Tuberous Sclerosis (Bourneville’s disease)

GENETICS
- AUTONOMOUS DOMINANT mutation:
  a) 10-20% - TSC1 gene (9q34) - product (HAMARTIN) is tumor suppressor.
  b) 80-90% - TSC2 gene (16p13) - product (TUBERIN) is tumor suppressor.

N.B. clinical-pathologic features caused by these different genes are indistinguishable!
- both HAMARTIN and TUBERIN have “coiled-coil” domains that interact with each other - hamartin and tuberin form tumor suppressor complex that inhibits protein complex mTOR (mammalian target of rapamycin) via GIT1-activating protein Rhob (Ras homolog enhanced in brain).
  *mTOR serves as major effector of cell growth (vs. cell proliferation) - when mTOR is constitutively activated (through mutations in either hamartin or tuberin) this results in hamartomatous lesions
- high spontaneous mutation rate (50-80% cases are sporadic).
- TSC1/TSC2 complex plays an important role in cortical development and growth control
- asymptomatic parents of affected child, have increased risk (~2%) overall of having additional affected children - result from parental mosaicism for one of TSC genes limited to germ line cells (true failure of penetrance is rare!).

EPIEDEMOLOGY
BIRTH INCIDENCE 1 in 5800
PREVALENCE 1 case per 10,000-170,000 population

PATHOLOGY, CLINICAL FEATURES
Long time; hallmark of tuberous sclerosis complex (TSC) was VOIGHT triad (29% of patients; 6% lack all three):
Seizures, Mental Retardation, and Adenoma Sebaceum

N.B. only <1/3 affected persons fit this classic constellation of symptoms!

TSC2 mutation is associated with more severe clinical disease!
Different organ systems are affected in different ways at different times (most patients manifest before age 10 years) - skin, kidneys, brain, heart, and vasculature

BEHAVIOR (90-95%)
- clinical significance - epileptogenic foci (surgery may be beneficial).
- seizures (80-90%), mostly within 1st year of age; up to third will suffer infantile spasms
- TSC is one of the leading causes of genetic epilepsy!!!

1 Tubers (hamartomas):
  a) cerebrum – typically as hard nodules projecting slightly above cortex surface
  b) cerebellum (may be only microscopic).
  c) rarely - brain stem, spinal cord.
- tubers arise developmentally: mutated neural progenitor cells in subependymal germinal matrix give rise to abnormally migrating daughter cells that in turn produce tubers.
  *seen on MRI as neuronal migration streaks
- white and firm to touch.
  *sebenic or neuronal migration streams in white matter
- number, size, and location of tubers vary widely.
- tubers may undergo cystic degeneration or calcification (do not necessarily imply malignant transformation).
- neurological findings (formal neurologic examination is typically nonspecific) - abnormalities in cognition (either global severe mental retardation or specific location-related deficits like language delays), autism, (intractable) epilepsies.
  *infantile spasms are characteristic; seizures may disappear in adult life
N.B. close relationship: onset of seizures at younger age (3-6) more severe mental retardation; mental retardation rarely occurs without seizures, but intellect may be normal, despite seizures.
30-50% patients have normal intelligence!
2. Subependymal nodules (SENs) (hamartoma) - discrete or roughly confluent areas of firm, rounded hyperplastic tissue in wall of lateral ventricles (esp. at caudothalamic groove in vicinity of foramen of Monro)
   - present at birth
   - sizes 2-25 mm; typically calcify (seen on CT!!)
   - on MRI, appear as enhancing localized projections into ventricular cavity ("candle-dripping" or "candle-guttering" appearance).
   - 5-15% degenerate into SUBEPENDYMAL GIANT CELL ASTROCYTOMA.

SENs → migration streaks in white matter → cortical tubers
   i.e. abnormality in radial glial-neuronal unit between germinal matrix and cortex

3. Subependymal giant cell tumors (SEGTAs) (old name - subependymal giant cell astrocytomas (SEGAs) - benign grade I tumors near foramen of Monro.
   - WHO grade I mixed glioneuronal cell tumors
   - SGCT is continuum of SENs (histopathologically identical mixed glioneuronal lineage) - serial imaging of SENs is strongly recommended
   - any lesion exhibiting growth on serial imaging or causing hydrocephalus is called SGCT
   - SEGA exhibits growth vs. hamartomas (SENs, tubers) do not grow
   - grow often in extremely indolent fashion → marked obstructive hydrocephalus.

4. White matter linear migration lines, transmantle cortical dysplasia

Microscopic examination of tubers and SENs:
1) decreased number of normal neurons, disturbed cortical architecture.
2) giant cell clusters (large, bizarre, and sometimes vacuolated "monster" cells with phenotype intermediate between glia and neurons)
3) proliferation of fibrillary astrocytes (well-marked fibrillary gliosis)
4) areas of demyelination.

