Approach to Genetic Disorders

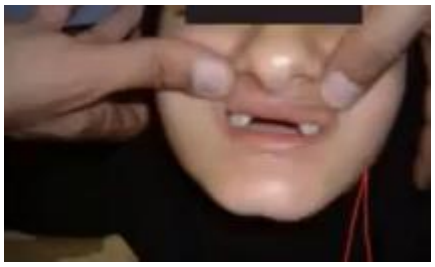
Dr Ali Hawamdeh Lectures

Please note that this sheet includes what the doctor covered in the lectures. *However,* ***for full enlightment regarding any disease*** *(like the diagnostic criteria for neurofibromatosis),* ***please refer to other sources****.*

Sorry for any mistakes.

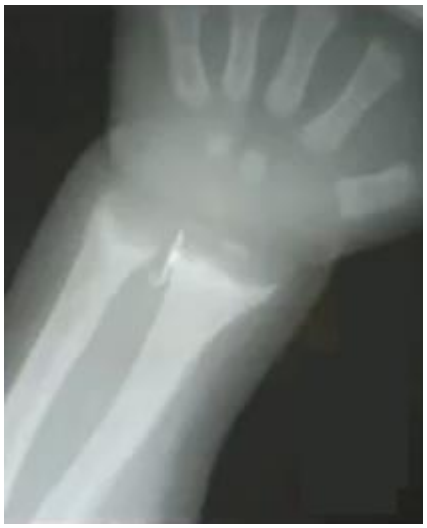
Approach to Genetic Disorders | Dr Ali Hawamdeh

A case of Genu varum (bowing of the legs), dental abnormalities, missing incisors, x-ray showing cupping, fraying, and widening of distal ulna and radius (osteopenia)



Diagnosis: **Rickets**.

What biochemical investigations in addition to x-ray to know the type for rickets?



- Calcium: **normal**.
- Phosphorus: **very low**.
- Alkaline phosphatase: **very high**.
- PTH: **normal** (since trigger for PTH is hypocalcemia or hyperphosphatemia).

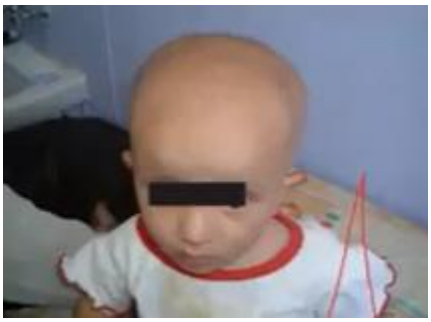
Conclusion: this type of rickets is called **hypophosphatemic rickets or vitamin D resistant rickets**.

Type of inheritance: **X-linked dominant**.

It affects both sexes; but usually lethal in males depending on the severity of the disease; mother says boys are stillbirth, but females are doing relatively well.

Treatment: supplement of one-alpha, vitamin D, in addition to high dose of phosphate (in large amounts) every 4 hours.

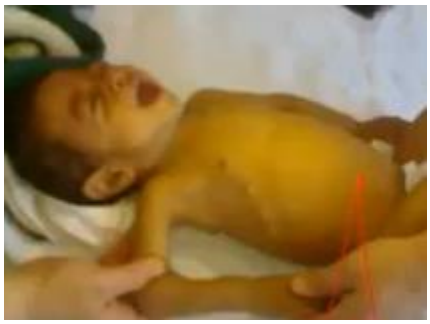
Vitamin D dependent rickets.



Type 1 ➔ Lack of one alpha hydroxylase

Type 2 ➔ Resistance in receptors the enzyme works on

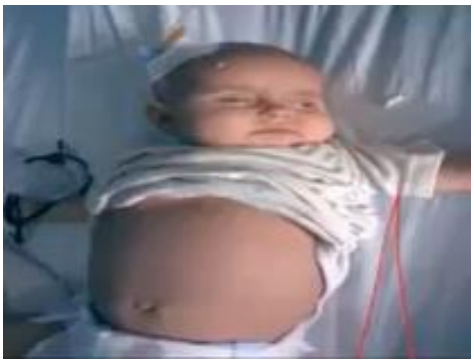
Pattern of inheritance: **autosomal recessive**.



Rickets Rosary (on the costochondral junction) and Widening of the wrist

<u>Vitamin D Resistant rickets</u> is X linked with no male-to-male transmission, while the opposite is true in vitamin D dependent rickets (autosomal recessive).

A Lethargic (no eye-to-eye contact), hypoactive baby with massive hepatomegaly. Glucocheck was done and was found to have very low glucose.



Any patient, even if diabetic, is tired and agitated ➔ check glucose level.

First initial management: IV glucose (notice how the IV canula is inserted through the scalp).

What do you think, what could cause massive hepatomegaly, hypoglycemia, and no splenomegaly?

This is a typical presentation of **Glycogen storage disease**.

- ***All are autosomal recessive except type 9 (X-linked).***

***Note:** Doctor said that only type 9 is x-linked in the lecture, but literature shows that type VIII is x-linked recessive while type XI is inherited as either as X-linked or autosomal recessive.*

Why do they not usually have splenomegaly?

Because glycogen deposition occurs in 3 places in the body: **liver, muscles, and the kidney**.

- **A patient, chubby, red cheeks, strangely no hepatomegaly, hypoglycemia, scars on liver (had liver biopsy)**
- Strangely, upon examination he did not have hepatomegaly.
- Simple liver biopsy does not tell you the type of glycogen storage disease as it only shows glycogen deposition unless you order the specific enzyme.
  ⇨ In developed countries, they do that through genetic testing (mutation based)

- **Upon physical examination: he had Hypoplastic genetalia and micro penis.**

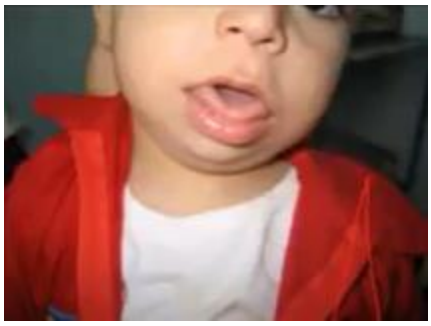
<u>What do you think is the diagnosis?</u>

Hypopituitarism and growth hormone deficiency, not glycogen storage disease (unlikely from presentation).

