Angelman Syndrome, Rett Syndrome, and Tuberous Sclerosis

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Continuum of Care

Angelman Syndrome

- Identified: 1965 by English physician Harry Angelman.
- Originally named the Happy Puppet Syndrome.
- First reports in North America were in the 1980s.
- Incidence: 1:15,000-30,000

Physical Characteristics in 100% of cases confirmed

- Developmental delay
- Speech impairment, none or minimal use of words.
- Movement or balance disorder: manifested as gait ataxia, or tremulous limb movements or both.

Clinical Characteristics

- Any combination of:
  - Frequent laughter
  - Frequent smiling
  - Apparent happy demeanor
  - Easily excitable
  - Hypermotoric behavior
  - Short attention span
- Seizures (this is actually 80 – 90%).

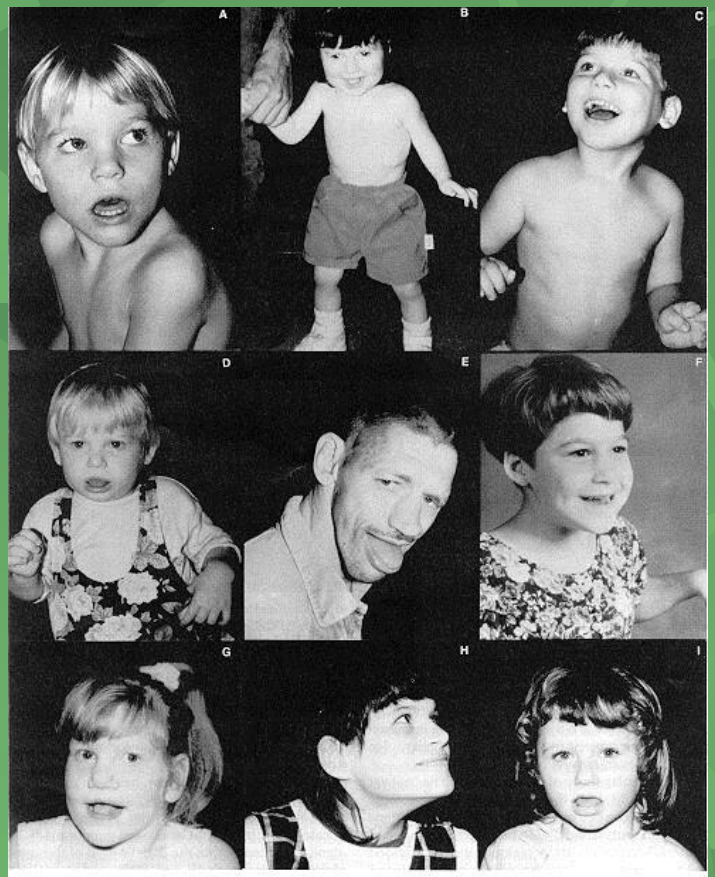


FIGURE 1. Composite of unrelated individuals with AS illustrating some typical behavioral and facial appearances. All individuals except C have typical large deletions of 15q11-13. Individual C has no abnormality yet detected of his chromosomes 15. See text for details.

Clinical Characteristics, seen in 20 - 80%

- Flat occiput
- Protruding Tongue
- Prognathia
- Wide mouth with widely spaced teeth.
- Feeding problems during infancy
- Excessive Appetite
- Frequent drooling
- Hypopigmented skin with light hair and eye color
- Strabismus
- Attraction or fascination with water
- Hyperactive lower limb deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Increased sensitivity to heat
- Sleep disturbance

Angelman Syndrome

- Generally not recognized until late infancy due to absence of speech development, and developmental delay.

FIGURE 2. Composite of unrelated infants and children with typical large deletions of 15q11-13. Facial dysmorphia or unusual facial appearance is typically not present at this age, although happy disposition may be evident. See text for details.

Diagnosis

- Four known genetic mechanisms can lead to Angelman Syndrome:
  - Deletion of chromosome 15 q11-13 (maternal)
  - Paternal Uniparental Disomy
  - IC (imprinting center) mutation.
  - UBE3A mutation.
  - Unknown.

Deletion 15 q11-13

- Seen in 65 – 75% of AS cases.
- Recurrence risk is less than 1%.
- Tested for with high resolution chromosome analysis which can detect up to 70%.
- Follow up testing with FISH (fluorescent in-situ hybridization) is needed due to the fairly high false positive and false negative results of the high resolution chromosome study.

Paternal Uniparental Disomy

- Seen in 3 – 5% of cases.
- Less than 1% recurrence rate.
- The patient has 2 paternal copies of chromosome 15.
- This represents a loss of the genetic information from the maternal chromosome 15.

IC (imprinting Center) mutation

- 7 – 9% of Angelman cases.
- The IC activates the maternal 15 q11-13 chromosomal material.
- In absence of the IC, the 15 q11-13 material is not activated, and Angelman syndrome results.
- Spontaneous mutations are associated with <1% recurrence rate.
- If mother carries the IC mutation the risk is 50%.

UBE3A Mutations

- Seen in 6 – 20% of cases.
- If the mutation is spontaneous the recurrence risk is <1%.
- If the mother carries the mutation the recurrence risk is 50%

UBE3A Mutation

- UBE3A encodes for the protein E6-AP.
- E6-AP is an enzyme necessary for normal protein turnover in the cell.
- In the normal child, only the maternal copy of the UBE3A gene is expressed in the brain.
- The paternal copy is silent.
- In mice the gene is active in the hippocampus, and cerebellum.

UBE3A Mutation

- Therefore:
  - No UBE3A gene segment

  - No E6-AP

  - Absence of breakdown of certain proteins within the brain.

Testing

- To test for Angelman Syndrome:
  - Call your local geneticist.

Seizures

- Seen in >80% of individuals with AS.
- Myoclonic seizures are the most common type witnessed.
- Generally the seizures are intractable.
  - Ketogenic Diet is the most effective treatment.

Aging

- Increased tendency for falling
- Worsening ataxia
- Coincides with the theory that the patient is unable to adequately able to break down certain proteins in the brain, specifically the cerebellum and hippocampus.

Rett Syndrome

- First described by Dr. Andreas Rett in Vienna Austria.
- Worldwide recognition followed a paper by Dr. Bengt Hagberg, and colleagues in 1983.

Rett Syndrome

- Commonly seen in girls
- Described in boys, but is usually lethal, causing miscarriage, stillbirth, or early death.

Rett Syndrome

- Occurs in 1:10,000-23,000 live female births.
- 75% have a genetic mutation (MECP2) on the X chromosome (Xq28).
- Affects people of all ethnic backgrounds.

Developmental Characteristics

- Usually show normal or near normal development until 6 – 18 months of age.
  - Sit independently
  - Finger feed at the expected time.
  - Most do not crawl, but tend to bottom scoot, or combat crawl.
  - Many walk at the expected time.

Developmental Characteristics

- They may begin to develop speech appropriately, then lose this ability.
- They develop an apraxia with loss of purposeful hand function
- Assessment of intelligence is complicated by the loss of speech, and apraxia.
- Secondary microcephaly.

Associated manifestations

- Seizures:
  - Non-existant to severe and intractable.
  - Tend to diminish with age.
- Atypical Breathing pattern:
  - Episodes of hyperventilation.
  - Aerophagia.
- Stereotypic hand movements
  - Hand wringing
  - Hand clapping
  - Hand mouthing

Associated Clinical Features

- Autistic Features:
  - Rapid regression
  - Irritability
  - Loss of social skills
  - Diminished eye contact
- Most of these features tend to decrease some with age.

Rett Syndrome and the brain

- Children have a normal head circumference at birth.
- Develop secondary microcephaly
- Imaging studies confirm a reduction in brain volume
  - Frontal cortex
  - Caudate nucleus
  - Decreased melanin in the substantia nigra.
  - Smaller neurons.

