Non-Glaucomatous Optic Neuropathy
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Glaucomatous vs. Non-Glaucomatous Cupping
- Distinction is often difficult
- Detailed history is crucial
  - Many ailments that mimic glaucoma leave clues in the history
- Systematic examination approach recommended
  - Demographic characteristics
  - Visual acuity
  - Optic disc characteristics
  - Visual field findings

Glaucomatous Optic Neuropathy
- Characterized by progressive loss of nerve fiber layer resulting in diffuse loss or notching of neuroretinal rim, especially to optic disc margin

Other characteristic features include optic disc hemorrhage crossing the neuroretinal rim, asymmetry of cupping in absence of asymmetry of disc size, and peripapillary atrophy

Glaucomatous Optic Neuropathy
- Current definition of glaucoma precludes IOP as a defining feature
  - Can be diagnosed even when IOP is "normal"
- Unfortunately, excessive cupping of optic disc is considered pathognomonic of chronic glaucoma
- Normal Tension Glaucoma (NTG) often diagnosed if IOP falls within an acceptable range without investigating non-glaucomatous causes

Good History Taking
- Mode of onset of visual loss an important clue to etiology of optic neuropathy
  - Rapid onset
    - Optic neuritis, ischemic optic neuropathy, inflammatory (non-demyelinating), traumatic
  - Gradual onset over months
    - Compressive, toxic/nutritional, hereditary
  - Protracted history over years
    - Compressive, hereditary
Good History Taking
- Diplopia and facial pain suggestive of multiple cranial neuropathies in inflammatory or neoplastic lesions
- Transient visual obscurations, transient diplopia and headache seen in elevated intracranial pressure
- Many medications associated with direct or indirect toxicity of optic nerve, especially antibiotics and immunosuppressive agents

History of DM, HTN, and hypercholesterolemia common in patients with NAION
- Inquiry into patient’s general health, eating, and social habits important in suspected toxic or nutritional optic neuropathy
- Detailed family history important in diagnosing hereditary autosomal and mitochondrial optic neuropathies

Demographic Characteristics
- Family history of glaucoma among first degree relatives is highly specific (96%) for glaucomatous cupping
- Age under 50 years is 93% specific for non-glaucomatous cupping

- Young patient with history of eye pain associated with eye movement and prior history of neurological symptoms (paresthesia, limb weakness, ataxia) is suggestive of demyelinating optic neuritis
- Neurological complaints can be misdiagnosed
  - Chronic arm paresthesia usually misdiagnosed as carpal tunnel syndrome
  - Diminution of vision following rise in body temperature (Uthoff’s phenomenon) associated with demyelinating optic neuritis, but can be reported in LHON, and optic neuropathy from sarcoidosis

Demographic Characteristics
- Older patient with optic neuropathy and symptoms of transient visual loss, diplopia, temporal pain, jaw claudication, and myalgia strongly suggestive of AION
- Children with history of recent flu-like illness or vaccination days or weeks before vision loss points to a para-infectious or post-vaccinal optic neuritis etiology

Visual Acuity
- Patients with non-glaucomatous cupping have significantly lower levels of visual acuity than glaucoma patients
  - Trobe et al found 20 patients with compressive optic neuropathy had loss of central vision
  - Greenfield et al found visual acuity < 20/40 to be 77% specific for non-glaucomatous cupping
  - Hupp et al described sparing of central acuity in 3 of 6 eyes with compressive lesions
Glaucomatous cupping
- Vertical elongation
- Cupping more than pallor
- Greater frequency of peripapillary atrophy
- Disc hemorrhage
  - Highly specific, but can also be seen in PVD, retinal vascular occlusive disease, or associated with DM or HTN

Non-Glaucomatous cupping
- Pallor of neuroretinal rim
  - Highly specific sign, but relatively insensitive
  - Absence of disc pallor does not exclude compressive lesions

Optic Nerve Appearance
- Baring of the circumlinear vessels and saucerization
  - Common in glaucoma
  - Can also be seen in compressive optic neuropathy

Visual Field Findings
- Glaucoma
  - Nerve fiber layer defects, bordering horizontal midline
    - Arcuate scotoma
    - Nasal step

