Neuro-cutaneous syndromes or phakomatoses

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By the end of the talk you will…

- Be able to define what is meant by neuro-cutaneous diseases
- List the most common phakomatosis
- Understand the pathophysiological bases of several phakomatosis
- Be able to list the components of follow-up visits for patients with phakomatosis

Neuro-cutaneous syndromes or phakomatoses

- Hereditary or congenital diseases that affect the nervous system
- Characterized by the presence of hamartomas
- Hamartomas: tumors from cells that normally form an organ
- The tissue elements are, however, poorly organized
- Phakoma: from Greek = tumor
Neuro-cutaneous syndromes or phakomatoses

- Ataxia-telangiectasia
- Hipomelanosis of Ito
- Incontinentia pigmenti
- Klippel-Trenaunay-Weber syndrome
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Sturge-Weber syndrome
- Tuberous sclerosis complex
- Von Hippel-Lindau syndrome
- Weber syndrome

Case one

- 12 month old girl
- first seizure at three months of age
- seizures are difficult to control
- progressive left side hemiparesis

This child’s diagnosis is?

Sturge-Weber syndrome
Sturge-Weber syndrome: overview
- Also known as encephalotrigeminal angiomatosis
- Genetics: sporadic disease
- 1:50,000 individuals
- Equal gender distribution
- Typical abnormality:
  - Facial angioma or Port-wine stain
  - Thin-walled dermal blood vessels
  - Usually 1st and 2nd branches of the trigeminal nerve
  - Usually unilateral

Sturge-Weber syndrome: clinical presentation
- Facial angioma in trigeminal distribution
- Leptomeningeal venous angiomatosis
- Seizures
- Hemiplegia
- Hemianopsia
- Glaucoma

Sturge-Weber syndrome: presumed etiology
- Abnormal development of venous drainage
  - Lack of regulation of angiogenic factor VG5Q?
    - VG5Q is an angiogenesis promoter
    - VG5Q binds to endothelial cells to promote cell proliferation
  - Small, thin-walled telangectasia over face
    - Port-wine stain
  - Telangectatic cortical venules resulting in abnormal cerebral venous drainage
    - Venous congestion
    - Venous thrombosis
    - Cortical ischemia / infarction
    * Brain atrophy and calcification

Sturge-Weber syndrome: radiology
- Plain films
  - Tram-track calcifications (unusual before age 2)
  - Thick diploic spaces
  - Enlarged paranasal sinuses
### Sturge-Weber syndrome: radiology

- CT scan
  - cortical atrophy
  - thick diploic spaces

- MRI
  - meningeal angiomatosis
  - cortical infarction
  - cortical atrophy

### Sturge-Weber syndrome: evolution

- Predictors of poor long-term outcome:
  - Early seizures
  - Difficult to control seizures
  - Early onset of stroke-like events
  - Large areas of hypometabolism in PET
- In most cases, disease progression stops around 5 years of age

### Sturge-Weber syndrome: management

- Seizure control
- Aspirin
- Ophthalmology
- Dermatology
- [www.sturge-weber.org](http://www.sturge-weber.org)
Sturge-Weber syndrome: bonus points

Case two

- 2 year-old girl
- Has many café au lait spots
Neurofibromatosis type 1: overview

- Also known as
  - Von Recklinghausen’s disease
  - peripheral neurofibromatosis
- Occurs in about 1:4000 individuals
- Worldwide and equal gender distribution
- Most common form of neurofibromatosis

Neurofibromatosis type 1: genetics

- Autosomal dominant with high penetrance but wide variability in expression
  - Genotype-Phenotype mismatch
- The mutation is found in *NF1* gene on chromosome 17q11.2
- High spontaneous mutation rate
- 50% of patients have *de novo* gene mutation
- Most common neurological disorder caused by a single gene mutation

This child’s diagnosis is?

- Neurofibromatosis type 1
Neurofibromatosis type 1: genetics

- *NF1* mutations result in loss of function of the protein *neurofibromin*
- Neurofibromin acts as a tumor suppressor by inhibiting the proto-oncogene *RAS*
- Increased *RAS* activity in neurocutaneous tissues results in proliferation and tumorogenesis

Neurofibromatosis type 1: diagnosis

Two or more of the following:
1. Family history of NF1
2. 6 or more "cafe-au-lait" spots
3. 2 or more neurofibromas
4. Plexiform neurofibromas
5. Axillary and/or inguinal freckling
6. Lisch nodules
7. Skeletal abnormalities: bowing of long bones, scoliosis, thinning of the cortex of long bones
8. Optic pathway glioma

Lisch Nodules

- They are accumulations of melanocytes on the iris
- They usually appear during puberty
- They do not affect vision

Optic pathway glioma

- The most common primary neoplasm of the optic nerve
- Found in 15% of patients
- Presenting symptom is decreased visual acuity
- The lesion is a grade I pilocytic astrocytoma
- The tumor grows slowly, and does not metastasize
### Neurofibromas

- Neurofibromas are peripheral nerve sheath tumors.
- The size and number of neurofibromas increase during puberty and pregnancy, reflecting a possible hormonal effect.
- Neurofibromas contain transformed Schwann cells and fibroblasts.
- As the tumors enlarge, the adjacent nerve fascicles are compressed and displaced without infiltration or invasion.