Genes

- There are approximately 37,000 genes in each cell's nucleus.
- Each cell type expresses a subset of the genetic material within the nucleus.
- The subset of genetic material expressed may be expressed only at specific times in development.
- Each cell needs to turn off about 25,000 its genes.

MECP2 Gene

- The MECP2 gene is transcribed and translated to MeCP2 protein.
- The MeCP2 protein has 2 functional domains.
- The 1st domain binds the MeCP2 protein to the region of a segment of DNA (at the beginning of genes).
- The 2nd domain recruits other proteins to inhibit transcription.

MECP2 Gene

- An MECP2 mutation exists in Rett syndrome.
- A common mutation is for a C residue to be changed to a T along the DNA.
- Less commonly, a block of 12 nucleotides is deleted.
- Mutations are usually sporadic, though in some cases a mutation exists in the X chromosome of one of the parents.

Father XY + mother XX

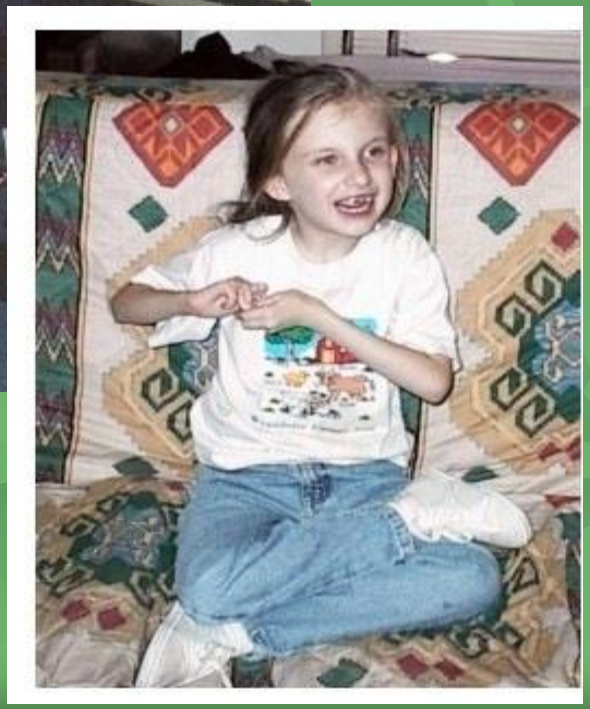
- Son (XY) healthy
- Daughter (XX) with Rett Syndrome

Father XY + Mother XX

- Son XY (usually embryonic lethal)
- Daughter XX Rett Syndrome

Recurrence Risk

- ≤0.5%
- Consult a Geneticist



Long term outcome

- Patients tend to improve after adolesence, but never return to normal.
- Death is common in early adulthood due to autonomic dysfunction leading to sudden cardiac death.

Tuberous Sclerosis

Background

- First described by Dr. Von Recklinghausen in 1862.
- Dr. Bourneville in 1880 is usually credited with the initial description of the disease.
- Vogt (1908) emphasized the association of adenoma sebaceum and cerebral scleroses.
- Triad:
  - Adenoma Sebaceum
  - Mental retardation
  - Seizures

Pathophysiology

- Autosomal dominant inheritance
  - 50 – 70% new mutations?
- Two gene loci have been identified so far.
  - Chromosome 9q34 (TSC 1) which produces the protein Harmartin.
  - Chromosome 16p13 (TSC 2) which produces the protein Tuberin.
  - Both proteins seem to play a role in the regulation of cell growth and differentiation.

Epidemiology

- Frequency: 1:5,800 – 30,000.
- No racial, ethnic, or sexual predilection.
- Morbidity and Mortality:
  - Highly variable depending on the severity with which an individual is affected.

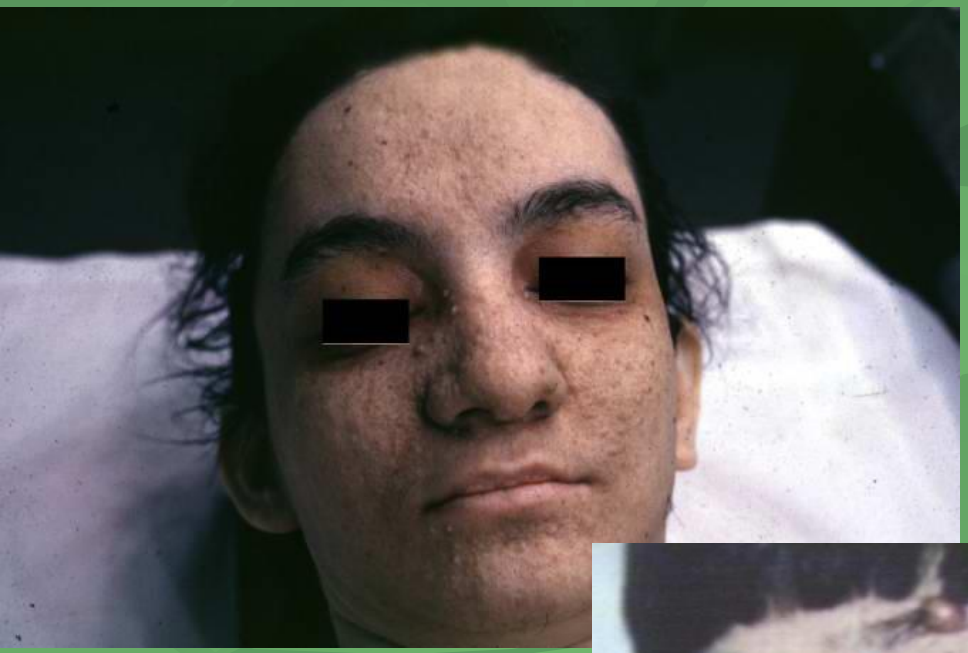
Diagnosis

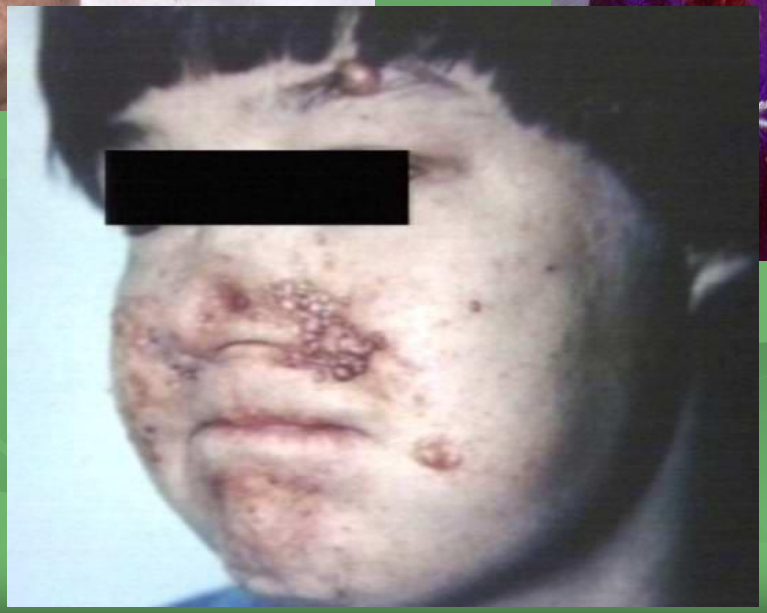
- Most children are diagnosed between the ages of 2 to 6 years.
  - Presentation is often Infantile Spasms
  - Cortical changes on imaging studies may not be apparent until 2 years of age.