Tuber (arrow) - lost distinction between grey and white matter:
**TUBEROUS SCLEROSIS**

Pha5

Firm, whitened gyri that are broader than surrounding normal gyri.

Source of picture: “WebPath – The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)

**SEGA**

A. Pleomorphic, multinucleated eosinophilic tumour cells. B. Longitudinal tumour cells forming streams.


**SEGA**: CT of typical subependymal calcifications in a patient with tuberous sclerosis. A. T1-weighted MRI showing mixed iso- and hypodense mass.

Multiple tubers (MRI):

Few but large tubers (MRI):

Source of picture: “The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)
Enhancing subependymal nodules ± probable giant cell astrocytoma in region of foramen of Monro.

CT - subependymal nodules; hypointense right frontal lesion represents tuber (extends from lateral ventricle through cerebral cortex).

Proton density-weighted MRI - bilateral isointense transcortical linear streaks (neuronal migration anomalies).

T2-MRI - multiple low-signal-intensity SENs and cortical tubers.

CT and contrast T1-MRI - large right frontal tuber.

T1-MRI in infant - multiple hyperintense cortical tubers and subependymal nodules.

Proton density and T2-MRIs - multiple cortical and subcortical hyperintensities represent tubers, with associated demyelination; single hyperintense subependymal nodule in right trigone.

Several calcified subependymal nodules (CT).

Cortical tubers ± associated abnormal signal radiating out from periventricular tissue to surface (migration abnormality).

(A) T2-MRI and (B) T1-MRI - multiple subcortical areas (tubers) with abnormal signal; small irregular subependymal nodules protruding into lateral ventricles.

Subependymal giant cell tumor in patient with tuberous sclerosis.
SKIN (90-95%): facial angiofibromas (i.e., adenoma sebaceum), hypopigmented macules (“ash leaf spots”), shagreen patches, subungual fibromas.

1. Adenoma sebaceum (archaic misnomer), s. angiofibroma, Pringle disease (best-known cutaneous manifestation! - cutaneous hamartoma of face, not related to excessive sebum or acne.
   - appears after age 4 yrs.
   - distributed symmetrically on nose and cheeks in butterfly distribution; spares upper lip!
   - typically progress: flat, reddish macules → increasing size, erythematous and papulonodular with friable surface that may bleed easily; may become disfiguring.

2. Hypomelanotic (“ash leaf”) macules (few mm ÷ 5 cm) – nonspecific!
   - difficult to visualize in light-skinned individuals H. Wood lamp (ultraviolet light)!
   - appear at birth or late life.
   - vary widely in location and number.
   - round or oval (resembling leaf of European mountain ash tree); sometimes irregular, reticulated appearance, as if white confetti paper had been strewn over skin (“confetti lesions”).
   - in scalp → area of poliosis (melanin amount↓ in hair).

Confetti lesions:
3. Fibromas - potentially anywhere in cutaneous or mucosal tissues:
   1) periungual (Koenen's tumors) - may cause erosions of tufts of distal phalanges.
   2) gingival - see below >>
   3) lower back (shagreen patch): appears after age 10 yrs; yellowish brown elevated
      plaques that have texture of pig skin; associated with dysraphism, osseous lesions, or
      mass effects on neural structures; occasionally itch or are associated with dysesthesia
      (patients wonder if "it is pinching nerve").
   4) forehead and face (fibrous plaques)
      - symptoms result from local irritation.

Dysplastic periungual fibroma
Typical ash leaf macules; reddish, nodular area at upper lumbar
area is shagreen patch.
HEART (50-60%) - develop during intrauterine life - present at birth or early life (may be presenting sign of TSC) - mostly rhabdomyomas:
- focal or diffuse and infiltrating
- spontaneous regression in first few years!!
- clinically (majority are asymptomatic) - hydrops fetalis (fetal death), outflow tract obstruction, interference with valvular function, decreased contractility and cardiomyopathy.
  N.B. lesions can involve conducting system → arrhythmias (even later in life).
- treatment - inotropic support, surgery.

**Atrial rhabdomyomas:**

**Nonobstructive ventricular rhabdomyomas:**

**Ventricular rhabdomyomas diffusely infiltrate myocardium:**

**TI cardiac-gated MRI - hyperintense left ventricular mass:**

EYES (50-80%):
- Congenital retinal hamartomas (phakomas) that calcify over time; rarely produce symptoms or require intervention:
UBEROUS CLEROSIS Pha5 (8)

