Neurocutaneous Syndromes (Phakomatoses)
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Suggested Reading: Robbins & Cotran, 9th edition, pp 2347-49, 1316-17, 298-300
Robbins “Basic Pathology, 9th ed., pp 806-8, 179, 847

These disorders share a few common manifestations:
- Lesions of the skin or mucous membranes
- CNS abnormalities
- A variety of ophthalmologic, visceral and endocrine disorders (usually neoplastic or hamartomatous)
- Genetic transmission (except Sturge-Weber), often as autosomal dominant traits.

Beyond these loose associations, they have little in common, and are quite distinct clinical syndromes.

The term PHAKOMATOSIS (Greek: "mother spot" or "birthmark") was coined in 1920 to refer to these syndromes. The group includes:

1. Neurofibromatosis type 1 - "Von Recklinghausen's disease"
2. Neurofibromatosis type 2 - "central neurofibromatosis"
3. Tuberous Sclerosis - Bourneville's disease
4. Von Hippel-Lindau disease - retino-cerebral angiomatosis
5. Sturge-Weber disease - encephalo-facial angiomatosis (sporadic)

VON RECKLINGHAUSEN'S DISEASE (NF-1)

NF-1 is the most common of these conditions, occurring in about 1 in 3,000 to 4,000 individuals. The gene is transmitted as an autosomal dominant trait, but approximately 1/3 of cases represent new mutations. It is located on chromosome 17 and codes for a protein termed “neurofibromin.” The disease is characterized by multiple nerve sheath tumors along the course of peripheral nerves, hence the term neurofibromatosis. These may be ordinary neurofibromas, schwannomas, or the distinctive plexiform neurofibroma, a lesion which is regarded as pathognomonic of Von Recklinghausen's disease. They are prone to undergo malignant progression.

The best-known skin lesion is the cafe-au-lait spot. These are brown macular lesions usually distributed over the trunk that increase in number and size with age. There is an increased amount of pigment in melanocytes; some have giant pigment granules (melanosomes). Although they were not recognized by Von Recklinghausen in his original description, they are often a useful tip-off to the diagnosis. Smaller axillary 'freckles' are often seen in "unaffected" relatives of
patients with the disease, and as an early skin change in affected individuals.

Neurofibromas are also found in the viscera, in wide distribution. Rather than enumerate the reported sites, it is best to point out that, since these are tumors of peripheral nerves, they may be expected to occur wherever peripheral nerves are found (Have we left out anyplace?). A variety of other tumors have been reported in patients with NF-1, including Gliomas and non-CNS lesions such as Wilm's tumor, pheochromocytoma, and leukemia.

Clinical diagnosis of NF1 can be made if a patient has 2 or more of the following:

- Six or more café-au-lait spots or hyperpigmented macules > 5 mm in diameter in children younger than 10 years or > 15 mm in adults
- Two or more neurofibromas of any type, or one plexiform neurofibroma
- Freckles in the axillary or inguinal regions
- Sphenoid wing dysplasia or congenital bowing of long bone cortex.
- Optic nerve glioma
- >2 pigmented nodules (Lisch nodules) on the iris
- A first-degree relative with NF1

Other CNS manifestations of NF-1:
Central Tumors
- Optic nerve glioma
  - most common brain tumor 1st decade of life in patients with NF-1
  - Bilateral optic gliomas – 100% have NF1 - May be asymptomatic
  - If visual acuity is good and no ↑ICP, may be followed without treatment.
- Brainstem glioma
- Astrocytoma
- Meningioma
- Ependymoma

Spinal Cord
- Dural ectasia
- Extramedullary intradural tumors (neurofibromas, meningiomas)
- Intramedullary tumors (astrocytomas, ependymomas) (infrequent)
- Syringomyelia
- Hyperpigmented patches over the midline of the back are often accompanied by underlying neurofibromas in the spinal cord or nerve roots.

Hydrocephalus
- Aqueductal stenosis
- Tectal tumors
- Other tumors obstructing CSF pathway
**NF-2**

Formerly known as “central” neurofibromatosis, this is now more frequently called “bilateral acoustic neurofibromatosis,” which should give you a very good idea of the characteristic pathology. The neoplastic and maldevelopmental lesions are primarily seen in the cranial cavity and vertebral canal. They include:

- bilateral acoustic schwannomas
- meningiomas (frequently multiple)
- gliomas
- ependymomas
- Schwann cell tumors of the spinal roots
- glial heterotopias
- syringomyelia

As you can see, this list is quite diverse, and none of the lesions is specific. However, the presence of bilateral acoustic schwannomas is usually interpreted as representing NF-2. The gene is located on chromosome 22, and codes for a protein called “merlin” which is believed to regulate membrane receptor signaling, including contact growth inhibition. It is transmitted as an autosomal dominant trait, and the disease affects approximately one in 50,000 individuals.