Physical Features

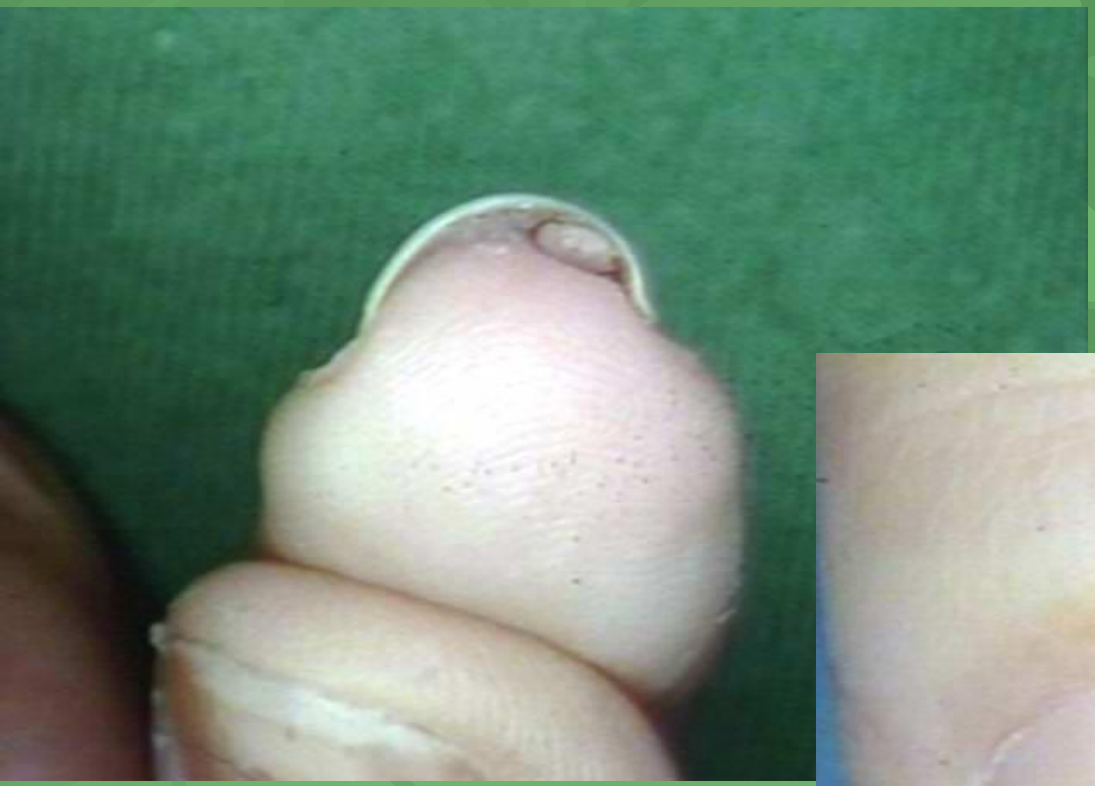
- Clinical Criteria have recently been revised and separated into major and minor features.
  - Definite TSC = 2 major features or 1 major + 2 minor features.
  - Probable TSC = 1 major feature + 1 minor feature.
  - Possible TSC = 1 major feature or 2 or more minor features.

