes or with epilepsy is usual, although the disease may remain latent until adolescence or adult life.

A definitive diagnosis of TSC requires two major features, and brain MRI, CT, renal US or echo. may be necessary.

A. Skin lesions: are found in 60-70% of cases, of four types and pathognomonic, include:

a. Angiofibromas — usually appear between the age of 3-10 years, and some times later, rarely present at birth or in infancy. They become more extensive at puberty and than remain unchanged. The lesions are firm, discrete, red-brown, telangiectatic papules of 1-10 mm in diameter, extended from the nasolabial furrows to the cheeks and chin, occasionally found in the ears. They may be numerous and conspicuous and very rarely may form large cauliflower-like masses, some times only few lesions confined to side of nose or chin.

b. Periungual fibromas (koren's tumours) — appear at or after puberty as smooth, firm, flesh-cloured excrescences emerging from the nail folds, usually 5-10 mm in length but may be very large, this can be the only clinically evident abnormality.

c. Shagreen patch —is an irregularly thickened, slightly elevated, soft, skin coloured, plaque, usually in the lumbosacral region.
d. Ash-leaf –shaped macules – white colour some times ovoid in shape, 1-3cm in length, most easily detectable by examination under Wood's light, are frequently present on the trunk or limbs. They are a valuable physical sign as they may be found at birth or in early infancy, some years before other signs of the disease develop and may suggest the correct diagnosis in infants with convulsions. However this hypopigmented macules are seen in 2-3/1000 of apparently normal newborn babies and therefore their presence alone is not indicative of TSC.

Other Cutaneous manifestations are: firm fibromatous plaque, especially on the forehead and scalp, soft pedunculated fibromas around the neck an axillae, and poliosis. Fibromatous tumours are occasionally present on the gum, palate and rarely on the tongue, larynx, and pharynx. Small pits commonly occur in the tooth in adult patients.

Mental deficiency – is present in 60-70% of cases, and may be progressive, which include gross behavior disorders, schizophrenia and depression, some times intracranial malignant changes and cord lesions.

Epilepsy – is seen in almost all mentally retarded patients and in some 70% of those with average intelligence. It usually begins in infancy or early childhood, thus often preceding the skin lesion by many years, less frequently the onset is delayed until puberty or adult life. The attacks may be focal, and often become progressively more frequent and severe.

Ocular signs – occur in 50% of cases, but may be hard to detect, include retinal phacomas (white streaks along retinal vessels or small rounded tumours near the disc), pigmentary changes, scotomas.

Cardiac and renal tumours – rhabdomyoma, renal angiomyolipoma, renal cyst.

Pulmonary changes are rare – pneumothorax, cor-pulmonale.

GIT tumours and endocrine disturbances may be present.

Partial forms is clinically evident.

*Diagnosis: is done by clinical findings and the following investigations:

*Radiological findings :-

**Skull – plain X-ray may show calcification in about 50% of cases, although it is not usually apparent until later childhood or adult life. CT and MRI findings include periventricular (subependymal) nodules, parenchymal hamartomas.

**Hand and feet – cyst-like lesions of the phalanges and irregular thickening of the cortex of the metatarsals and metacarpals, also similar lesions localized in vertebrae, pelvis or long bones.

**Lungs – shows irregular reticulation of the lung field, like other types of interstitial fibrosis.

**Kidneys – CT and US and angiography to detect hamartomas.

*Electroencephalographic findings (EEG)- of epilepsy.

*D.D: angiofibroma from acne.
Epithelioma adenoids cysticum – firm, skin colored papules.

Prenatal diagnosis is possible in about 60-70% of cases who represent new mutations.

*Course and prognosis –* the expectation of life for severely affected infants is poor, 3% die in the first year, 28% under 10 years and 70% before the age of 25 years. Death is usually due to epilepsy or intercurrent infections, but occasionally it is due to tumors, cardiac failure or pulmonary fibrosis.

The prognosis for older child or young adult with cutaneous stigmata and epilepsy is unpredictable.

*Treatment*: pulsed dye laser for cosmetic appearance, CO2 laser for larger lesions on the face, surgery may be required for tumors of intracranial organs, drugs for epilepsy.

3. Gardner's syndrome:

It comprises: *multiple epidermoid cysts*, *fibrous tissue tumors*, *osteomas* and *polyposis of colon*, it is inherited as Autosomal dominant gene of variable expressivity, it's gene is located on chromosome 5q.

