Ocular manifestations of the phakomatoses

I. Definition of phakomatoses

   A. Greek word *phakos* means “spot, lens”

   B. Ophthalmologist Jan van der Hoeve coined term phakomatosis in 1920 for three disorders (neurofibromatosis, tuberous sclerosis, von Hippel-Lindau syndrome), which affect the nervous system, eye and skin

   C. Conditions commonly included as phakomatoses today

      i. Neurofibromatosis 1
      ii. Neurofibromatosis 2
      iii. Tuberous sclerosis
      iv. von Hippel-Lindau syndrome
      v. Ataxia telangiectasia
      vi. Sturge-Weber syndrome
      vii. Incontinentia pigmenti
      viii. Gorlin syndrome (Nevoid basal cell carcinoma syndrome)

II. Neurofibromatosis 1

   A. Inheritance: Autosomal dominant

      i. Mutations in the *NF1* gene that encodes the protein neurofibromin, a GTPase activating protein

   B. Prevalence: 1:4,000

   C. Systemic manifestations

      i. Tumors

         a. Neurofibroma, MPNST, glioma, leukemia

      ii. Other features
a. Café-au-lait macules, skin-fold freckling, skeletal dysplasia, vascular disorder, learning disability

D. Ocular manifestations

i. Lisch nodules (iris hamartomas)
   a. In ~90% of NF1 patients
   b. Multiple, bilateral, lightly pigmented, raised nodules on the anterior surface of iris
   c. Comprised of pigmented cells and fibroblast-like cells

ii. Glaucoma
   a. In ~50% of NF1 patients
   b. Multiple mechanisms may contribute: infiltration of anterior chamber angle by neurofibroma, malformation or immature development of the anterior chamber angle, secondary angle closure due to infiltration of the ciliary body/choroid
   c. Almost always associated with globe enlargement (buphthalmos)
   d. Frequently associated with iris ectropion

iii. Neurofibromas (eyelid, orbit, uvea)
   a. Choroidal abnormalities detected in 100% of NF1 patients by scanning laser ophthalmoscopy
   b. Ovoid bodies – hyperplasia of Schwann cells around axons, found in choroidal neurofibromatosis

iv. Optic nerve glioma

v. Orbital bony malformations
   a. Absence of the greater and lesser wings of sphenoid

III. Neurofibromatosis 2

A. Inheritance: Autosomal dominant

   i. Mutations in the \( NF2 \) gene that encodes the protein merlin, which has pleiotropic effects

B. Prevalence: 1:40,000

C. Systemic manifestations

   i. Tumors
      a. Schwannoma, meningioma, ependymoma, glioma
D. Ocular manifestations

i. Cataract
   a. Juvenile posterior subcapsular cataracts are found in 80% of NF2 patients
   b. Displaced lens and Wedl/bladder cells are found just anterior to the posterior lens capsule

ii. Epiretinal membrane
   a. In majority of NF2 patients, likely congenital
   b. Immunophenotype and ultrastructural features are most consistent with Muller cell origin

iii. Retinal hamartoma

iv. Optic nerve meningioma

v. Intraocular schwannoma
   a. Arise from the long ciliary nerves

vi. Neurotrophic keratopathy
   a. Vestibular schwannoma → CN VII dysfunction → poor lid closure → corneal damage from exposure

IV. Tuberous sclerosis

A. Inheritance: Autosomal dominant
   i. Mutations in TSC1 and TSC2 genes that encode the proteins hamartin and tuberin, which inhibit mTOR signaling

B. Prevalence: 1:6,000

C. Systemic manifestations
   i. Tumors
      a. Facial angiofibroma, ungual fibroma, cardiac rhabdomyoma, renal angiomyolipoma, subependymal giant cell astrocytoma
   ii. Other features
      a. Cortical tubers, subependymal nodule, hypomelanotic macule, shagreen patch, pulmonary lymphangiomyomatosis, renal nodular hamartomas

D. Ocular manifestations
i. Retinal hamartomas
   a. In ~50% of TS patients
   b. Cells comprising the lesion may have mixed neuronal and glial features

V. von Hippel-Lindau syndrome
   A. Inheritance: Autosomal dominant
      i. Mutations in the VHL gene that encode an E3 ubiquitin ligase, which regulates the cellular response to hypoxia
   B. Prevalence: 1:50,000
   C. Systemic manifestations
      i. Tumors
         a. CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumor, endolymphatic sac tumor, broad-ligament cystadenomas
      ii. Other features
         a. Renal cysts