### Scoliosis

- Scoliosis is common in NF1.
- Appears early in childhood.
- Periodic spine X-rays and physical examinations are needed to determine if corrective measures are required.
- A brace may be used to prevent progression of the problem; more serious cases require corrective surgery.

### Plexiform neurofibroma

- Elongated fibromas that grow along nerves.
- Appear within the first 2 years of life.
- Two types:
  - nodular
  - diffuse aka elephantiasis neurofibromatosa
    - overgrowth of epidermal and subcutaneous tissue.
- May become malignant.
- Bleed profusely.

### Other manifestations

- Macrocephaly (50% of patients).
- Short stature (not due to endocrine disease).
- Learning disabilities (60% of patients).
- Hypertension:
  - Pheochromocytoma
  - Renal artery stenosis.
- Increased risk for developing tumors:
  - Pheochromocytoma, malignant peripheral nerve sheath tumors, chronic myeloid leukemia.
- Pain.
Follow-up of patients with NF1

- Genetic counseling and parental evaluation
- Yearly physical exam
  - Special attention: bone dysplasia and scoliosis
  - Evaluate development, language, learning
- Yearly ophthalmology evaluation
  - If abnormal: MRI
- Regular blood pressure checks
- Surgery for painful neurofibromas and malignant tumors

Case three

- 5 year-old-boy is evaluated for seizures
- As infant he had infantile spasms
- On exam he has:
  - mild mental retardation
  - a raised plaque of skin on his lower back
  - a tumor-like lesion in one peri-ungual area
  - mother has a history of seizures as a child
The diagnosis is?

Tuberous sclerosis complex
Tuberous sclerosis complex: overview

- Disease occurs in 1:8,000 individuals
- Wide phenotypic spectrum that may include:
  - seizures
  - mental retardation
  - renal dysfunction
  - dermatologic findings
- Findings depend on the size, number, and location of lesions and organs involved
- @ 90% of TSC patients have skin findings
- @ 90% of TSC patients have seizures

Tuberous sclerosis complex: genetics

- Tuberous sclerosis complex is an autosomal-dominant disorder
- However, 60% of cases are de novo mutations
- Organs — systems commonly affected:
  - Brain
  - Eyes
  - Skin
  - Heart
  - Kidneys

Tuberous sclerosis complex: genetics

- It is caused by mutation in one of two different tumor suppressor genes:
  - 9q34.3 for TSC1
    - TSC1 encodes for the protein hamartin
    - This mutation is more common in families, less severe
  - 16p13.3 for TSC2
    - TSC2 encodes for the protein tuberin
    - 70% of sporadic cases are caused by TSC2 mutation
- During development tuberin and hamartin are highly expressed in glia and neurons
- Tuberin and hamartin work together to regulate cell growth and differentiation
  - Two different genes, two different proteins = one disease

Tuberous sclerosis complex: major features

- Brain:
  - Cortical tubers, subependymal nodules, subependymal giant cell astrocytomas
  - Retina:
  - Retinal nodular hamartomas
  - Skin:
  - 3 or more hypomelanotic macules, facial angiofibroma, ungual fibroma, Shagreen plaque
  - Heart:
  - Rhabdomyoma
    - Most common benign congenital tumor
    - May cause: outflow obstruction, arrhythmias, and thromboembolic disease
  - Kidney:
  - Angiomyolipomas
Tuberous sclerosis complex: **minor** features

- Mouth:
  - Dental enamel pits
  - Gingival fibromas
- Retina
  - Hypomelanotic patches
- Skin:
  - Multiple confetti-like skin lesions
- Kidney:
  - Multiple renal cysts

Tuberous sclerosis complex: **diagnosis**

- Definite TSC:
  - 2 major features + 1 minor feature, or
  - 1 major feature + 2 minor features
- Possible TSC:
  - 1 major feature + 1 minor feature
- Probable TSC:
  - 1 major feature, or
  - 2 or more minor features

Tuberous sclerosis complex: neurologic manifestations

- Seizures
- Developmental delay / mental retardation
- Autism spectrum disorders
  - Equal gender distribution