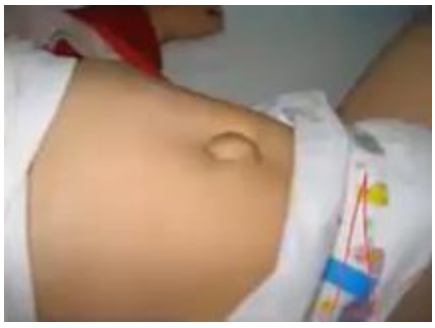
So, there are other causes of hypoglycemia that we should think of; endocrine causes like hyper insulinoma, idiopathic hyperinsulinemia hypoglycemic

2 years a bit too late for growth hormone, but we started him on growth hormone replacement therapy. Could be **primary** (generalized or specific hormone), inherited as autosomal dominant or recessive (sometimes) or **secondary** depending on destructive lesions.

Another patient with hypoglycemia, macroglossia, facial hemangioma, umbilical hernia, crease on hand in physical examination, cause of hypoglycemia was hyperinsulinemia.



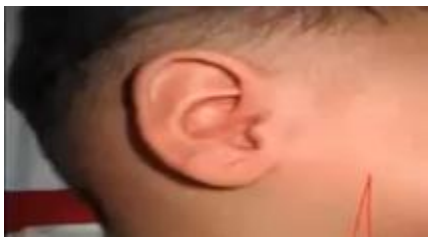
➔ **Bickwith-Wiedman Syndrome**.



<u>Triad of hyperinsulinemia:</u>

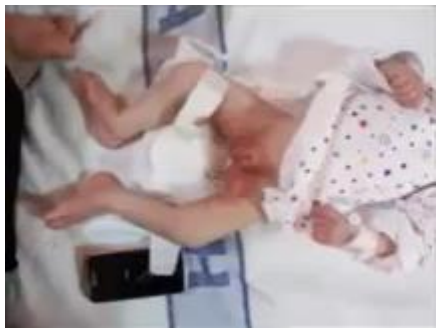
1) Macrosomic or overgrowth.

2) Difficulty in controlling hypoglycemia. (hyperinsulinemia as a cause of hypoglycemia need >15mg/kg/min) while normally we usually need 4-8mg/kg/min.



3) Ketones in urine: always negative.

A patient with chronic severe diarrhea, dermatitis, and alopecia.

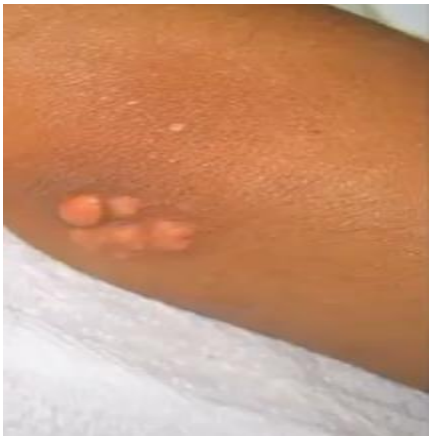


- Side note: **B3 nicotinic acid deficiency** comes with a triad of dementia, diarrhea, dermatitis.
- We can make the diagnosis without the skin biopsy.

Acrodermatitis enteropathica related to zinc deficiency.

- Inheritance pattern: **autosomal recessive**.
- Complete rapid recovery after a few days upon starting zinc therapy.

A patient presented with severe abdominal pain, skin lesion found on elbow upon physical examination, and other similar skin lesions found on the knees. Plasma after centrifugation looks like butter.



Diagnosis: Hyperlipidemia

While in celiac disease: it presents as vesicular lesion on buttocks and lower limbs with no abdominal pain.

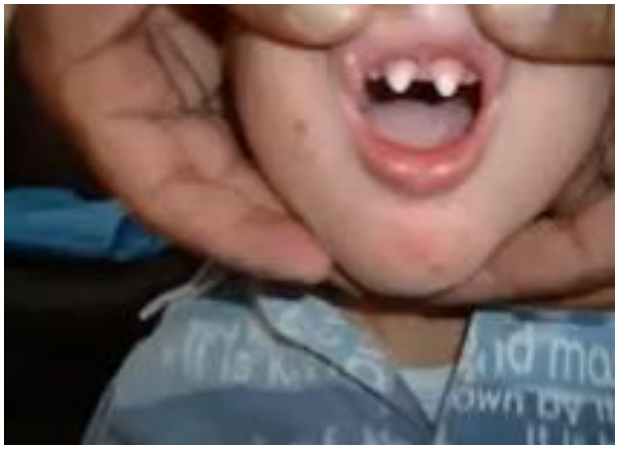
Why did she have severe acute abdominal pain?

Acute pancreatitis.

- Hyperlipidemia Can be inherited or due to acquired causes.
- In adults hypercholesteremia type 2a inherited as autosomal dominant
- **Mixed HyperTriglyceride-cholesterolemia** autosomal recessive
- Lipids are usually <u>in the thousands</u> due to defects in the apoproteins.

Very difficult to treat, a patient had MI and died early.

  - **Xanthoma** on extensor surface of the joint
  - If on eyes: **xanthelasma**



A patient referred to us due to fever of unknown origin.

