The Essentials of

Orbital Neurofibromatosis Type 1

- **Terminology**
  - Neurocutaneous disorder (inherited tumor syndrome) with distinct orbitocranial features

- **Imaging**
  - Constellation of features is characteristic of orbital NF1
    - Plexiform neurofibroma (PNF)
    - Optic nerve glioma (ONG)
    - Sphenoid dysplasia (SD)
    - Buphthalmos
    - Optic nerve sheath ectasia
  - Orbitofacial NF1 typically unilateral

- **Top Differential Diagnoses**
  - Plexiform neurofibroma
    - Rhabdomyosarcoma, infantile hemangioma, venolymphatic malformation, lymphoma
  - Optic nerve glioma
    - Glioma without NF1; nerve sheath meningioma
  - Sphenoid dysplasia
    - Congenital cephalocele, traumatic cephalocele
  - Buphthalmos
    - Congenital glaucoma; staphyloma
• Optic nerve sheath ectasia
  o Normal variant; intracranial hypertension

• Pathology
  • Autosomal dominant, 50% new mutations

• Clinical Issues
  • Presenting features: Infiltrative periorbital masses, proptosis, & ptosis

• Diagnostic Checklist
  • Orbital manifestations are progressive over time
  • Rapid change worrisome for malignant degeneration of PNF

TERMINOLOGY

• Abbreviations
  • Neurofibromatosis type 1 (NF1), plexiform neurofibroma (PNF), optic nerve glioma (ONG), sphenoid dysplasia (SD)

• Synonyms
  • von Recklinghausen disease

• Definitions
  • Neurocutaneous disorder (inherited tumor syndrome) with distinct orbitofacial and cranial manifestations

IMAGING

• General Features
  • Best diagnostic clue
    o Constellation of orbital & intracranial features is pathognomonic of NF1

  • Location
    o Orbitofacial NF1 typically unilateral

  • Morphology
    o Plexiform neurofibroma (PNF)
- Serpentine, unencapsulated infiltrative masses
- May involve cranial nerves, intraorbital branches, muscles, optic nerve sheath, and sclera
- Associated enlargement of skull base foramina
- Frequently trans-spatial, with contiguous tumors in preseptal orbit, temporal fossa, and skull base
  - Optic nerve glioma (ONG)
    - Tubular or lobular enlargement of optic nerve
    - May involve any segment of nerve
    - May extend posterior to chiasm and brainstem
  - Sphenoid dysplasia (SD)
    - Bony defects, decalcification, or remodeling of greater sphenoid wing & lateral orbital wall
    - Enlargement of middle fossa with herniation of intracranial contents into orbit
    - Associated middle fossa arachnoid cyst common
  - Buphthalmos
    - Increased axial and AP globe diameter
    - Remodeling & enlargement of anterior orbital rim
    - Thickening of uveal/scleral layer
    - Associated with anterior orbit PNF
  - Optic nerve sheath ectasia
    - Nontumorous enlargement of dural sheath
    - Increased CSF surrounding optic nerve

- Radiographic Findings
  - Radiography
    - Defect of greater sphenoid wing
    - Enlarged egg-shaped anterior orbital rim
o "Harlequin eye" appearance
o Optic canal &/or superior orbital fissure enlargement

- **CT Findings**
  - **NECT**
    o PNF
      - Hypodense **infiltrative** soft tissue masses
      - Increased overall orbital fat density due to small PNF of cranial nerve branches
    o ONG or nerve sheath ectasia: Enlarged nerve/sheath contour
    o SD: Bony defect with **herniation** of middle fossa into orbit; **proptosis** may be marked
  
- **MR Findings**
  - **T1WI**
    o PNF: Hypointense **ill-defined** soft tissue masses
    o ONG: Isointense ON mass ± cystic hypointensity
  - **T2WI**
    o PNF: Hyperintense nodular masses with central low signal "**target**" sign
    o ONG: Hyperintense **fusiform** optic nerve mass
    o Buphthalmos: Enlarged globe, thickened sclera
    o Nerve sheath ectasia: Increased **perioptic fluid**
  - **T1WI C+**
    o PNF: Irregular infiltrative **serpentine** masses; variable enhancement, may be intense
    o ONG: Variably enhancing optic nerve mass
      - Isolated tumors without NF1 often show more enhancement
  
- **Ultrasonographic Findings**
  - **PNF**: Irregular, compressible, highly reflective
• ONG: Smooth nerve enlargement, minimally reflective
• SD: Defect of posterior bony orbital wall
• Buphthalmos: Increased axial eye diameter

• Imaging Recommendations
  • Best imaging tool
    o MR ideal for assessment of orbital, extracranial, and intracranial lesions
  • Protocol advice
    o Dedicated brain and orbit examinations indicated for extensive abnormalities
    o NECT without sedation in child offers structural evaluation and gross tumor assessment

DIFFERENTIAL DIAGNOSIS
• DDx of Plexiform Neurofibroma
  • Infantile hemangioma
  • Venolymphatic malformation
  • Rhabdomyosarcoma
  • Lymphoma
  • Langerhans cell histiocytosis
  • Leukemia
  • Orbital pseudotumor
  • Orbital cellulitis