2. Hypopigmented areas (retina, iris, eyelashes) are analogous to hypomelanotic macules of skin:

LUNGS (40%) – symptomatic almost exclusively in women ≥ 30 yrs.
1. Multifocal micronodular pneumocyte hyperplasia (MMPH) – hyperplasia of type II pneumocytes; men = women, asymptomatic; CT - nodular densities.
2. Pulmonary cysts (single or multiple); rupture → pneumothorax (50% patients with pulmonary involvement), multiple cysts → respiratory insufficiency, pulmonary hypertension with cor pulmonale.
3. Lymphangioleiomyomatosis (LAM) – abnormal proliferation of smooth muscle cells → compromise of bronchioles, venules, and lymphatic structures → alveolar destruction → pulmonary elasticity is lost (progressive restrictive lung disease) → pulmonary hypertension → cor pulmonale. Inexorably progressive - ultimately results in death!
   • most sensitive diagnosis - high-resolution CT (interstitial thickening, alveolar destruction, honeycomb lungs).
   • treatment - lung transplantation (LAM occasionally has recurred in transplanted lungs).
LAM - multifocal pulmonary cysts:

KIDNEYS
1. Autosomal dominant polycystic kidney disease (2-3%) – result of genetic abnormality affecting both TSC2 gene and PKD1 gene adjacent to it – presents in infancy + early childhood: hypertension, hematuria, renal failure.
   • highly susceptible to UTI or nephrolithiasis.
   • treatment - renal transplantation
2. Isolated renal cysts (20% males, 10% females) - rarely if ever symptomatic.
3. Angiomyolipomata (AML) (50-90%) – hamartomas – abnormal smooth muscle, fat, and blood vessels:
   • either multiple small AMLs studding kidney surface or few larger lesions.
   • bilateral.
   • may give hematuria, flank pain (larger lesions).
   • rupture of dysplastic, aneurysmal blood vessels (highest risk in large AMLs > 6-8 cm) → destruction of adjacent normal renal parenchyma (renal failure), life-threatening retroperitoneal hemorrhage.
• treatment of bleeding AML - selective embolization (pretreatment with steroids - to prevent postembolization syndrome); standard surgical resection can result in excessive bleeding, with nephrectomy being end result.

4. Renal cell carcinomas (AML is much more common – serial MRIs can differentiate between two to avoid unnecessary nephrectomy).

MOUSE

1. Pitting of dental enamel (100% in permanent teeth; 30% in deciduous teeth, esp. numbers > 14).
2. Gingival fibromas (70% adults, 50% children, 3% children with only deciduous teeth) → local irritation, interfere with dental alignment; treatment - surgical resection.

DIGESTIVE SYSTEM
- seen primarily in adults:
2. Hepatic cysts, racemose angiomas, and AMLs (24%; female-to-male ratio 5:1) - asymptomatic and nonprogressive.

BONE
- ossified & hypertrophic lesions seen primarily in adults.

DIAGNOSTIC CRITERIA

Major features:
1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macules (> 3)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas (phakomas)
6. Cortical tuber (when cerebellar cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis).
7. Subependymal nodule
8. Subependymal giant cell tumor
9. Cardiac rhabdomyoma (single or multiple)
10. LAM*
11. Renal AML*

Minor features:
1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps (histologic confirmation is suggested).
3. Hypomelanotic macules (> 3)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas (phakomas)
6. Cortical tuber (when cerebellar cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis).
7. Subependymal nodule
8. Subependymal giant cell tumor
9. Cardiac rhabdomyoma (single or multiple)
10. LAM*
11. Renal AML*

Definite TSC:
- two major features*
- ≥ 2 minor features

Probable TSC:
- one major feature + one minor feature

Possible TSC:
- one major feature
- ≥ 2 minor features

*When both are present together, other features are also required for diagnosis.

When both LAM and renal AMLs are present, other features of tuberous sclerosis should be present before definite diagnosis is assigned (60% non-TSC women with sporadic LAM have renal or other AMLs).

DIAGNOSIS

Genetic testing identifies 75-80% mutations (negative genetic test does not exclude diagnosis).

Three routine imaging procedures:
1. Brain CT / MRI
TUBEROUS SCLEROSIS

Pha5 [10]

- fluid-attenuated inversion recovery (FLAIR) sequence is superior for identification of tubers
- cortical tubers appear as broad cortical gyri with abnormalities in adjacent white matter.
- NAB: tubers expand gyri (vs. unidentifiable bright objects of NF1)
- tubers and SENs may enhance (do not necessarily imply malignant transformation!!!).
- tubers and SENs are:
  - in neonates (unmyelinated white matter) - T1 hypointense and T2 hypointense;
  - older children - T1 hypointense and T2 hyperintense.
- SEGAs – diagnostic criteria: tumor location near the foramen of Monro, > 0.5 cm in diameter, with any documented growth, and intense gadolinium enhancement

2. Renal ultrasounds
   - to assess change in AMLs or cysts - repeated every 5 years if no or small lesions are seen
   - every 2-3 years in late adolescence through adulthood (cysts and AMLs usually start grow significantly after puberty).
3. Echocardiograms:
   - not repeated if no lesions are seen (if rhabdomyomas are seen, echocardiography is repeated as indicated clinically).