Sadly, we are used to think of infection when having any case of fever. However, you must always think of other causes:

1. **Collagen vascular disease.**
2. **Malignancy.**
3. **Munchausen by proxy.**

Lips are swollen, peg teeth, parents noticed they never saw him sweating, eyebrows is scanty.

Problem with sweat glands, teeth, hair.

⇨ Problem in ectoderm

If you do not sweat, of course your body temperature will increase.

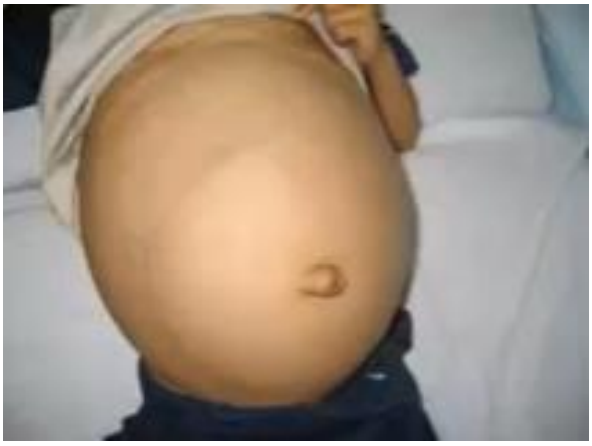
Is there such a disease?

➔ **Anhidrotic ectodermal** dysplasia inherited as **X-Linked**

- **Hidrotic** inherited as **autosomal dominant**.

Clinical diagnosis based on the findings.

A patient with abdominal distention, everted umbilicus, and massive hepatosplenomegaly.

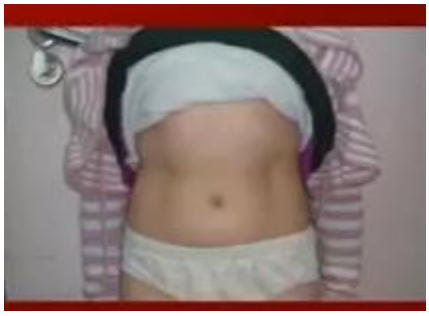


- **Lysosomal storage disease: Goucher disease**
- **Goucher disease is the most common lipid storage disease**.
- **Tay-Sachs disease** and **Wolman's disease** are other examples of lipid storage diseases.

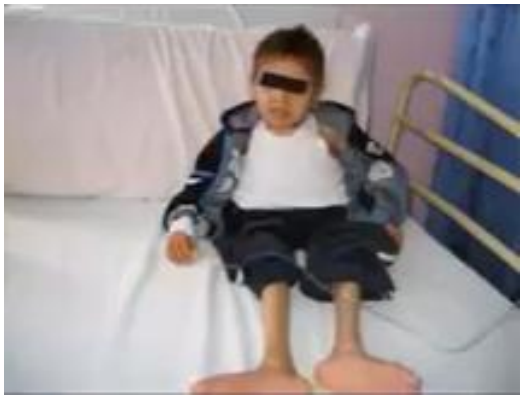
Missing enzyme in this patient is unavailable in the labs, or is too expensive, unfortunately ☹

As a palliative treatment: we did splenectomy to improve the quality of life.

Another patient, with no liver and no spleen, underwent enzyme replacement therapy.



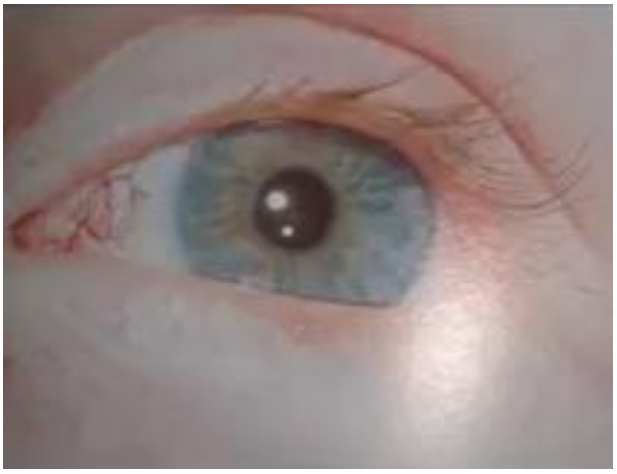
This patient has Neimann pick disease (not sure)



A patient presented to our clinic with ataxia, upon physical examination, telangiectasia was found in the conjunctiva.

➔ **Ataxia and telangiectasia**

Inherited as **autosomal recessive**.



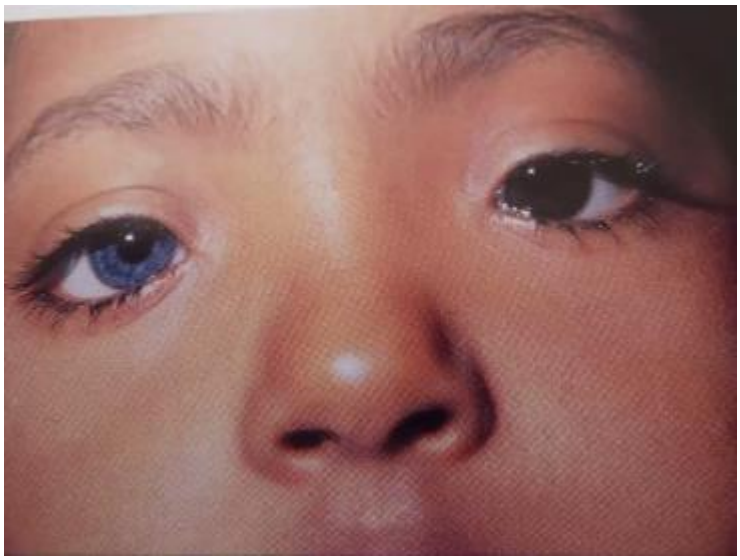
A patient presented with excessive tearing, photophobia and buphthalmos.