• DDx of Optic Nerve Glioma
  • Optic pathway glioma (isolated)
  • Optic nerve sheath meningioma

• DDx of Sphenoid Dysplasia
  • Congenital sphenorbital cephalocele
  • Post-traumatic sphenoid cephalocele
**DDx of Buphthalmos**
- Congenital glaucoma
- Staphyloma

**DDx of Optic Nerve Sheath Ectasia**
- Normal variant
- Idiopathic intracranial hypertension
- Optic nerve sheath meningioma

**PATHOLOGY**

**General Features**

**Etiology**
- Disorder of histogenesis, classified as neurocutaneous inherited tumor syndrome
- **Constellation** of orbital NF1 findings is characteristic
  - Features typically not isolated due to complex underlying interactive pathogenesis

**Genetics**
- **Autosomal dominant**; variable expression
- 50% **new mutations**; gene locus = 17q11.2
- Loss of NF1 **tumor suppressor** gene function

**Associated abnormalities**
- **CNS tumors** typical signal foci on brain imaging
- Characteristic foci of ↑ T2 signal in basal ganglia (nonneoplastic)
- Diffuse soft tissue neurofibromas; skeletal deformities
- Orbital features of NF1 have interrelated underlying pathology
  - In particular, SD and PNF intimately associated

**Staging, Grading, & Classification**
• Diagnostic criteria for NF1 established by NIH consensus statement on neurofibromatosis

• Treatment-based classification of orbital disease
  o Orbital soft tissue with seeing eye
  o Soft tissue & bone involvement with seeing eye
  o Soft tissue & bone involvement with blind malpositioned eye

• Gross Pathologic & Surgical Features
  • Plexiform neurofibroma
    o Worm-like infiltrating tortuous masses
    o May involve eyelid, anterior periorbita, scalp, orbit, temporal fossa, and skull base
  • Optic nerve glioma
    o Diffuse nerve enlargement; tan-white tumor
    o Cystic component with mucinous changes
  • Sphenoid dysplasia
    o Bony defect of posterior lateral orbit
    o Middle cranial fossa expansion with arachnoid cyst
  • Buphthalmos
    o Associated with PNF in anterior orbit
    o Enlargement of anterior orbital rim

• Microscopic Features
  • Plexiform neurofibroma
    o Myxoid endoneural accumulation early
    o Schwann cell proliferation, collagen accumulation
  • Optic nerve glioma
    o Spindle-shaped astrocytes with hyperplasia of fibroblasts and meningotheelial cells
- Circumferential perineural infiltration with arachnoid gliomatosis
- Sphenoid dysplasia
  - Bone decalcification; premature suture closure
- Buphthalmos
  - Periscleral infiltration by plexiform tumors

**CLINICAL ISSUES**

- **Presentation**
  - **Most common signs/symptoms**
    - Infiltrative periorbital masses, proptosis, and ptosis
  - **Other signs/symptoms**
    - Plexiform neurofibroma
      - Bulky soft tissue masses; *"bag of worms"* texture
      - PNF anywhere is pathognomonic for NF1
    - Optic nerve glioma
      - Visual deficit, often relatively mild
      - Proptosis associated with poor vision
    - Sphenoid dysplasia
      - **Pulsatile exophthalmos** due to orbital encroachment by middle fossa contents
    - Buphthalmos
      - Enlarged eye; impaired vision
      - May present with glaucoma

- **Clinical profile**
  - Child with progressive proptosis, visual impairment, soft tissue masses, & cosmetic deformities

- **Demographics**
  - **Age**
Findings may not be evident at birth
Cutaneous signs present at birth or 1st year
Tumors begin to appear in childhood

**Gender**
- No significant gender predilection

**Ethnicity**
- No significant race or ethnicity predilection

**Epidemiology**
- NF1 is **most common** inherited tumor syndrome
- Prevalence 1:2,500-5,000
- Orbital involvement in up to 1/3 of NF1

**Natural History & Prognosis**
- Orbital features of NF1 are progressive developmental lesions rather than simply congenital defects
- **Progressive worsening** of complications over time
  - Glaucoma, optic nerve compromise, blindness
  - Proptosis, corneal exposure
  - Muscle impairment, amblyopia
- PNF may undergo **sarcomatous degeneration** to malignant peripheral nerve sheath tumor (2-16%)
- Decreased life expectancy
  - Malignancy most common cause of death

**Treatment**
- Plexiform neurofibroma
  - Generally not surgically curable due to infiltrative nature
  - Anterior orbit and eyelid procedures most common
  - Debulking may be required for vision or cosmesis
- Transcutaneous lift after excision improves cosmesis
- Radiation therapy not effective

- Optic nerve glioma
  - Observation unless vision threatened
  - Radiation therapy and surgery for bulky tumors

- Sphenoid dysplasia
  - Transcranial reconstruction with bone grafts for severe posterior defects
  - Management of resultant proptosis; may ultimately require enucleation
  - Debulking of associated PNF

- Buphthalmos
  - Medical ± surgical therapy for glaucoma

**DIAGNOSTIC CHECKLIST**

- **Consider**
  - Although NF1 is inherited disorder, orbital manifestations are progressive and develop over time

- **Image Interpretation Pearls**
  - Rapid change in appearance of tumor worrisome for malignant degeneration