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%).
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.
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 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.
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 of its genes.
MECP2 Gene

- The MECP2 gene is transcribed and translated to MeCP2 protein.
- The MeCP2 protein has 2 functional domains.
- The 1\textsuperscript{st} domain binds the MeCP2 protein to the region of a segment of DNA (at the beginning of genes).
- The 2\textsuperscript{nd} 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

- $\leq 0.5\%$
- Consult a Geneticist
Long term outcome

- Patients tend to improve after adolescence, 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
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?