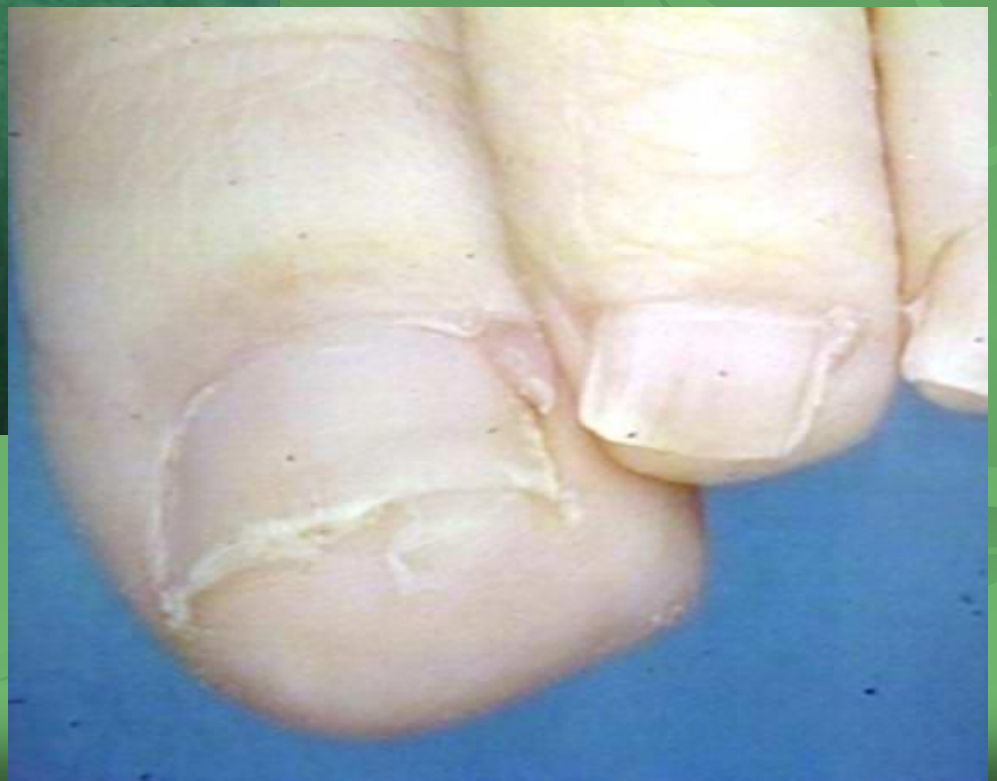
Adenoma Sebaceum



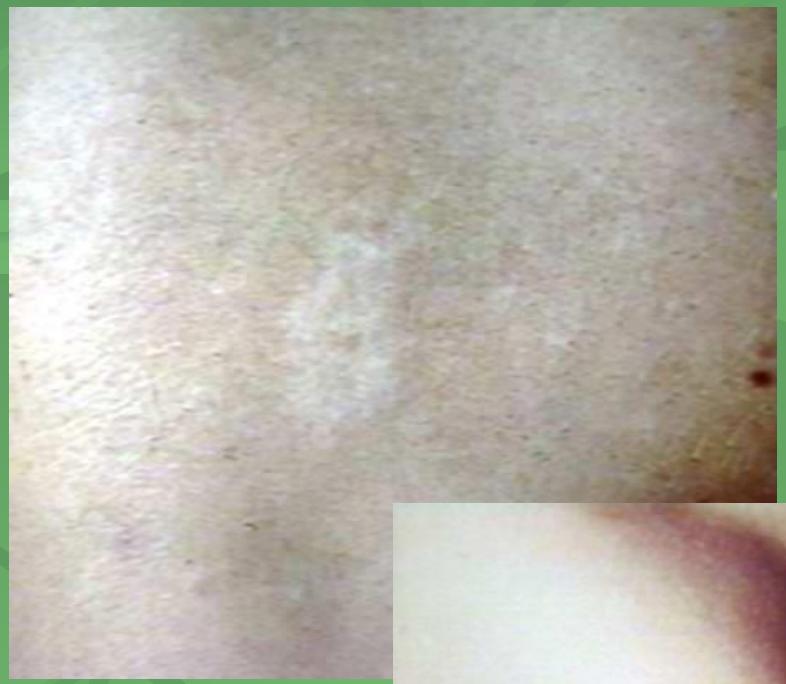


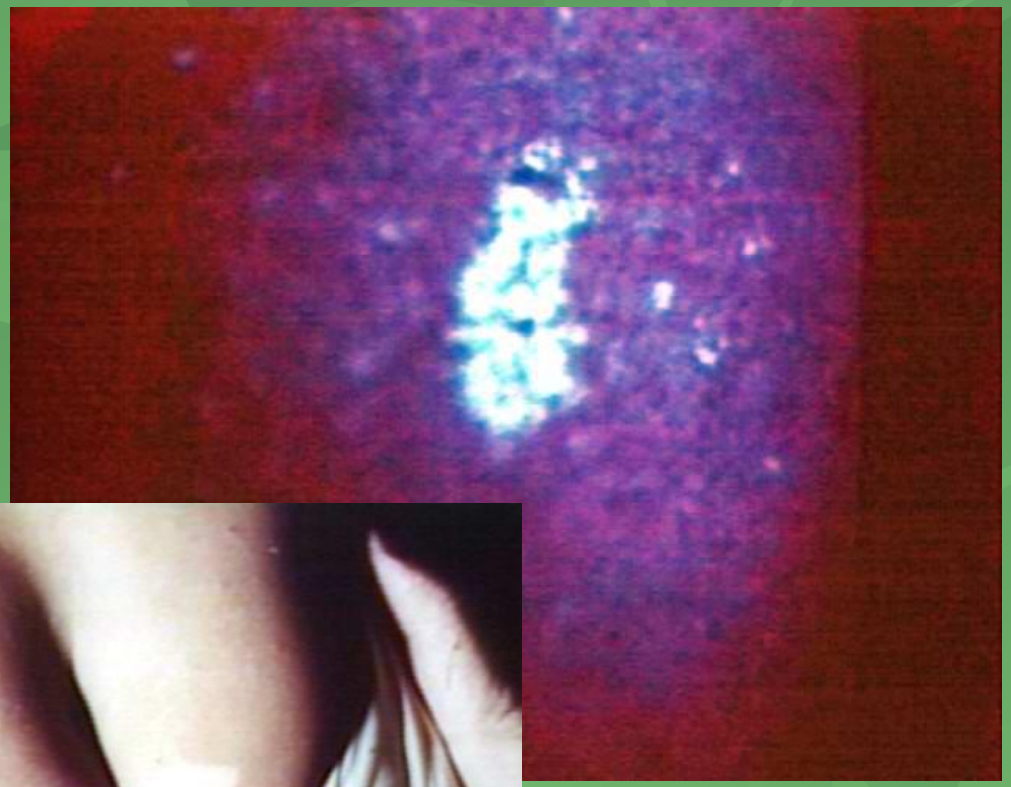
Ungual or Periungual fibromas



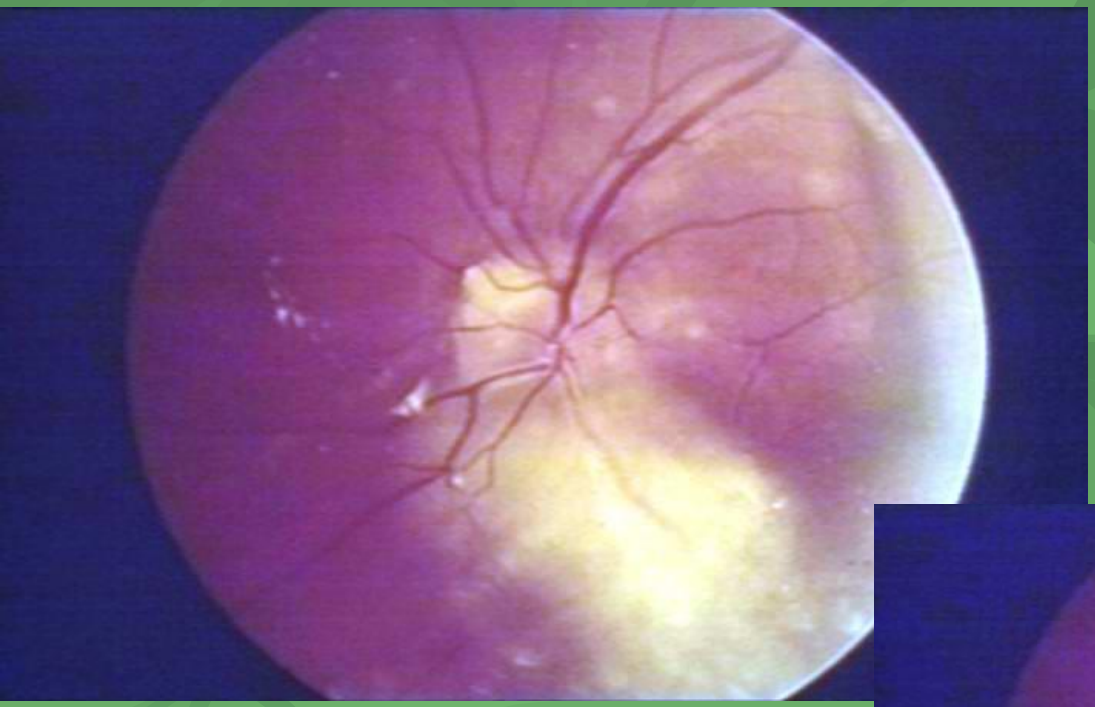


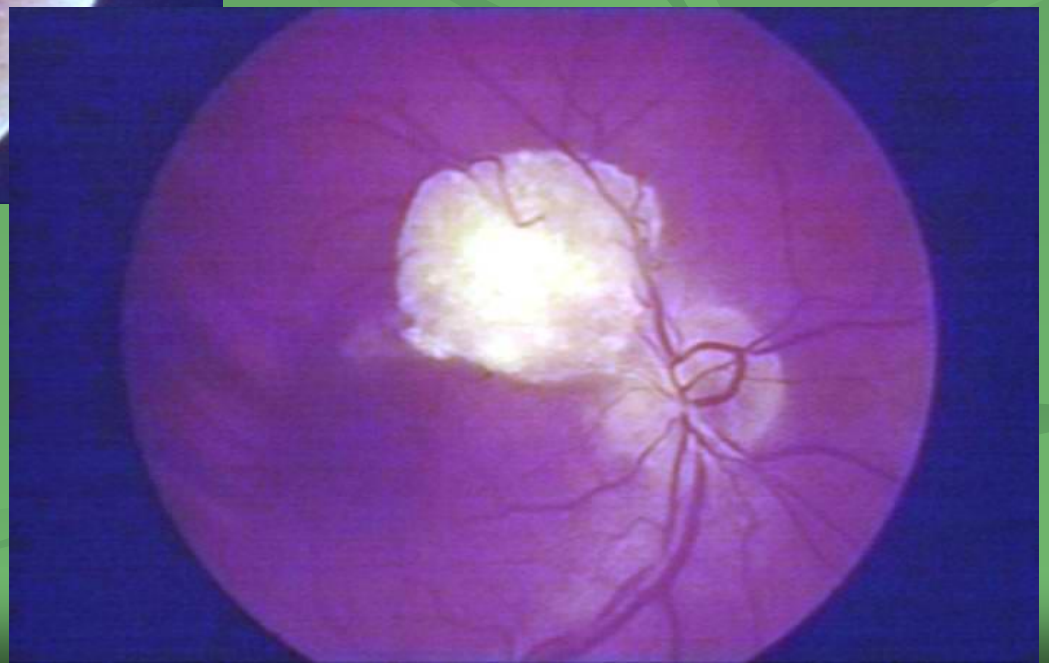
Hypomelanotic macules ≥ 3



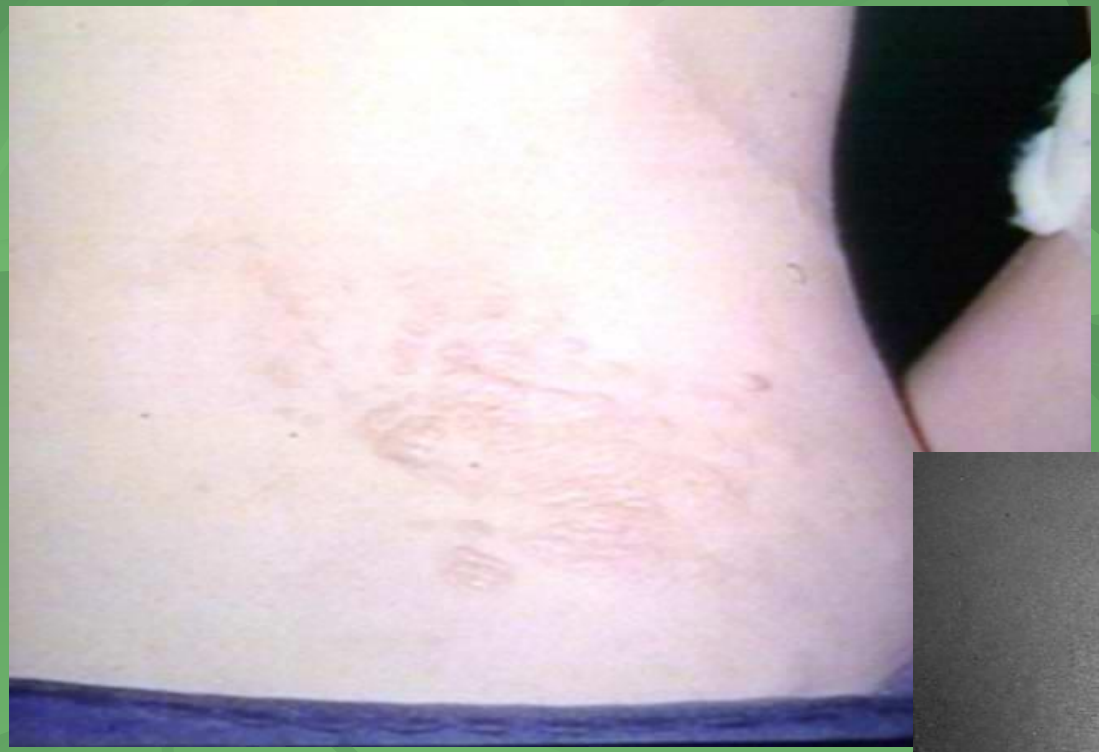


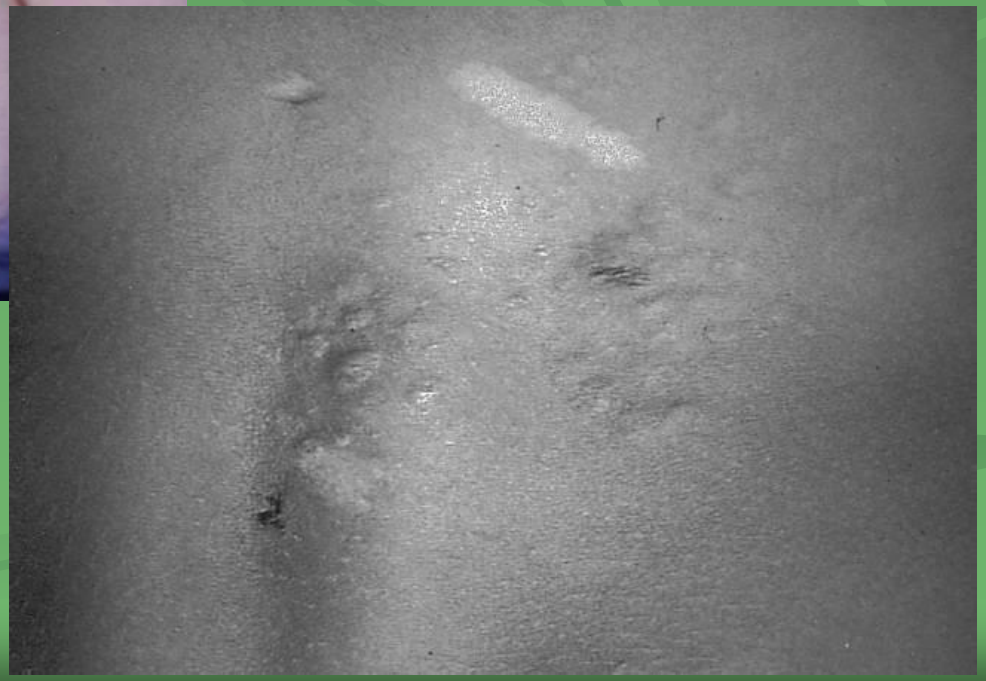
Retinal Harmartomas



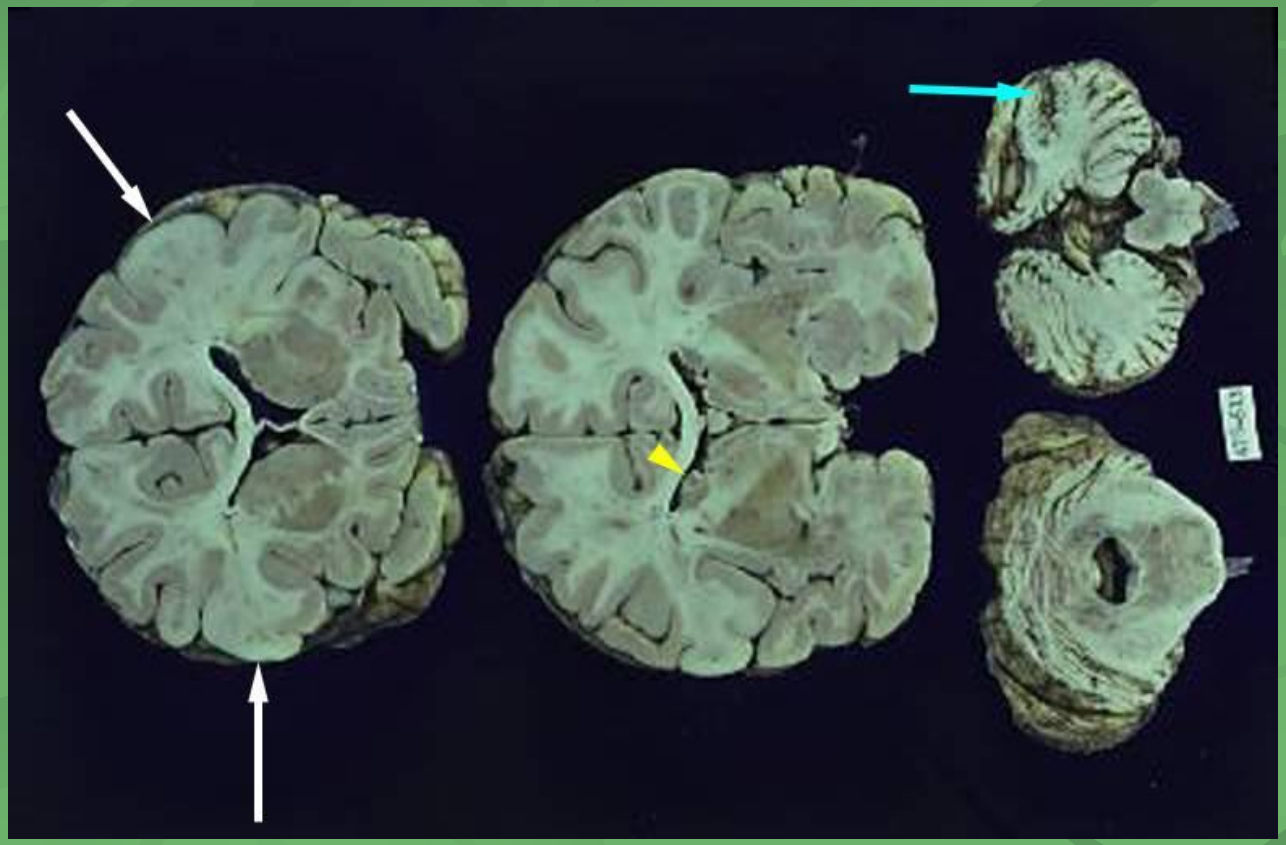


Shagreen Patch

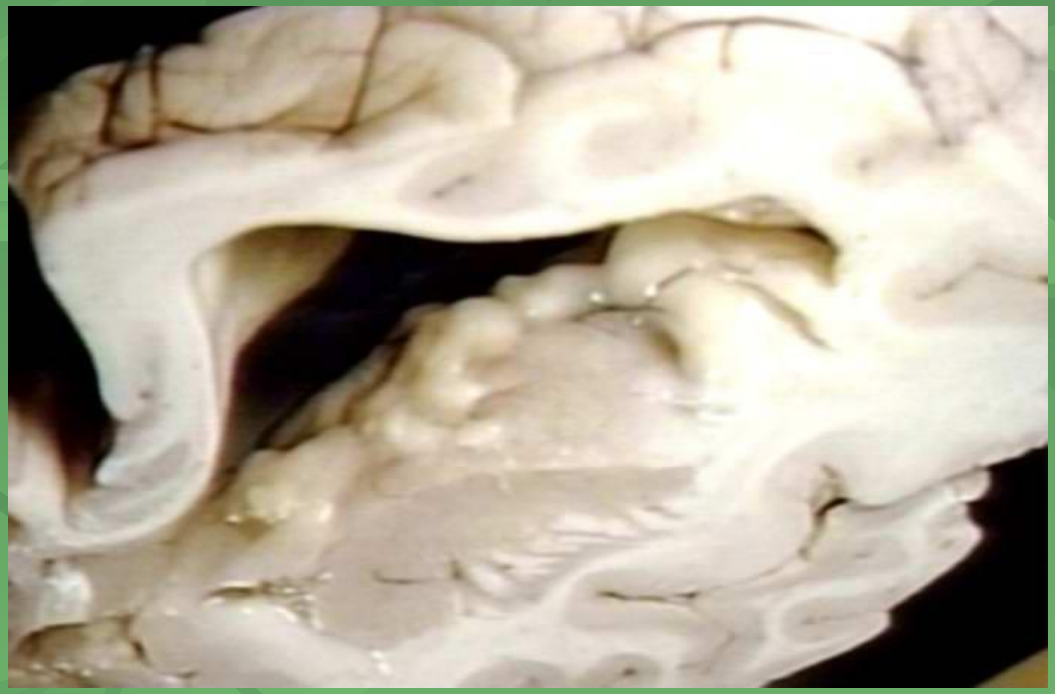


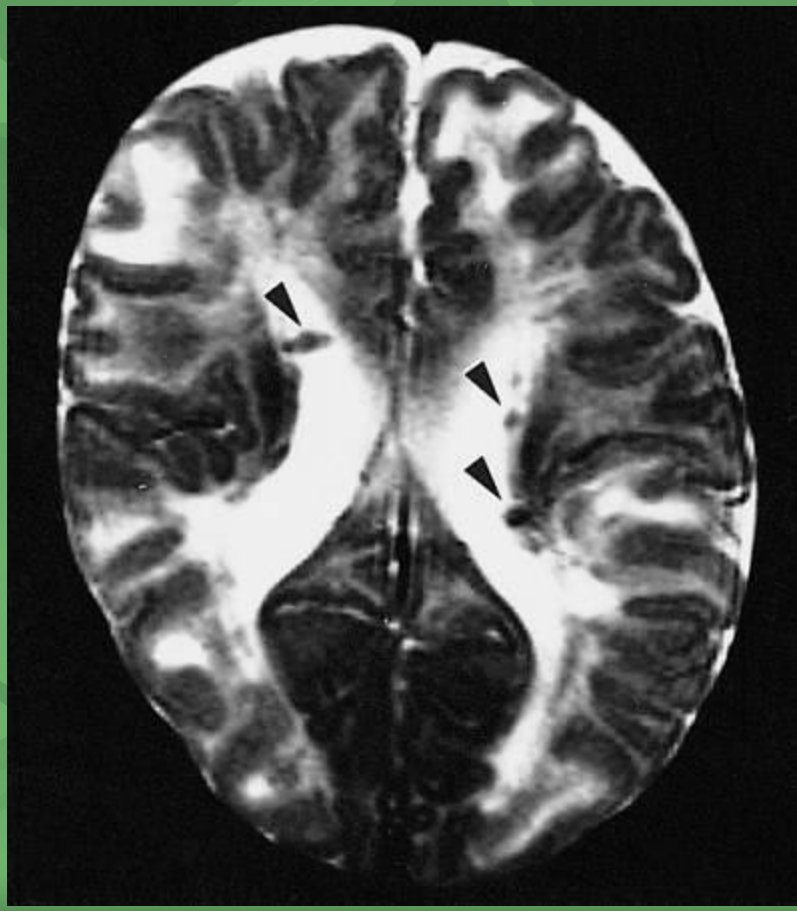