Visual Field Findings
- Compressive lesion
  - Central scotoma
  - Temporal hemianopia
  - Incongruous hemianopia respecting vertical meridian
  - *Glaucomatous types of visual field defects can occur*

NTG and Neuroimaging
- Some physicians routinely obtain neuroimaging studies in NTG patients
- Cost-to-benefit ratio of performing studies unclear
  - Ahmed et al found 4 of 62 patients with NTG had clinically significant intracranial lesions
  - Steward and Reid reported 2 of 53 patients evaluated for NTG had compressive lesions
  - Greenfield et al found zero patients diagnosed with glaucoma had compressive lesions
Who needs neuroimaging?
- Presence of headache or other neurological symptoms
- Symptoms of decreased vision, fluctuating vision, or visual field loss not typically associated with glaucoma
- Atypical visual field loss for glaucoma
  - Visual field defect respecting vertical meridian
  - Junctional scotoma
  - Central or cecocentral scotoma
- Atypical rate of progression of visual field loss
- Monocular or binocular
- Pallor greater than cupping
- Asymmetric cupping
  - Especially if progressive changes while IOP remains symmetric and well controlled

Most likely NTG if:
- Vertical elongation of cupping
- Presence of notch
- Presence of splinter hemorrhage
- Family history of glaucoma

Differential Diagnosis
- Compressive or infiltrative lesions of the optic nerve
- Previous ischemic optic neuropathy
  - Non-Arteritic and Arteritic
- Hereditary optic neuropathy
- Traumatic optic neuropathy
- Inflammatory (non-demyelinating) and demyelinating optic neuritis
- Infectious and toxic optic neuropathies

Compressive Optic Neuropathy
- Visual loss is usually gradual and progressive
- Common causes include orbital and intracranial meningiomas, pituitary adenomas, intracranial aneurysms, craniopharyngiomas, and gliomas of the anterior visual pathway
- Vision loss, can also be fast and dramatic, as in pituitary apoplexy or ruptured aneurysm
- Visual field testing aids in the localization of the lesion and neuro-imaging with MRI of the brain and orbit is essential

Compressive Optic Neuropathy
- Can also occur in thyroid eye disease
- Usually presents as asymmetric progressive visual loss
- Requires prompt therapy
  - Orbital radiation
  - Orbital decompression
  - High-dose systemic steroids
**Compressive Lesions**
- Usually present in patients younger than average glaucoma patient
- May exhibit visual fields that resemble glaucoma pt.
- Optic nerve pallor in excess of cupping, particularly of temporal rim, should prompt clinician to seek non-glaucomatous etiology
- Vertical step in visual field from involvement of optic nerve and/or optic chiasm, or cecocentral scotoma with decreased acuity also suggestive of compression

**Compressive-related Symptoms**
- Headache
- Vision loss, particularly peripherally
- Nausea and vomiting
- Weakness
- Less frequent or no menstrual periods
- Body hair loss
- Sexual dysfunction
- Increased frequency and amount of urination
- Unintended weight loss or gain

**Infiltrative Optic Neuropathy**
- Optic nerve can be infiltrated in systemic malignancies such as lymphoma, leukemia, multiple myeloma, and carcinoma
- MRI disc can be swollen or normal in appearance
- MRI of the brain and orbit may show meningeal and optic nerve enhancement
- Spinal tap is recommended in cases of suspected CNS malignancy
- Localized optic nerve infiltration with no evidence of systemic disease may require direct optic nerve sheath biopsy for histopathological diagnosis

**Ischemic Optic Neuropathy**
- Can be Non-Arteritic (NAION) or Arteritic (AION)
- NAION is most common acute optic neuropathy in elderly
- Patients with NAION are usually over 50 years old and have systemic vascular risk factors such as DM, HTN and smoking
- Pathophysiologic hypotheses include hypoperfusion of microcirculation, dysautoregulation, and venous insufficiency
- Classically described as a unilateral condition, however 14-40% of patients with NAION show contralateral involvement months or years after initial event

