Genodermatoses / Dermatology

Prof. Dr. Khudair Kh. Al-Kayalli
College of Medicine , Diyala University

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 (46chromosomes- 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 psedo-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 44chromosomes .

*__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 mach donors and recipients in the transplantation of human tissues . The HLA region is located on the short arm of chromosome6 , 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 4or5 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 with out 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 (46chromosomes) , wear as gametes (ova and sperm) are haploid (23chromosomes) , 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 affected .
e. The age of onset and severity of disorder may be variable and the affected individual may remain with out signs or symptoms i.e. remain well into adult life .
f. some AD disorders shows reduced pentrance i.e. person who inherits the gene dose not develop the disorder .

E.g. acute intermittent porphyria , epidermplysis 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 disorders 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 gene carrier .
g. Are often sever 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 hear 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 hear malformations in 40% of cases .**
***duodenal atreasia .**
***Skin** – at birth is normal , early childhood is soft and velvety , between 5-10years become increasingly dry and less elastic , 15years 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 45chromosomes 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 lymphengiectic oedema .
*Small stature and primary amenorrhea .
*Increased number of melanocytic naevi , with increased risk for melanomas .
*Skeletal abnormalities .
*Cardiovascular abnormalities in 25% especially coaractation 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 5mm in greatest diameter in prepubertal individuals and over 15mm 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 with out pseudoarthrosis .

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

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 it's 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 22.6years (range 2-52years) , **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 , periangual 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 5years 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 3-10years , 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 1-10mm 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 (konen's tumours)* –** appear at or after puberty as **smooth , firm , flesh-cloured excrescences** emerging from the nail folds , usually 5-10mm 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 coloure 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 there fore 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 sever .

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) , pigmentery 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 10years and 70% before the age of 25years . Death is usually due to epilepsy or intercurrent infections , but occasionally it is due to tumours , 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 tumours of intracranial organs , drugs for epilepsy .

3.Gardner's syndrome:-

It comprises : ***multiple epidermoid cysts , *fibrous tissue tumours , *osteomas and *polyposis of colon ,** it is inherited as Autosomal dominant gene of variable expressivity , it's gene is located on chromosome5q .

***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 20years , in 40% of patients the polyps shows malignant changes within 15-20years .

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 4-10years , and ultimately present in almost all cases .

c. Ostiomas –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 , libomas and leiomyomas(of stomach or ileum) .

***Diagnosis** –by clinical criterias .

***Treatment –** if needed surgical interference of skin lesions , ostiomas 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 1/100000 births , 90% of cases are males , the complete syndrome dose not occur in females , but females are a 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 sever 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 dyspasia : 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 sever 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 , pigmentary 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 xerodermoid(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 appears first on the face and hands , and later on the other exposed parts , the neck , lower legs , lips and the conjunctiva , and in sever 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 out door working during daylight hours .
- Early and adequate excision of all tumours is essential , including premalignant lesions , by topical 5-flurouracil , chemical peeling , dermabrasion , plastic surgery and grafting . Oral retinoid reduce the occurrence of skin cancers .
- Artificial tears and soft contact lenses for eyes .