Cortical tubers

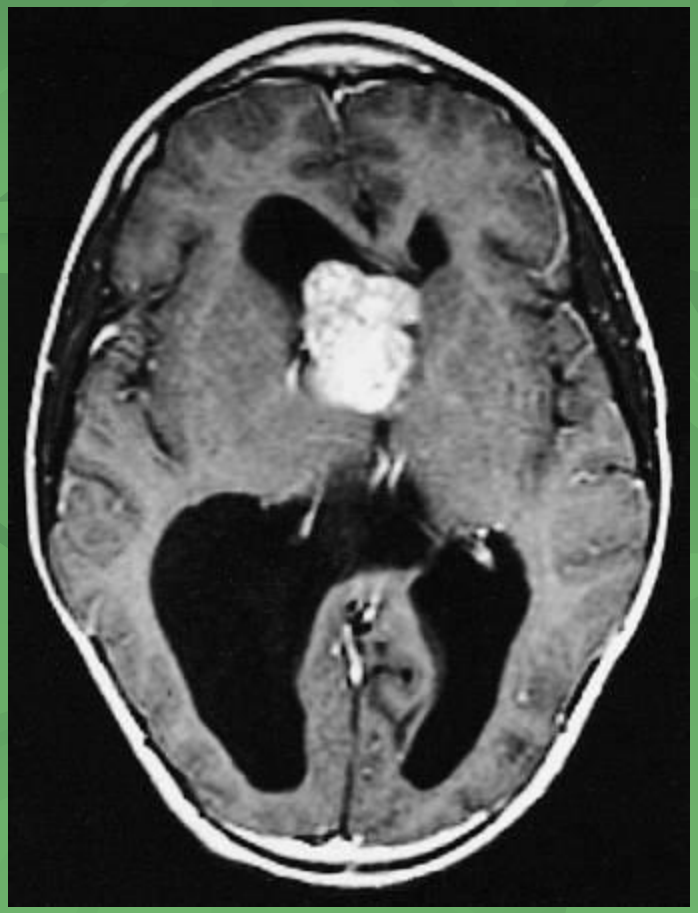


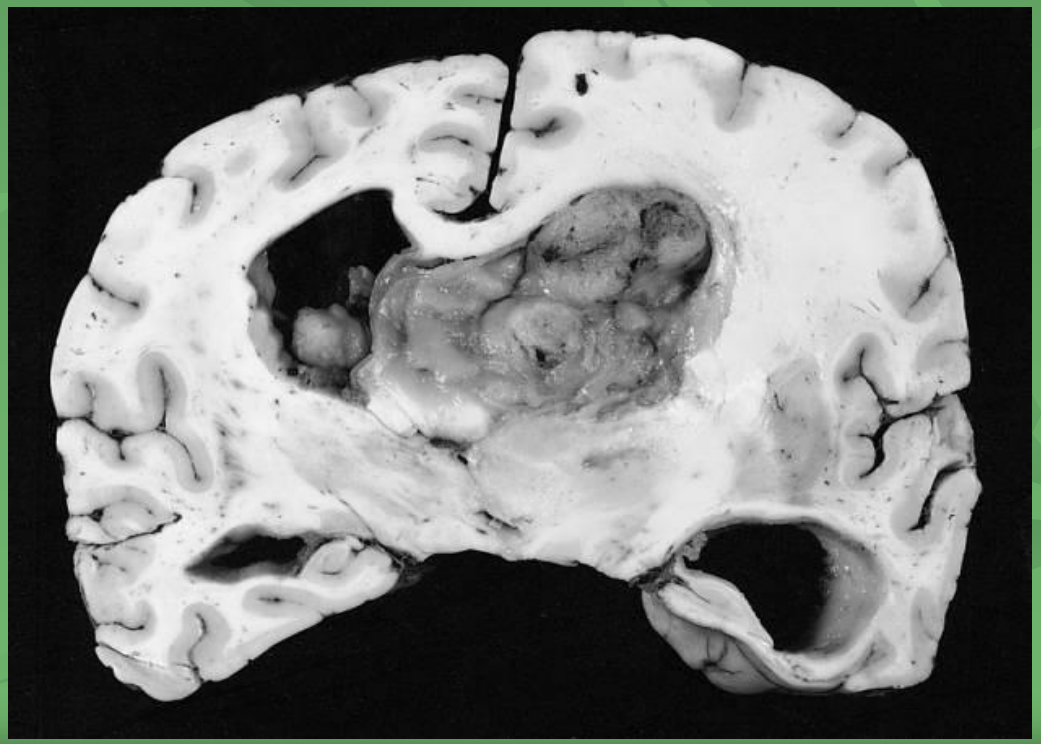
Subependymal Nodules



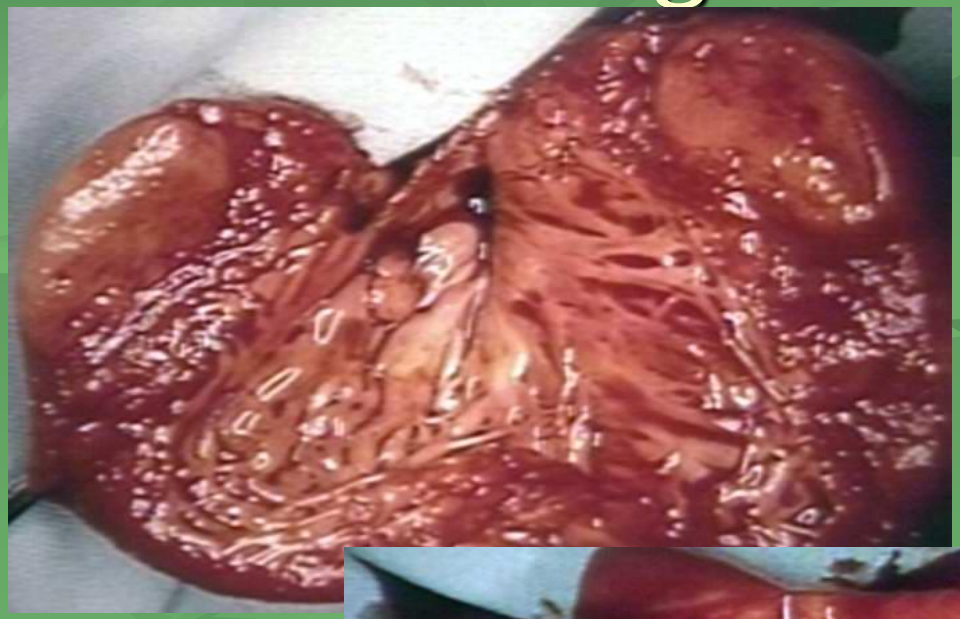


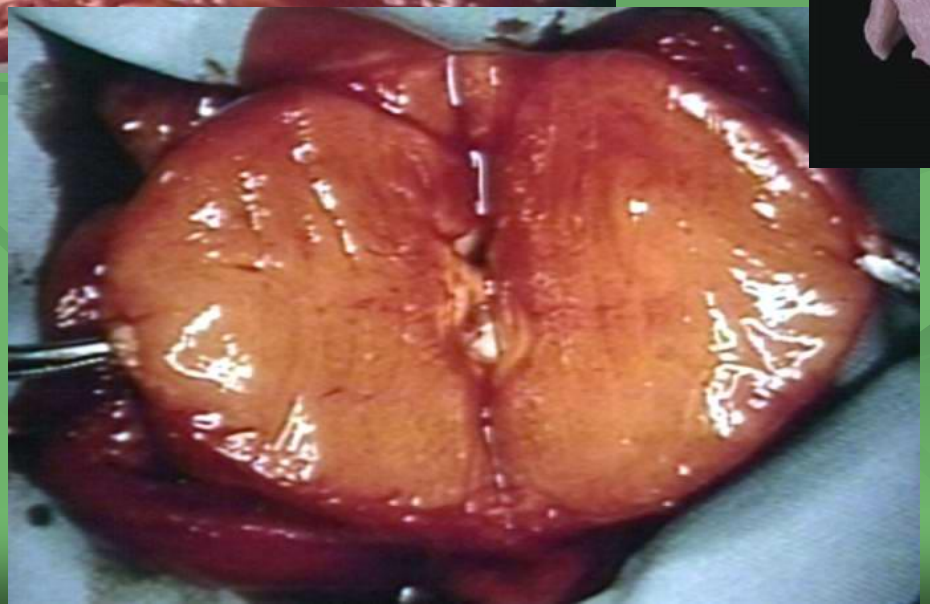
Subependymal Giant Cell Astrocytoma

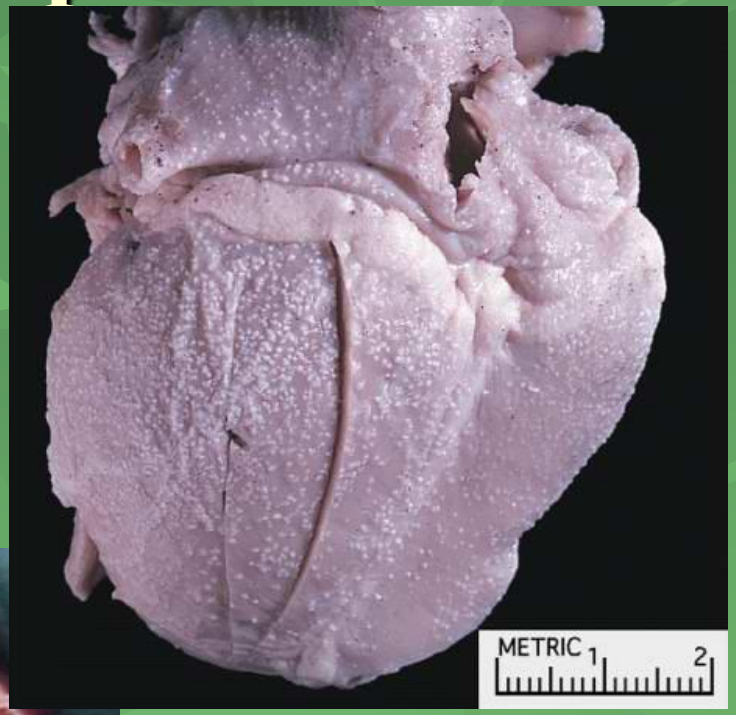




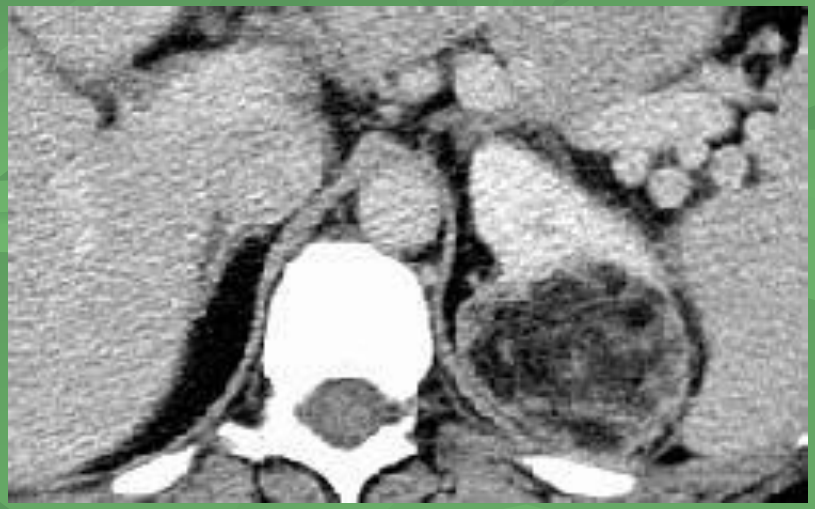
Cardiac Rhabdomyoma single or multiple

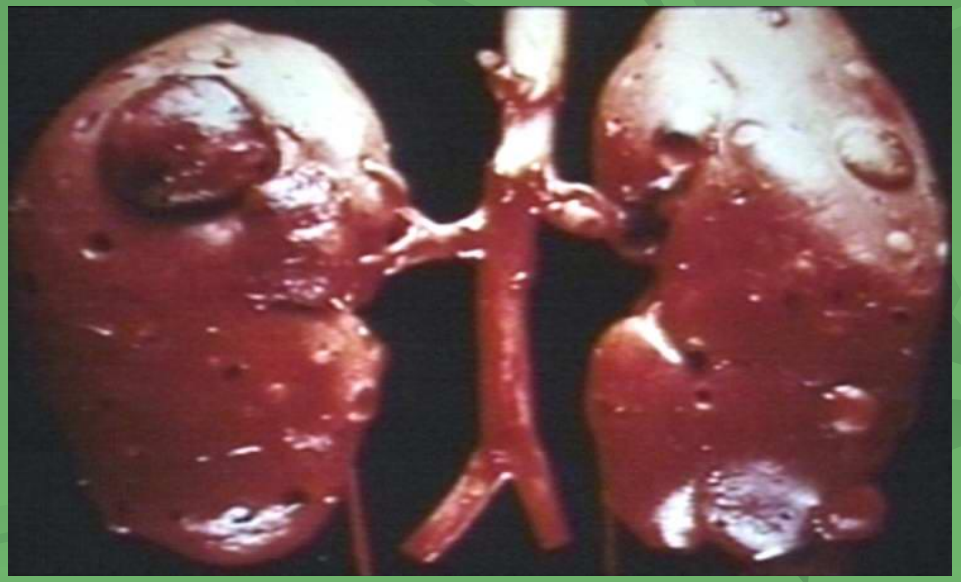




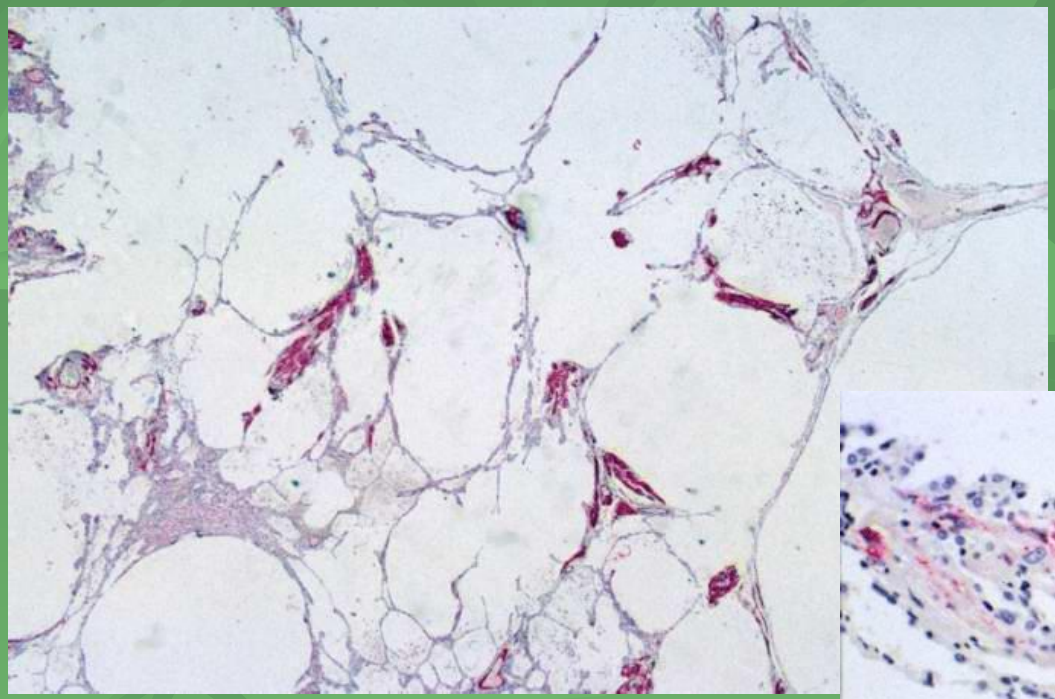


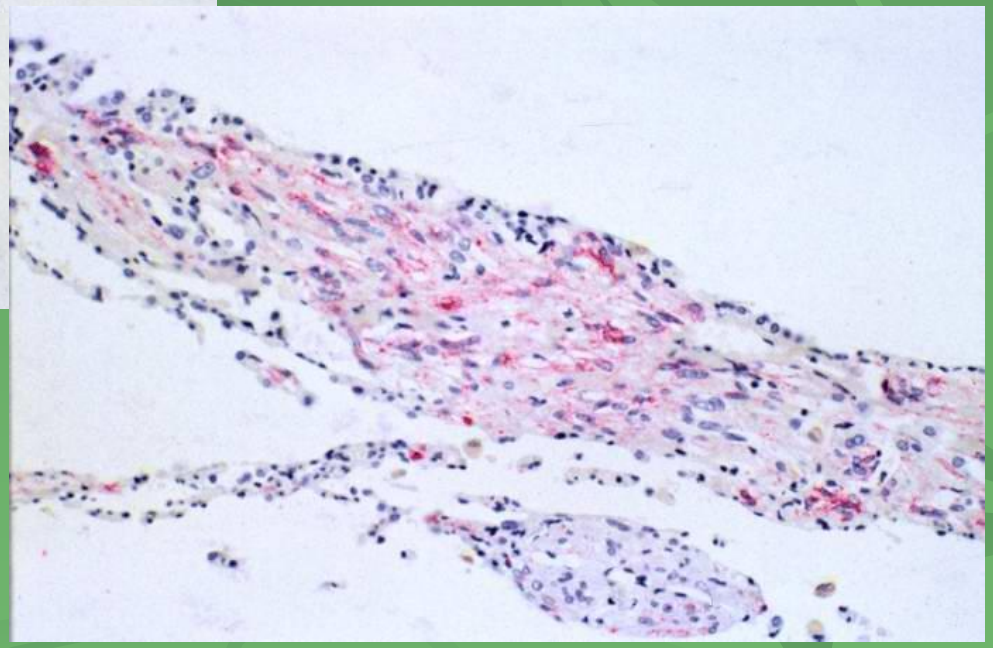
Renal Angiomyolipoma





Lymphangioleiomyomatosis