**NAION**
- Visual acuity can be normal or severely affected
- Visual field usually shows inferonasal arcuate or altitudinal defect
- Predominately affects small discs, aka “discs at risk”, with small or absent optic cup
- Disc edema and hemorrhages characterize acute stage
- Resolution of disc edema occurs and disc pallor ensues 4-6 weeks after the acute event,
- Main abnormalities are optic nerve head pallor without cupping, reduced visibility of the RNFL, and retinal vessel attenuation

**AION**
- Typically caused by temporal or giant cell arteritis
- Should be strongly considered in patients over 60 years of age with features of ischemic optic neuropathy
- Typically presents unilaterally and is classed as an ophtalmic emergency
- Without treatment, can rapidly progress to bilateral disease
- Careful medical history should be obtained, inquiring about temporal pain, jaw claudications, transient visual or diplopia, fever, weight loss, myalgias and fatigue
**AION**
- Clinical features that may help distinguish AION from NAION include cup-to-disc ratio of greater than 0.2 in the other eye, early massive or bilateral simultaneous visual loss, and markedly pallid disk edema often described as “chalky-white”

**AION**
- End-stage optic disc appearance in AION characterized by marked cupping with pallor and should not be confused with glaucomatous cupping
- Lab evaluation should include CBC, ESR, and CRP
- Elevated CRP was found to be more sensitive (97.5%) than ESR (76%–86%) for the detection of GCA
- ESR and CRP combined give the best specificity (97.0%) and sensitivity (99%) for diagnosis

**AION**
- Steroid treatment should be instituted in patients considered at high risk to have GCA based on the clinical and laboratory features
- Definitive diagnosis of AION is established by temporal artery biopsy and histopathological confirmation

**Hereditary Optic Neuropathy**
- Broad category including autosomally inherited diseases (dominant or recessive) and diseases caused by inheritance of defective mitochondrial genome
- Patients with dominant optic neuropathy (Kjers’ type) often present in the first decade of life with bilateral symmetric visual loss
- Visual acuity can range from 20/20 to 20/400
- Visual field testing frequently reveals bilateral central or cecocentral scotomas

**Hereditary Optic Neuropathy**
- Optic disc shows temporal pallor and in some cases severe excavation and cupping
- Various responsible genetic mutations occur in the OPA1 gene located on the chromosome 3q region
- Recessive optic neuropathy is rare and tends to present in the first year of life
- Can be associated with diabetes mellitus, diabetes insipidus, and deafness (Wolfram syndrome)

**Leber Hereditary Optic Neuropathy**
- Classically presents with acute unilateral, painless, profound visual loss (<20/200) with dyschromatopsia
- Sequential bilateral involvement may occur weeks or months later
- Visual field defects tend to be central or cecocentral as the papillo-macular bundle is first and most severely affected
- Fundoscopy may show disk swelling, thickening of the peripapillary RNFL and peripapillary telangiectatic vessels which do not leak on FA
Leber Hereditary Optic Neuropathy
- Frequently misdiagnosed because of the wide age range (6–80 years old) at presentation
- Young patients are often diagnosed as optic neuritis
- Older patients as ischemic or infiltrative optic neuropathy
- Four primary mitochondrial genome mutations: G11778A, G3460A and T14484C and T10663C
- Male predominance 4:1
- No definitive treatment and goal should be symptomatic treatment of vision loss and consider genetic testing for at risk family members

Traumatic Optic Neuropathy
- Anterior indirect TON is caused by a sudden displacement of the globe
- Injury occurs at the anterior portion of the optic nerve, usually at the level of the lamina cribrosa
- Posterior indirect TON, the most common form of TON, is most often caused by a frontal or midfacial blow
- Injury occurs further along the course of the optic nerve than in anterior indirect TON

Traumatic optic neuropathy
- Usually from history of craniofacial trauma, but occasionally from mild orbital or eye injury
- Can also be seen with history of shock or severe low blood pressure intra-operatively or post-operatively
- Direct TON occurs with penetrating injuries of the optic nerve and results in severe, immediate, irreversible visual loss
- Indirect TON occurs following blunt trauma to the eye or closed head injuries
  - occurs in 0.5–5% of cases of closed head trauma

Traumatic Optic Neuropathy
- Indirect TON has a better prognosis than direct TON with up to one-third of cases experiencing some spontaneous recovery of vision
- TON should be suspected in any patient with optic nerve dysfunction following head trauma

Traumatic Optic Neuropathy
- Acute changes of optic nerve head are common in anterior indirect TON
- Ring hemorrhage around the optic nerve head with absence of the optic disc is found with partial or complete optic nerve avulsion
- Frank tears in the nerve head, scattered retinal hemorrhages, arterial or venous occlusion, and optic disc edema can also be present
- Posterior indirect TON rarely causes any changes at the optic disc in the acute phase, and the optic nerve head usually appears normal on examination.