D. Ocular manifestations
   i. Retinal hemangiomas
      a. Multifocal and bilateral

VI. Ataxia Telangiectasia
   A. Inheritance: Autosomal recessive
      i. Mutations in the ATM gene that encodes a protein involved in DNA repair
   B. Prevalence: 1:30,000
   C. Systemic manifestations
      i. Tumors
         a. Lymphoid malignancy
      ii. Other features
         a. Early onset progressive cerebellar ataxia, immunodeficiency, recurrent infections, oculocutaneous telangiectasias, absent/rudimentary thymus, insulin-resistant diabetes, radiosensitivity
   D. Ocular manifestations
i. Conjunctival telangiectasias

ii. Oculomotor abnormalities
   a. Nystagmus, pursuit and saccade abnormalities, strabismus, poor convergence

VII. Sturge-Weber syndrome
   A. Inheritance: Sporadic
   B. Prevalence: 1:50,000
   C. Systemic manifestations
      i. Port-wine stains/nevus flammeus
      ii. Seizures, intellectual impairment, migraine headache, hemiparesis, hemianopsia
   D. Ocular manifestations
      i. Glaucoma
         a. In ~30% of SWS patients
         b. Usually ipsilateral to the port-wine stain
      ii. Diffuse choroidal hemangioma
         a. In ~70% of SWS patients
         b. Ipsilateral to the port-wine stain
         c. “Tomato ketchup” appearance of fundus exam
      iii. Episceral/conjunctival hemangioma
      iv. Iris heterochromia
      v. Buphthalmos
      vi. Retinal pigment degeneration
      vii. Retinal detachment
      viii. Optic disc coloboma
      ix. Cataract
      x. Nevus of Ota

VIII. Incontinentia pigmenti
   A. Inheritance: X-linked dominant
i. Mutations in the *NEMO* gene that encodes a protein critical for NF-κB activation

B. Prevalence: 1:390,000

C. Systemic manifestations
   i. Disturbance of skin pigmentation, leading to a “marble cake” appearance
   ii. Seizures, spastic paralysis, microcephaly, mental retardation
      a. Secondary to compromised vascularization of the developing brain
   iii. Alopecia, anodentia, nail dystrophy

D. Ocular manifestations
   i. Retinal ischemia, leading to reactive neovascularization and fibrovascular scarring
      a. In ~30-40% of IP patients
      b. May be complicated by retinal detachment

IX. Gorlin syndrome (Nevoid basal cell carcinoma syndrome)

A. Inheritance: Autosomal dominant
   i. Mutations in *PTCH1* gene that encodes a transmembrane protein, which inhibits hedgehog signaling

B. Prevalence: 1:60,000-1:260,000

C. Systemic manifestations
   i. Tumors
      a. Multiple basal cell carcinomas, medulloblastoma, fibroma, rhabdomyosarcoma
   ii. Other features
      a. Odontogenic keratocysts of the jaws, hyperkeratosis of palms and soles, epidermoid cysts, multiple nevi, skeletal abnormalities, intracranial ectopic calcifications, facial dysmorphism

D. Ocular manifestations
   i. Hypertelorism
   ii. Exophthalmos
   iii. Rotary nystagmus
   iv. Internal strabismus
v. Congenital cataracts
vi. Orbital cysts
vii. Coloboma of iris, choroid and optic nerve
viii. Microphthalmia
ix. Chalazions
x. Transient milia on the palpebral conjunctiva
Ocular manifestations of the phakomatoses

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Definition of phakomatoses

- Greek word ϕακός, phakos, means “spot, lens”
- Ophthalmologist Jan van der Hoeve coined the term phakomatosis in 1920 for three disorders (neurofibromatosis, tuberous sclerosis and von Hippel-Lindau syndrome), which affect the nervous system, eye and skin

Café-au-lait spot

Karahan E et al. (2007) Internet J Ophthalmol Vis Sci
Conditions included as phakomatoses

- Neurofibromatosis 1
- Neurofibromatosis 2
- Tuberous sclerosis
- von Hippel-Lindau syndrome
- Ataxia telangiectasia
- Sturge-Weber syndrome
- Incontinentia pigmenti
- Gorlin syndrome (Nevoid basal cell carcinoma syndrome)
Neurofibromatosis 1

- Inheritance: Autosomal dominant
- Prevalence: 1:4,000
- Systemic manifestations:
  - Tumors:
    - Neurofibroma
    - MPNST
    - Glioma
    - Leukemia
  - Other features:
    - Café-au-lait macules
    - Skin-fold freckling
    - Skeletal dysplasia
    - Vascular disorder
    - Learning disability
NF1 gene encodes the protein neurofibromin, a GTPase activating protein
Neurofibromatosis 1: Ocular manifestations

- Lisch nodules (iris hamartomas)
- Glaucoma
- Neurofibromas (eyelid, orbit, uvea)
- Optic nerve glioma
- Orbital bony malformations
  - Absence of greater and lesser wings of sphenoid
Lisch nodules

- In ~90% of NF1 patients
- Multiple, bilateral, lightly pigmented, raised nodules on the anterior surface of the iris