Congenital glaucoma.

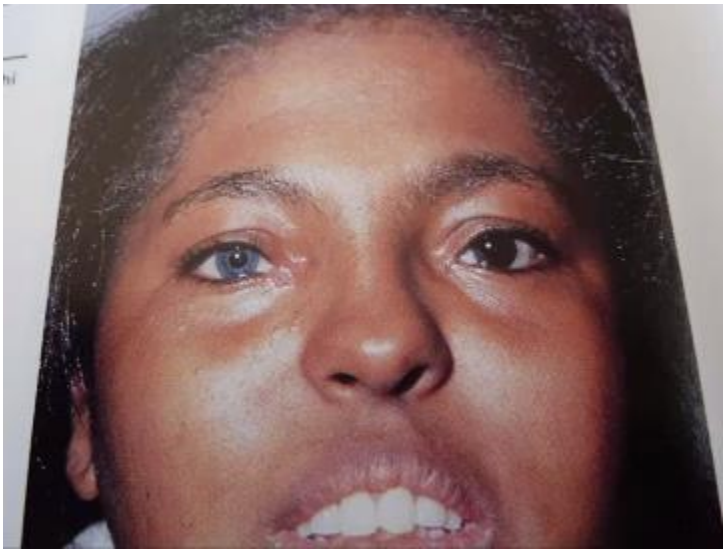
Any glaucoma in the first 3 years of life is considered as congenital glaucoma.

Approach to Genetic Disorders | Part (2)

A case of heterochromia iridis, hypertelorism (eyes widely spaced), could be a normal finding but this patient also had deafness.



This is her mother.

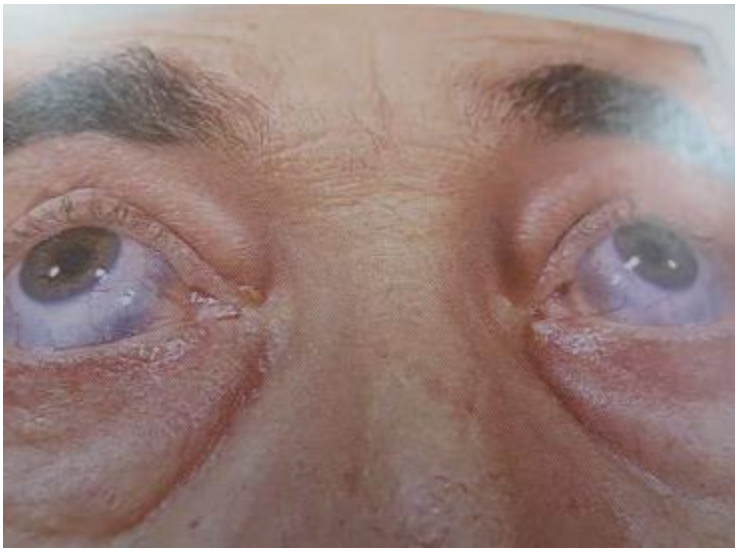


Waardenburg syndrome

Pattern of inheritance:
Autosomal dominant

When the disease manifests directly; the mother is affected, and the daughter is affected…this means the diease is autosomal dominant.

A case of osteogenesis imperfecta, defect in collagen type 1 causing the sclera to be very transparent.



- **Side note:** blue sclera can be normally seen in neonatal and infancy period because it is still not well developed.

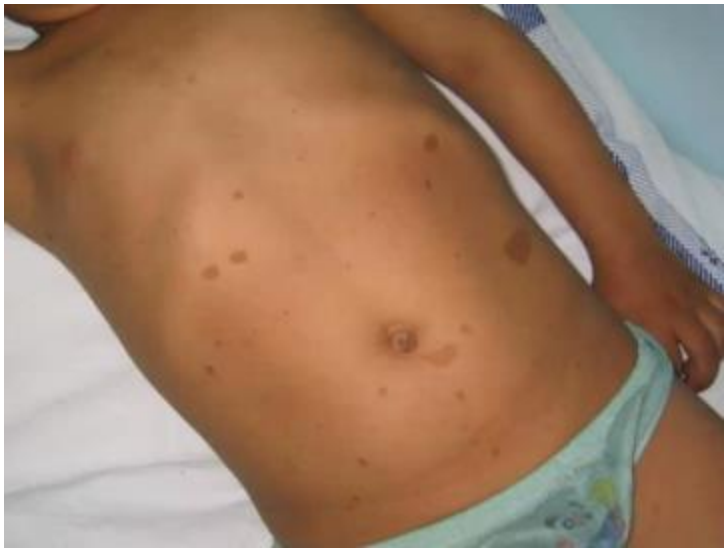
Can be also seen in elderly, we do not see **rickets** in elderly but **osteomalacia**. If affected eyes: **Keratomalacia**

A case with hypoglycemia, absent red reflex.

Classical galactosemia.

Typical Congenital infection associated with cataract: **Congenital Rubella.**

A case of neurofibromatosis, **café au late spots** (hallmark of type 1 neurofibromatosis)

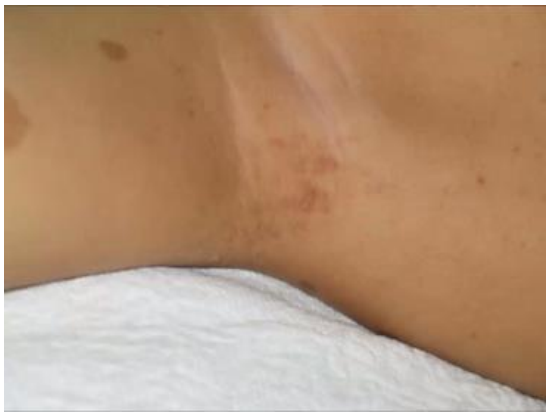


Many people develop café au late spots. However, to be considered significant:

1. Prepubertal more than 6 and size more than 0.5 is significant to be a NF type 1.
2. Post pubertal more than 6 and size more than 1.5 cm is significant to be a NF type 1.