Minor Features

- Multiple randomly distributed dental enamel pits.
- Harmartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Non-renal harmartomas
- Retinal achromatic patch
- Confetti Skin lesions
- Multiple renal cysts

Diagnostic Studies

- CT or MRI scans of the brain:
  - Use to diagnose Tuberous Sclerosis.
  - Baseline in a patient with known TS.
  - The imaging study is not particularly helpful in diagnosing long term outcome.
  - Repeat imaging should be done every 1 – 3 years to assess for sub-ependymal giant cell astrocytomas.

Diagnostic Studies

- EEG
  - Useful in evaluation of seizure foci
  - May be repeated if clinically warranted.
- ECG
  - Baseline should be done to assess for arrhythmias
  - Wolf-Parkinson-White is the most common type of arrhythmia seen in TS.
  - Repeat ECG every 2 – 3 years until after puberty.

Diagnostic Studies

- Echocardiography
  - Should be performed in neonatal period if recognized clinically.
  - Can be performed in older children to confirm a diagnosis.
  - Repeat echocardiography is not necessary.

Diagnostic Studies

- Renal ultrasound
  - Should be performed as a baseline
  - Repeat imaging every 5 years before puberty
  - Repeat imaging every 2 – 3 years in adults (especially over 30 years)
- CT scan of the chest with contrast:
  - This should be done in women at least once in women around the age of 20 – 30 years to assess for lymphangioleiomyomatosis.

Treatment

- Generally treatment is symptomatic
- Cognitive outcome is anywhere from normal to profoundly mentally retarded.
- Seizures can range from none, to easily controlled, to intractable.

Questions?