*Clinical features:*

a. **Polyposis of the colon or rectum** – usually arises during the second decade, but may occur in early childhood, present in about 50% of cases by the age of 20 years, in 40% of patients the polyps shows malignant changes within 15-20 years. Cutaneous and skeletal changes may present without polyposis.

b. **Epidermoid cysts** – may be numerous, are usually irregularly distributed on the face, scalp, and extremities, and less frequently on the trunk, may first appear between 4-10 years, and ultimately present in almost all cases.

c. **Ostomas** – mainly in the maxilla, mandible and sphenoid bone, other bones of skull, and less frequently long bones, usually small and multiple, present in some 50% of cases.

d. **Fibromas, lipomas and leiomyomas (of stomach or ileum).**

*Diagnosis* – by clinical criterias.

*Treatment* – if needed surgical interference of skin lesions, ostomas and polyposis.

Ectodermal dysplasias:

Are a heterogeneous group of disorders in which there is a defect in one or more epidermal appendages (more than 150). Freire-Maia classified this group into '1' indicates hair dysplasia, '2'dental dysplasia, '3'nail dysplasia, '4'sweat gland dysplasia.
1. Hypohidrotic ectodermal dysplasia, X-linked, SYN. ANHIDROTIC ECTODERMAL DYSPLASIA:

**Definition:** is a disorder characterized by partial or complete absence of sweat glands, hypotrichosis and hypodontia.

**Aetiology:** inherited as an X-linked recessive gene on chromosome Xq12-q13. Prevalence 1/10000 births, 90% of cases are males, the complete syndrome does not occur in females, but females are carriers and may show dental defects, sparse hair, reduced sweating and dermatoglyphic abnormalities.

**Clinical features:**
The essential features of the syndrome are *absent or reduced sweating, hypotrichosis and total or partial anodontia*. In complete forms, the appearance of the patient is distinctive, with prominent frontal ridges and chin, saddle nose, sunken cheeks, thick everted lips, large ears and sparse hair. The skin is smooth, soft, dry finely wrinkled (especially around the eyes) and appears prematurely aged.

*Absent or reduced sweating* cause heat intolerance, and the patient may present with unexplained fever in infancy or childhood, extreme discomfort can follow exertion or eating hot foods.

*The temporary and permanent teeth* may be entirely absent, or there may be a few teeth present, the incisors and/or canines are characteristically conical and pointed, jaws are normal, gums may be atrophic, mouth may be dry from hypoplasia of salivary glands and the lacrimal glands may also be deficient, atrophic rhinitis, persistent foul smelling nasal discharge and crust formation, chronic respiratory infection and hearing problems. Aplasia or hypoplasia of the breast.

*Alopecia is often the first feature*, to attract attention, but it is seldom total, the scalp hair is sparse, dry, fine and usually remains short, eye brows are sparse or absent, but the lashes are usually normal, the beard, pubic and axillary hair are often spares.

*The nails are abnormal* in about 1/2 the cases and may be brittle, thin or ridged, but are seldom grossly deformed.

*Corneal and lenticular opacities* have occurred, and *atopic eczema and asthma* are often present.

*General physical development* may be somewhat stunted, but *sexual development* is usually normal, occasionally *primary hypogonadism*.

*Mental development is retarded* in 30-50% of cases. *The expectation of life* is normal or only slightly reduced.

**Diagnosis:** is rarely made until the child is old enough for deficiencies of hair and teeth to arouse parental anxiety, but should be suspected in unexplained hyperthermia. **In full syndrome** the characteristic faces is pathognomonic, and in partial forms the pointed conical teeth provide the most reliable indication and should suggest the need for sweat testing and skin biopsy.
**Treatment : little can be offered**, except advice concerning restriction of physical exertion, choice of suitable occupation, avoidance, if practicable of warm climates, special schooling and psychological support, use of dentures in early age.

2. Hypohidrotic ectodermal dysplasia: two types, Autosomal dominant and recessive. Its features are indistinguishable from those of the X-linked form, except that, complete syndrome occurs in both sexes, and sweating deficiency is less severe in AR form, because sweat glands are reduced in number and not absent, and the mutant gene is located at 2q11-q13.

3. Hidrotic ectodermal dysplasia: SYN. CLOUSTON'S SYNDROME.

   It is characterized by **nail dystrophy**, defects of hair, palmo-planter keratoderma, inherited as **Autosomal dominant gene**, the homozygous state may be lethal, the gene is located at chromosome 13q.

   **Clinical features:**

   **Nail dystrophy** is the key feature of the syndrome, and in some 30% of those affected, there may be no other obvious defect, the nail are thickened, striated, often discoloured and grow slowly, less often they are short, thin and brittle, persistent paronychial infections are frequent.

   **The skin is thickened** beneath the free edges of the nails, over the finger joints, knuckles, and some times over the knees and elbows. **Diffuse hyperkeratosis** of the palms and soles, and may be severe with fissuring, which is some time troublesome.