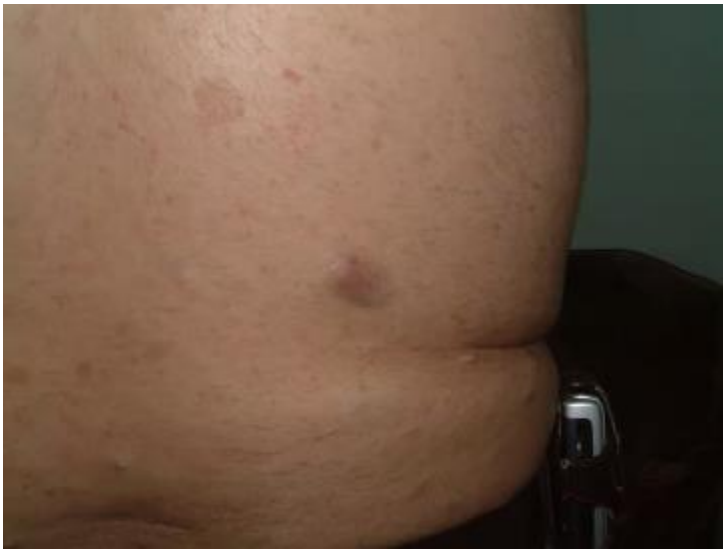
Hallmark of type 2 neurofibromatosis is **bilateral acoustic neuroma**.

Axilla freckling, hyperpigmented spot in the axilla



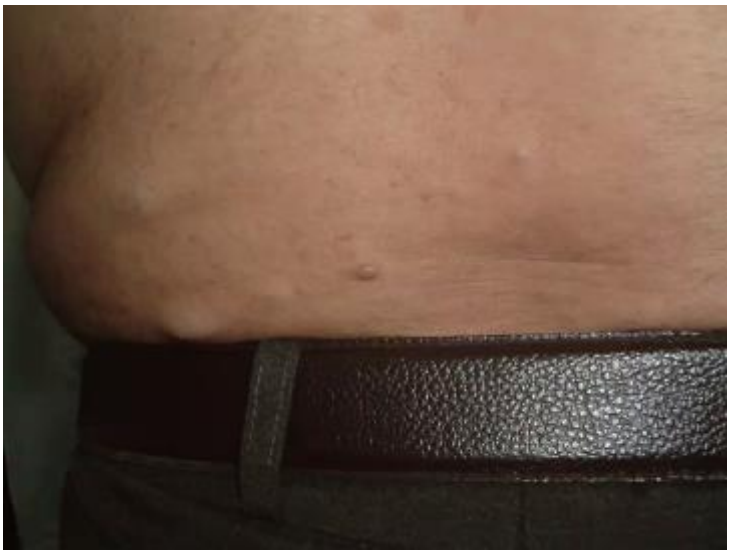
- **One of the major criteria for diagnosing neurofibromatosis**. (Just like rheumatic fever where multiple major and minor criteria are needed since it is a clinical diagnosis).

Neurofibroma

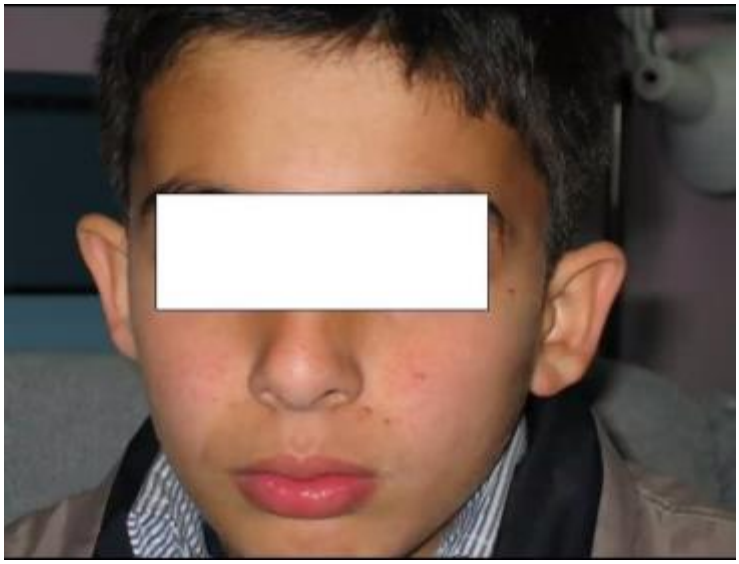


Neurofibromas in his father

Autosomal dominant



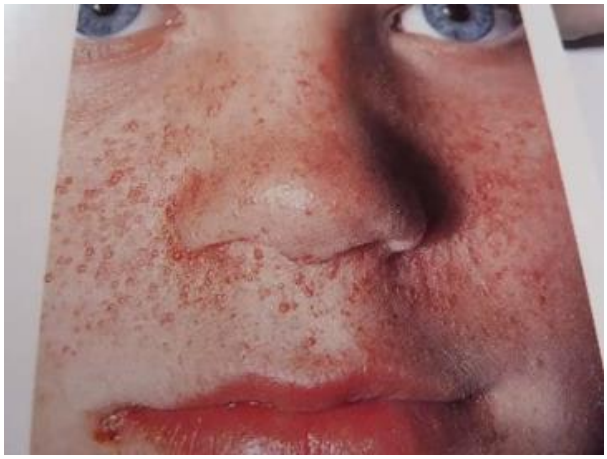
Patient referred from the dermatology clinic for having: Severe acne in the face that doesn't go ➔ **Angiofibroma**