The skin lesions in NF2 are less common and less numerous than in NF1. They include café-au-lait spots in about one third of patients, but very few have as many as 6 spots, the diagnostic level in NF1. There are also subcutaneous tumors, mostly schwannomas and neurofibromas.

**TUBEROUS SCLEROSIS**

Tuberous sclerosis affects approximately one in 10,000 to one in 30,000 individuals. It has at least two distinct genetic loci: one, on chromosome 9(TSC1), codes for a protein called hamartin and one on chromosome 16 (TSC2), codes for a protein called tuberin. Transmission is autosomal dominant, but new mutations account for more than 50% of cases. The clinical and pathologic features associated with the different mutations are indistinguishable.

The disorder is recognized by the triad of seizures, mental retardation, and skin lesions, especially "adenoma sebaceum", a nodular, reddish brown rash on the face, particularly in the nasolabial folds. Other skin lesions include:

- "Depigmented nevi" - these are regarded by many as being the earliest sign of tuberous sclerosis
- "Shagreen patches" - irregularly shaped raised pale patches with the feel of untanned leather
Subungual "fibromas" - actually angiofibromas, as are adenoma sebaceum
The CNS manifestations are quite remarkable and include the classic "tuber"
which appears as a grotesque, enlarged gyrus on the surface. Microscopically, it
demonstrates a loss of normal lamination, and the presence of enlarged bizarre
cells that contain both neural and glial markers.

Other CNS lesions include:

- subependymal nodules which have similar histologic features to the tubers,
  and appear as small lumps bulging into the ventricular system. These
  have been referred to as "candle gutterings" because they resemble the
  solidified drops of wax that drip from a candle.

- intracranial calcifications - present in 60-70% of cases - often associated
  with subependymal nodules

- "subependymal giant-cell astrocytoma" - A tumor-like proliferation of the
  same sort of bizarre cells that are seen in the tubers and the
  subependymal nodules. These are not malignant, but may obstruct CSF
  flow and result in hydrocephalus.

The visceral manifestations of tuberous sclerosis are quite variable and
include an array of hamartomatous lesions which often involve more than one
germ layer (endoderm +mesoderm, etc.) The most common of these are cardiac
rhabdomyomas, which may cause death by mechanically interfering with cardiac
contraction. Other common sites are the lungs, kidneys and gastrointestinal
tract.

VON HIPPEL-LINDAU DISEASE
Genetics:
- Autosomal dominant with high penetrance
- VHL Gene mapped to distal short arm of chromosome 3 (3p25-p26)

Incidence: 1 in 39,000 live births
Clinical
- Retinal hemangioblastomas
  - Children > 5 years
  - 10% have an intracranial tumor
  - May cause ↓ vision from hemorrhage
- Cerebellar hemangioblastomas
  - 60% patients
  - Polycythemia may be associated
  - Usually develops >15 years
- Hemangiomas of brain stem, spinal cord, cerebral hemispheres – less
  frequent
- Renal lesions
- Cysts
- Adenomas
- Hemangiomas
- Renal cell carcinomas – 28%

- Pancreatic cysts, hepatic cysts, splenic cysts
- Pheochromocytoma – 7%
- Adrenal adenoma – less common

**STURGE-WEBER SYNDROME**

**Incidence:**
- Sporadic; about 1 in 50,000

**Skin:**
- Hemangioma ophthalmic division of V (port wine stain) usually above the palpebral fissure – upper eyelid, frontal region or both.
- May involve buccal mucosa, tongue, palate and pharynx.
- Unilateral in 70%.
- Present at birth.

**CNS:** Venous angioma pia mater (ipsilateral to facial hemangioma)
- Occipital most common
- Temporal
- Parietal
- Underlying cortex has neuronal loss, gliosis and calcification

**Clinical**
- Seizures 75-90% onset first months of life - partial + 2º generalization
- Homonymous hemianopsia (contralateral to facial angioma)
- Hemiplegia – 30%-50% (contralateral to facial angioma)
- Mental retardation – 50% (75% with seizures)
- Intracranial hemorrhage does not occur
- Glaucoma – 30%

**OBJECTIVES FOR THE PHAKOMATOSES**

1. Describe the inheritance pattern of these diseases.

2. Define and describe the important features of NF-1, NF-2 and tuberous sclerosis, including:
   a) characteristic and/or pathognomonic lesions
   b) pathogenesis
   c) types of tumors encountered
   d) types of skin lesions
   e) associated visceral lesions and their clinical significance

3. Be aware of the lesions seen in Von-Hippel-Lindau disease and Sturge-Weber
syndrome.