   **In complete forms**, scalp hair is very sparse, fine, pale and brittle or completely lacking, may be more or less normal in infancy, but seldom remains after puberty, the eye brows are thinned or absent, especially in their outer two thirds, lashes are few and small, vellus, pubic and axillary hair are sparse or absent.

   **The teeth are often normal**, the skull is sometimes thickened.

   **General physical development** is normal, but affected individual may be short.

   **Genital maturation** and life expectation are unaffected, **mental development** may be retarded, but is often normal.

   **Diagnosis** is made by clinical criteria's of the syndrome, and **no treatment** is available.

   **Syndromes associated with DNA instability.**

1. Xeroderma pigmentosum (XP):

   **Definition:** It is a rarer Autosomal recessive disease characterized by: **photosensitivity**, pimentary changes, premature skin ageing, neoplasia and some time neurological complications, due to abnormal DNA repair.

   Both sexes are equally affected, and all races, frequency is 1/250000 in Europe and USA, 1/40000 in Japan. There are at least eight different subtypes that are recognized, designated complementation groups A-G and PX variant.
Aetiology: It is AR disorder in which there is lack of the normal capacity to repair UV radiation damaged DNA, 80% of patients with XP show a defect in the initiation of DNA excision repair of UV photoproducts.

Nucleotide excision repair: is process, where by damaged DNA is removed and replaced by new DNA.

Pigmented xerodermodid (PX) variant: the other 20% of patients called PX variant, have normal NER, but have a defect in an alternative repair process, known as post-replication or daughter-strand repair, which manifest as a reduced molecular weight of newly synthesized DNA in UV-irradiated cell and a delay in the production of intact high-molecular-weight DNA strands following UV radiation.

Clinical features:
The skin is normal at birth, the first symptoms are noticed between the sixth month and the third year in over 75% of cases. Most cases begin in early childhood, have reached the tumour stage before the age of 20 years.

*Freckling and increasing dryness* on light-exposed surface are usually the earliest manifestations, they may follow an acute sunburn or more persistent erythema. The freckles appear first on the face and hands, and later on the other exposed parts, the neck, lower legs, lips and the conjunctiva, and in severe cases the trunk is affected, the freckles are varying in colour from light brown to dark brown, and in size from a pinpoint to a centimeter or more, or may fuse to form irregular patches of pigmentation, fading at first in the winter months, they soon become permanent.

*Telangiectases and angiomas* – on exposed skin appears interspersed among freckles with the progress of condition, also these lesions appears on exposed skin, and on the lingual and buccal mucosa have been reported.

*Atrophic spots* – small, round or irregular, white, atrophic spots are soon added to the picture.

*Superficial ulcers* – healing with difficulty leave disfiguring scars and contractures may produce ectropion and obliterate the outline of the eyelids.

*Keratoacanthomas* – may form even in mildest cases and resolve spontaneously in a few months.

*Actinic keratoses* – are frequent, they may separate spontaneously or may undergo malignant changes.

*Basal cell carcinoma (SCC)* – is also common and may involve the anterior tongue as a result of exposure to UV radiation.

*Melanoma* – arise and may be multiple, angiosarcoma, and fibrosarcoma may rarely occur.
*Ocular lesions* – in 80% of cases the eyes are affected, photophobia, and conjunctivitis, ectropion, destruction of the lower lids, ulceration, pigmented macules on the conjunctiva, pterygium, corneal opacities, epitheliomas of lids, conjunctiva and cornea.

*Neurological complications* – occurs in 20% of cases, include: mental retardation, areflexia or hyporeflexia, spasticity, ataxia, sensor-neural deafness, dysphasia, abnormal EEG findings.

*Small stature and poor physical development*.

*Dominant form* of XP – these patients had a mild clinical course.

**Diagnosis:** fully developed cases are easily diagnosed clinically, the mild or early cases must be differentiated from ordinary freckling, other forms of photosensitivity and premature ageing, include progeria, acrogeria, Rothmund-Thamson syndrome, Bloom's syndrome, Cockayn's syndrome, Hartnup's syndrome and hydrovacciniforme. Prenatal diagnosis by amniocentesis is possible.

**Treatment:** It is untreated disease.

- Sunlight protection, by every possible means, avoidance of outdoor working during daylight hours.
- Early and adequate excision of all tumours is essential, including premalignant lesions, by topical 5-fluorouracil, chemical peeling, dermabrasion, plastic surgery and grafting. Oral retinoid reduce the occurrence of skin cancers.
- Artificial tears and soft contact lenses for eyes.