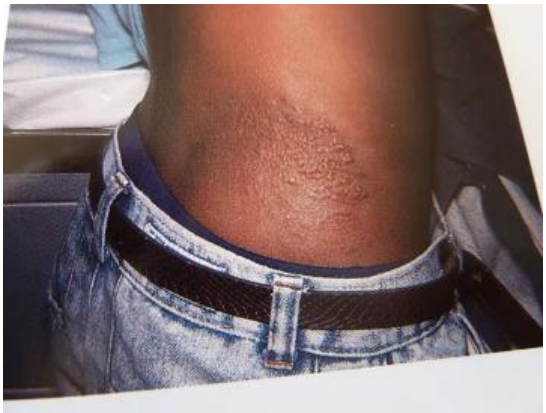
Lesion in face and seizure. What comes to your mind of **neurocutaneous diseases?** (Meaning CNS and skin manifestation): **Tuberos sclerosis**.

Inheritance pattern: **autosomal dominant** (most of neurocutaneous diseases are autosomal dominant)

Angiofibroma of a very severe tuberous sclerosis



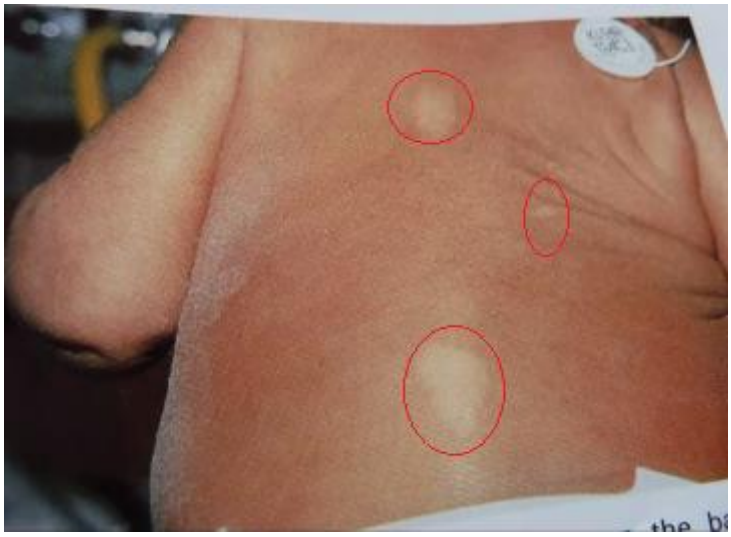
Shagreen Patch



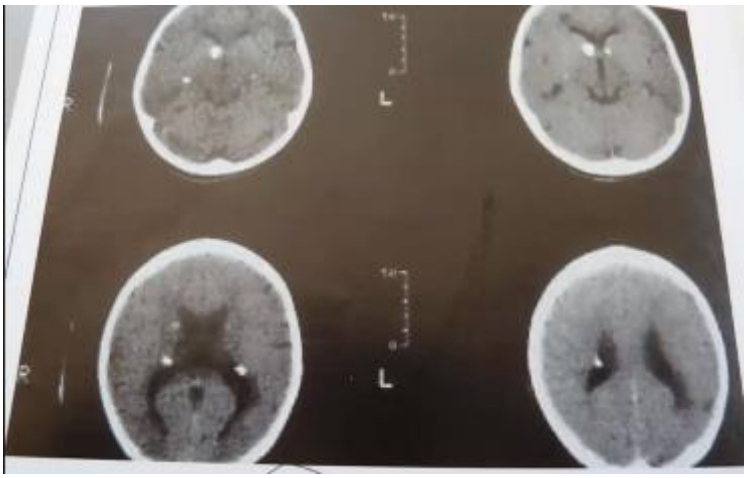
Hypopigmented patch.

Ash-leaf macule: must be 3

CT scan periventricular calcifications also called **Candle sign**.

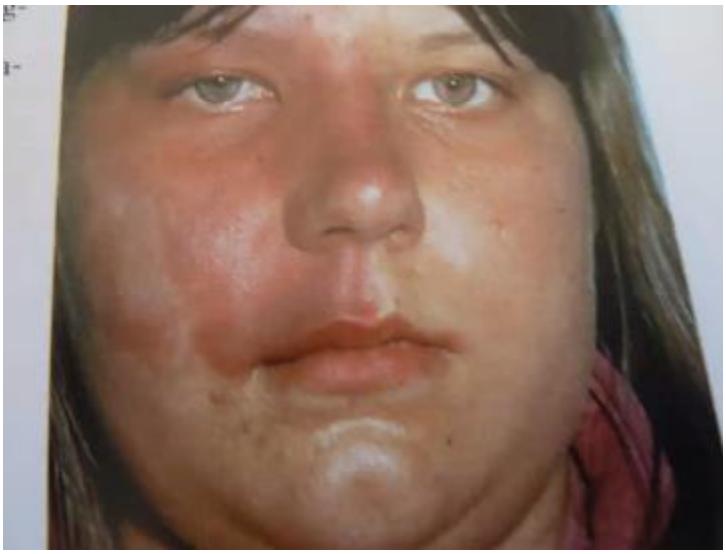


A PATIENT SUSPECTED TO HAVE INTRACRANIAL CALCIFICATIONS ➔ MRI IS NOT SENSITIVE TO DEMONSTRATE CALCIFICATIONS ➔ ORDER A CT.



Congenital infection causes Periventricular calcifications and microcephaly ➔ **congenital CMV**

A patient presented with seizures.



Port wine hemangioma ➔ **Sturge weber syndrome**.

If presented with hemiplegia, would it occur on left side or right side?
On left side, contralateral to the lesion.

There is a risk to have glaucoma because trigeminal nerve has three branches: ophthalmic, maxillary, and mandibular. **If ophthalmic is affected**, there is a high risk of glaucoma associated with this disease.