SPECT or PET with 18-fluorodeoxyglucose imaging – identifying epileptogenic tubers before epilepsy surgery.

- usually preoperative SEEGER (necessary if suspect that one tuber likely will need ablation, may use larger SEEG bolt that will admit laser probe after SEEG is done).

ECG (to detect cardiac arrhythmias) - at diagnosis and every 2-3 years until puberty.

TREATMENT

mTOR inhibitors
1. RAPAMYCIN (sirolimus) - subependymal giant cell astrocytoma may regress!!!
2. TONEMILIMUS (CCI-779)
3. EVEROLIMUS (Afinitor, Novartis) – FDA approved for TSC-associated subependymal giant cell astrocytoma (SEGA) – for patients ≥ 1 yo who require therapy but are not candidates for surgical resection.
   - appears to reduce brain lesions (results in a rapid initial reduction in tumor volume, followed by a phase of slower reduction or stabilization of residual mass; dose escalation seems to be logical in long-term SEGA treatment to reduce the risk of adverse effects while maintaining the therapeutic effect)
   - reduces seizure frequency
   - may alleviate hydrocephalus

ONCOLOGICAL SURGERY

- no need to remove SEGTC if it is asymptomatic - may stabilize or stop growing spontaneously after puberty
- first line treatment in symptomatic SEGA (hydrocephalus, worsening seizures) or SEGA with documented growth
  - often large and difficult to resect by time they produce clinical symptoms, so lesions fulfilling criteria for SEGA should be removed as soon as growth has been confirmed.
  - operative approach to SEGTC:
    a) simple shunt placement
    b) early tumor resection at first symptoms or documented growth (modern approach)

- early tumor resection at first symptoms or documented growth
  - *(modern approach)*
  - *(1) shunts can in some cases be avoided, (2) smaller lesions may lend themselves to easier operative resection, (3) cases of sudden death associated with SEGTCs have been reported, (4) excessive morbidity and mortality is associated with delayed therapy.
  - transcortical or transcortical (potentially epileptogenic in already susceptible patients) or endoscopic.
  - perioperative mortality related to acute hydrocephalus remains catastrophic but potentially avoidable

EPILEPTIC SURGERY

- particular challenges in presurgical workup - multiple tubers*, high frequency of multiple seizure types, and multifocal scalp electroencephalographic abnormality; SEGTC is indicated.
  - even when multiple tubers are present, epileptogenic activity can often be localized to 1 or 2 tubers (usually the most “angry” looking tuber) – enough to address that dominant tuber and keep observing others

RESective SURGERY

Outcomes in children (surgery at age < 19 yrs):

- median time to seizure recurrence - 240.3 ± 12.7 months.

ANTIEPILEPTICS
- mainstay of therapy for most patients – drugs are selected according to seizure type (VEMENTA in is often drug of first choice).
  - only 1/3 of patients achieve seizure freedom with AEDs

SRS
- for SEGA
- not currently recommended as data on efficacy and safety are limited.
• Engel Class I achieved in 65% - 50% - 45% - 43% patients at 1 – 2 – 3 – 4 year follow-up, respectively.

• factors associated with longer duration of seizure freedom:
  1) younger age at seizure onset* (HR: 2.03, 95% confidence interval [CI]: 1.03-4.00, \( P = 0.04 \))
  2) larger size of predominant tuber* (HR: 1.03, 95% CI: 0.99-1.06, \( P = 0.12 \))
  3) resection larger than tuberectomy (HR: 2.90, 95% CI: 1.17-7.18, \( P = 0.022 \))

  - epilepsyptogenic zone may include cortex surrounding presumed offending tuber! - this limits the role of tuberectomies!

  *those were not predictors of seizure freedom in the multivariate analysis

  - using invasive recording via depth electrodes, Major et al (2009) demonstrated electrical silence within tubers while surrounding cortex demonstrated epileptiform activity

  - vs. Australian experts think that it is enough to resect/ ablate the center of tuber (esp. important if tuber is in eloquent area)

FOLLOW UP

Age-dependent SEGA monitoring: every 2 years before the age of 20 years; from the third decade onwards (SEGA is less frequent in adults and there is a lower potential for existing SEGA growth):

- stable SEGA - no monitoring
- growing SEGA - continued monitoring

Size-dependent SEGA monitoring: MRI repeated after 6 months for tumours > 1 cm.

PROGNOSIS

Long-term outcome is not universally poor, as has been classically thought!

Causes of death (in decreasing order of frequency):

1) renal disease
2) intracranial tumors
3) hemorrhage (such as from aortic aneurysms or lymphangiomynomatosis of lung)
4) status epilepticus
5) cardiac rhabdomyomas

BIBLIOGRAPHY for ch. “Phakomatoses” → follow this LINK >>