Atlasgeneticsoncology.org
Lisch nodules

- Iris hamartomas comprised of pigmented cells and fibroblast-like cells

Perlman JI et al. (2005) EOPS
Glaucoma

- In ~50% of NF1 patients
  - Some cases are congenital

- Multiple mechanisms may contribute:
  - Infiltration of anterior chamber angle by neurofibroma
  - Malformation or immature development of the anterior chamber angle
  - Secondary angle closure due to infiltration of ciliary body/choroid

- Almost always associated with globe enlargement (buphthalmos)
Glaucoma

Normal retina

Ganglion cell layer

Ganglion cell loss

ganglion cell
Glaucoma

- Frequently associated with iris ectropion
Choroidal neurofibromatosis

- Choroidal abnormalities detected in 100% of NF1 patients by scanning laser ophthalmoscopy

Diffuse thickening of the choroid

- Normal choroid
- RPE
- Choroid
- Sclera
- Ovoid body
Neurofibromatosis 2

- Inheritance: Autosomal dominant
- Prevalence: 1:40,000
- Systemic manifestations:
  - Tumors:
    - Schwannoma
    - Meningioma
    - Ependymoma
    - Glioma

Vestibular schwannoma

[Image source: Commons.wikimedia.org]
*NF2* gene encodes the protein merlin, which has pleiotropic effects

Asthagiri AR et al. (2009) Lancet
Neurofibromatosis 2: Ocular manifestations

- Cataract
- Epiretinal membrane
- Retinal hamartoma
- Optic nerve meningioma
- Intraocular schwannoma
- Neurotrophic keratopathy (vestibular schwannoma → CN VII dysfunction → poor lid closure → corneal damage from exposure)
Cataract

- Junvenile posterior subcapsular cataracts are found in 80% of NF2 patients
Epiretinal membrane

- In majority of NF2 patients, likely congenital
Epiretinal membrane (OS)
Epiretinal membrane
Epiretinal membrane

- Immunophenotype and ultrastructural features are most consistent with Muller cell origin
Intraocular schwannoma

long posterior ciliary nerve
Intraocular schwannoma
**Tuberous sclerosis**

- **Inheritance:** Autosomal dominant
- **Prevalence:** 1:6,000
- **Systemic manifestations:**
  - **Tumors:**
    - Facial angiofibroma
    - Ungual fibroma
    - Cardiac rhabdomyoma
    - Renal angiomyolipoma
    - Subependymal giant cell astrocytoma
  - **Other features:**
    - Cortical tubers
    - Subependymal nodule
    - Hypomelanotic macule
    - Shagreen patch
    - Pulmonary lymphangiomatosis
    - Renal nodular hamartomas

*Two tubers thicken the cortex and obscure the grey-white junction*

[Image source: Commons.wikimedia.org]
**TSC1** and **TSC2** encode the proteins hamartin and tuberin, which inhibit mTOR signaling

*Orlova KA and Crino PB (2010) Ann NY Acad Sci*
Tuberous sclerosis: Ocular manifestations

- Retinal hamartomas occur in ~50% of TS patients

Syed NA et al. (2004) EOPS
Retinal hamartoma

Syed NA et al. (2004) EOPS
Ataxia telangiectasia

- Inheritance: Autosomal recessive
- Prevalence: 1:30,000
- Systemic manifestations:
  - Tumors:
    - Lymphoid malignancy
  - Other features:
    - Early onset progressive cerebellar ataxia
    - Immunodeficiency and recurrent infections
    - Oculocutaneous telangiectasias
    - Absent/rudimentary thymus
    - Insulin-resistant diabetes
    - Radiosensitivity

Cutaneous telangiectasias

Emedicine.medscape.com
**ATM** encodes a protein involved in DNA repair

Fredrick A et al. (2010) FEBS
Ataxia telangiectasia: Ocular manifestations

- Conjunctival telangiectasias
- Oculomotor abnormalities
  - Nystagmus
  - Pursuit and saccade abnormalities
  - Strabismus
  - Poor convergence

Conjunctival telangiectasias
Conjunctival telangiectasias

Normal conjunctiva

Conjunctival telangiectasia
Amphicytes

- Bizarre enlargement of cell nuclei to 2-5 times normal size is found in many organs in AT

Amphicytes in conjunctival epithelium
Is the term phakomatoses still useful?

- Lack of consensus as to which conditions are phakomatoses
- Conditions are due to mutations in distinct genes
- For the most part, clinical features are nonoverlapping
- Commonalities raise similar genetic testing and patient care issues
  - Inherited as autosomal dominant, autosomal recessive or X-linked dominant traits (with the exception of Sturge-Weber syndrome, which is sporadic)
  - Chronic
  - Progressive
  - Pleiotropic