Cortical tubers (FLAIR image)

- Most common symptomatic lesions
- Comprised of non-malignant, poorly differentiated cells
- Static lesions
- May be used as biomarker of disease severity
- Cause seizures; in infants tend to cause infantile spasms
Subependymal nodules

- They appear as subependymal masses along the walls of the lateral ventricles
- Lesions continue to grow and increase in number up to second decade of life
- They tend to calcify

Giant cell astrocytomas

- They originate from subependymal nodules
- Can obstruct the flow of cerebrospinal fluid
- Lesions continue to grow into the second decade of life

Adenoma sebaceo of scalp

Tuberous sclerosis complex: follow up

- Genetic counseling and parental evaluation
- Brain MRI every one to three years
- EEG for seizure management
- Neurodevelopmental evaluations
- Renal ultrasound every one to three years
- Echocardiography if cardiac symptoms indicate
Case four

- 17 year-old previously healthy female
- Chief complaints: tinnitus and decreased hearing in her left ear
- Audiologic evaluation: sensory-neural hearing loss in the left ear
- Other findings: two 2.5 cm in diameter café au lait spots on her left shoulder and arm

The diagnosis is? Neurofibromatosis type 2

Neurofibromatosis type 2: overview

- It accounts for 5% to 10% of all cases of neurofibromatosis
- Autosomal dominant disorder
- Mutation of NF2 gene at 22q12.2
- NF2 encodes for merlin
- Merlin mutations cause proliferation of Schwann cell lines
- Genotype-Phenotype correlation
Neurofibromatosis type 2: diagnosis

- Individuals with the following clinical features have confirmed neurofibromatosis type 2:
  1. Bilateral vestibular schwannomas, OR
  2. A first-degree with neurofibromatosis type 2 and either:
     • Unilateral mass of the eighth cranial nerve at an age younger than 30 years, or
     • Any 2 of the following: neurofibroma, meningioma, glioma, schwannoma

Neurofibromatosis Type 2

- Acoustic neuromas are schwannomas from the vestibular portion of the VIIIth cranial nerve
- Bilateral schwannomas occur in 70% of patients
- The most common initial symptoms are: hearing loss and tinnitus
- Other symptoms include: vertigo, ataxia, facial weakness, and headache

Neurofibromatosis Type 2: Tx

- Surgery
- Surveillance for at-risk individuals from families with neurofibromatosis type 2
- MRI screening should start early in childhood for patients from families with neurofibromatosis type 2
Case five

Diagnosis?

Ataxia-telangiectasia

Ataxia-telangiectasia

- A disease of abnormal DNA repair
- Progressive cerebellar ataxia
- Telangiectasia of the skin and conjunctiva
- Apraxia of eye movements
- Choreaathetosis
- Increased susceptibility to infections
- Increased susceptibility to malignancies

Genetics of AT

- AT is inherited as an autosomal recessive trait
- The gene locus for AT maps to chromosome 11q22-23
- The defective gene is designated ATM
- In vitro, the cells derived from these patients have defective DNA repair
AT signs & symptoms

- Early motor development is usually normal
- Cerebellar ataxia is the initial symptom
  - From Purkinje and granule cell degeneration
    - May manifest early as postural instability
- Abnormalities of bulbar function may develop
  - Speech may never be normal
  - Disorders of chewing and swallowing coordination

Telangiectasia arise from the venous system and are found on:
- the conjunctiva, the bridge of the nose, ears, neck, antecubital fossae, and popliteal areas

Other cutaneous manifestations:
- hyperpigmentation, hypopigmentation, cutaneous atrophy

Ocular features:
- impaired smooth pursuit, impaired sacadic movements, nystagmus, absence of optokinetic nystagmus

Non-neurologic manifestations: abnormal cell differentiation

- Homozygotes for AT have a 100 fold risk of cancer, lymphomas are the most common
- Patients have few T-cells, low IgA, E, G
- Infections of the sinuses and lungs are often seen, resulting in chronic bronchitis and bronchiectasis (CF-like)
- Premature aging
Case six

Klippel-Trenaunay-Weber syndrome
- Triad of port-wine stains, varicose veins, and bony and soft tissue hypertrophy
- Confused with Sturge-Weber
- Potential neurological manifestations
  - Macrocephaly
  - Glaucoma
  - Compressive neuropathy
- Sporadic

Klippel-Trenaunay-Weber syndrome and the US Supreme Court

Casey Martin

This is the end of the talk, you are now able to…
- Define what is meant by neurocutaneous diseases
- List the most common phakomatoses
- Explain the pathophysiological bases of several phakomatoses
- List the components of follow-up visits for patients with phakomatoses
Thank you!