Pattern of inheritance: **Sporadic, not inherited**.

All neurocutaneous diseases are autosomal dominant except this one.

Twins presented with Congenital microcephaly.

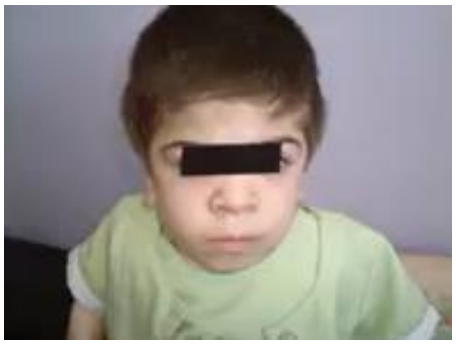
Head circumference at birth is around 35 cm.

- **First year increases 12 cm**
  - First 3 months: 6 cm
  - Second 3 months: 3 cm
  - Second 6 months: 3 cm.
- **Second year increases: 2 cm.**

Most important increase in head circumference occurs in the first year of his life since it's when maximum growth of the brain occurs. If it doesn't occur, we called it **microcephaly** which is an inherited disease.

Pattern of inheritance of microcephaly: can be autosomal dominant or recessive or X-Linked.

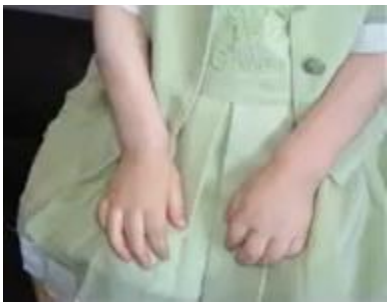
Hair is thick, coarse facial features, hirsutism, and widening of the wrist.



Typical of **Mucopolysaccharidosis** and there are of the lysosomal storage diseases.

All lysosomal storage diseases are autosomal recessive except 2 (hunter)

Whereas all glycogen storage diseases are autosomal recessive except type 9



Rule out hypothyroidism

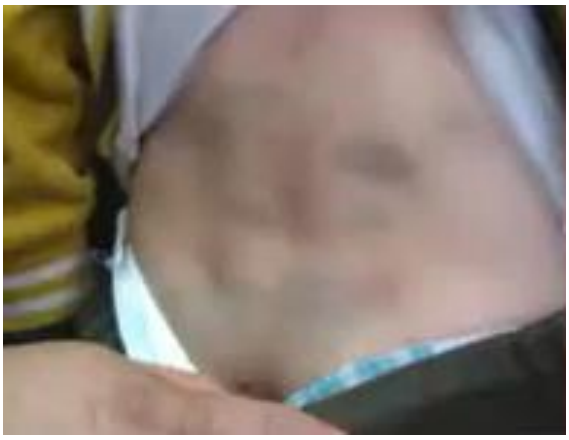
Umbilical hernia because they have hepatosplenomegaly.

This patient same disease but came with bluish discoloration around the eyes, called **raccoon eyes**.

If such a patient came with this physical finding at the ER, what's the important thing to rule out?

Basal skull fracture ➔ They are more prone to injuries.

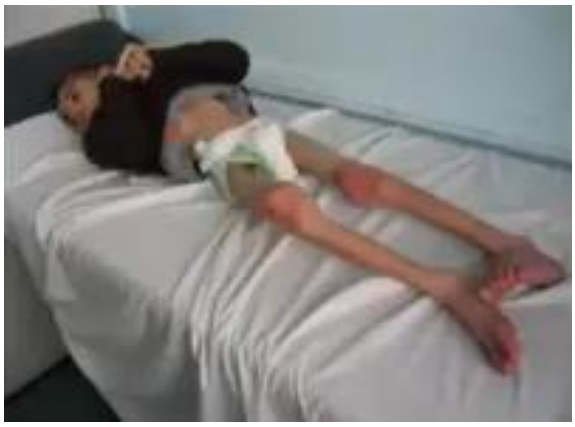
Bluish discoloration of the back ➔ Mongolian spot, which can be a normal finding.



However, if excessive and extensive Mongolian spots, you must think of certain metabolic diseases.

If sudden ➔ think of Child abuse.

A patient, who cannot walk, looks like skin and bone on physical examination; severe muscle wasting with bed sores, and diaper dependent.



Muscle wasting occurs with both UMN and LMN, more excessive with LMN disease. This is an UMN disease.

Amino acid profile: showed increased levels of valine, leucine, and isoleucine.

Typical of **Maple Syrup Urine Disease**; one of the metabolic diseases.

His younger brother, also affected, got better with formula.

A patient with blue eyes, blond (black hair father), mental retardation, and seizure.

Phenylketonuria.

Phenylalanine is an essential amino acid, meaning the body cannot salvage it and is needed in the diet.

He needs phenylalanine for the growth of the brain! But you need to give it in selected amounts with monitoring.

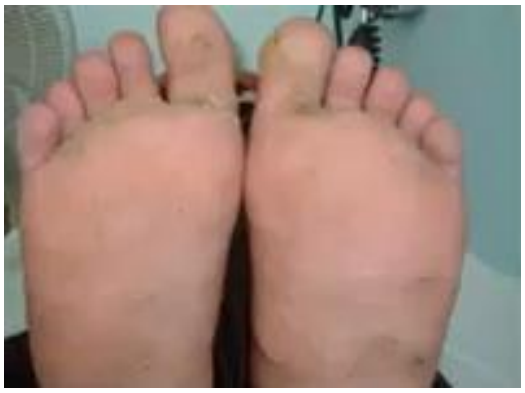
***The only contraindication for breast feeding in metabolic disease is* classical galactosemia**.

A patient with Hypoglycemia, hepatomegaly, and absent red reflex, died same night at 1 week of age☹, because he was given formula containing lactose.

Early diagnosis in metabolic diseases is very important as you can provide proper treatment for a disease that could be totally preventable!

Tyrosinemia type 2:

Hyperkeratosis of the toes and corneal ulcer.



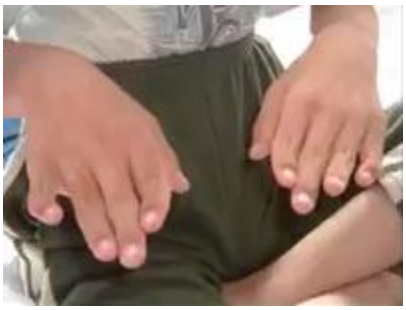
A patient with down syndrome, at 12 hours of age, bile-stained vomiting, what do you think of?

Biliary obstruction indicates level of obstruction distal to ampulla of vater.

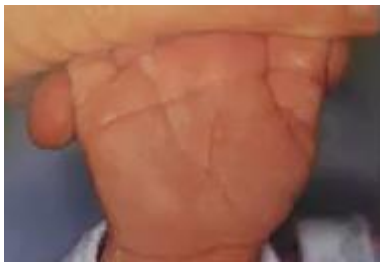
Duodenal atresia.

Plain AXR: double bubble sign.

Clinodactyly: little finger inverted.



Single palmar crease



Haploid number of humans is 23 chromosomes.

Any increment of haploid ➔**Polyploid** (46, 69)

Any number that is not polyploid ➔ **Aneuploid** (47)

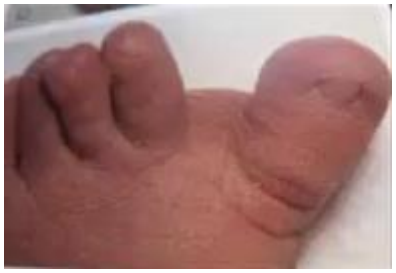
The most common aneuploidy is **Down syndrome**.

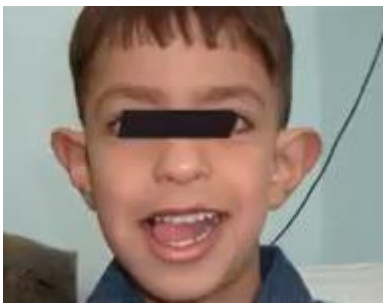
What question do you like to ask the mother?

Maternal age because most trisomy's are associated with increased maternal age.

Wide gap between big toe and the other toes.

Sandal sign or hallux varus.





Most common cause of inherited mental retardation in a male: **Fragile X Syndrome**

Inheritance pattern: **X-linked**.

Does it affect females? Yes, because it is one of the trinucleotide repeats, depends on the number of repeats.

50-200 premutation.

>200: fragile x syndrome.

The concept of genetic imprinting

The number of chromosomes inherited from each parent is 23; 23 chromosomes from the mother and 23 chromosomes form the father to have an overall number of 46 chromosomes.

This applies to each chromosome in the body. For example, chromosome 15 should be inherited as single copy from the father and single copy from the mother.

Clinical manifestation of deleted chromones depends on origin of chromosomes, whether it is coming from the mother, or the father.

Deleted ch15 from mother: Angelman syndrome

Deleted ch15 from the father: Prader–Willi syndrome (PWS)

Uniparental disomy; instead of getting ch15 one from father, and one from mother, we could take both ch15 from the mother or both ch15 from the father.

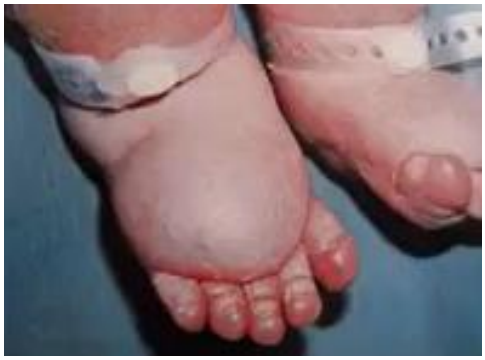
That is why important to know from where the chromosome is coming when doing chromosome testing.

Extreme obesity, developmental delay, and they do not feel full no matter the amounts they eat.

In infancy: they present with extreme hypotonia and refuse to breastfeed but after one-year, exaggerated appetite occurs leading to requiring lots of breast-feeding.

Inappropriate laughing ➔ **Angelman Syndrome**.

Dorsal edema of both feet in a female, Turner syndrome (45XO)



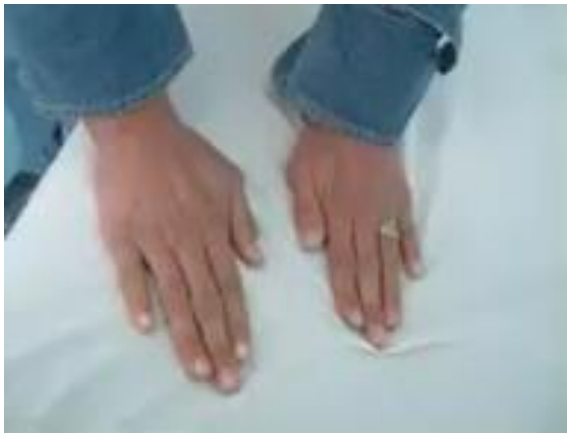
Most common congenital heart disease in turner syndrome: coarctation of the aorta.

Most common congenital heart disease in Down syndrome: endocardial cushion defect (AV canal defect).

A patient with extremely short stature, the most common congenital skeletal dysplasia: **Achondroplasia**.

Inheritance pattern: autosomal dominant.

A very long stature patient, arachnodactyly, and wears glasses (dislocation of the lens and myopia)



Marfan's Syndrome.

The associated cardiovascular complication: **Aortic dissection**.