Traumatic Optic Neuropathy
- Pallor of the disc becomes apparent in severe cases of TON 3-4 weeks after injury and rapidly progresses to gross pallor and complete optic atrophy
- In less severe cases, disc pallor occurs later, and in some cases remains undetectable
- Optic disc excavation can occur but is uncommon
**Acute Demyelinating Optic Neuritis**
- Optic neuritis is an acute, usually unilateral, inflammatory optic neuropathy
- Most commonly seen in otherwise healthy individuals (idiopathic) or in those with additional evidence of multiple sclerosis (MS)
- Optic neuritis is more common in females with a peak age of onset between 30–40 years

**Optic Neuritis - Acute**
- In acute phase of optic neuritis, the involved optic disc can have a normal appearance or can be swollen
- Any swelling is usually nonspecific and diffuse, with mild to moderate edema
- A markedly swollen optic nerve head or sectoral edema is uncommon.
- The absence of swelling indicates a retrobulbar neuritis.
- Optic Neuritis Treatment Trial found that two-thirds of patients with optic neuritis had retrobulbar neuritis at presentation and remaining one-third had disc swelling

**Optic Neuritis - Chronic**
- Loss of retinal nerve fibers begins within one month of acute attack and continues for 3–6 months
- Loss is associated with reduced RNFL visibility
- Optic disc pallor has been described in up to 71% of eyes and is most commonly segmental
- Optic disc excavation is greater in eyes with thinner RNFL and poorer visual acuity, and might be a prognostic indicator

**Optic Neuritis**
- Optic neuritis improves in 90% of cases over several weeks to near normal visual acuity
- Use of intravenous steroids was found to hasten the visual recovery but not the final visual outcome
- Lack of improvement after about 4–6 weeks with or without steroids is atypical of optic neuritis and should prompt searching for an alternative causes such as inflammatory, infiltrative or compressive

**Inflammatory (Non-Demyelinating) Optic Neuropathy**
- Caused by many entities involving optic nerve by either an ocular or systemic inflammatory or infectious process
  - Sarcoidosis
  - SLE
  - Behcet’s
  - IBD
  - Sjogren’s syndrome
  - Wegener’s granulomatosis
  - Syphilis
  - Lyme disease

**Inflammatory Optic Neuropathy**
- Optic disc swelling frequently occurs with posterior uveitis and retinitis
- When evaluating optic disk swelling it’s useful to look for evidence of anterior or posterior segment inflammation.
- Features that should raise suspicion of an inflammatory optic neuritis include lack of spontaneous improvement of visual function after 30 days, or exquisite steroid-responsiveness and steroid-dependency
- In such cases, spinal tap and additional lab studies directed by history and neuro-ophthalmic examination are indicated
Infectious and Toxic Optic Neuropathies

- These primary types of acquired optic neuropathy are increasingly called mitochondrial optic neuropathies, due to their common pathophysiology
- Toxins can disrupt mitochondrial function, and nutrition-dependent, metabolically active structures can particularly run into trouble because their mitochondria have higher demands.
- Characterized by damage to the papillomacular bundle because these fibers are small, unmyelinated, and chock-full of mitochondria

Infectious and Toxic Optic Neuropathies

- Classically cause decreased visual acuity, a central or cecocentral scotoma, and dyschromatopsia
- Almost always bilaterally symmetrical and involve a painless, insidious onset

Nutritional Optic Neuropathy

- Largely due to deficiency in Vitamin B₁₂ and Folic Acid
- Can result from wide range of underlying factors
  - Eating disorders, fad diets, gastric bypass surgery, hyperemesis gravidarum
  - Some vegetarians may be at risk (particularly strict vegans)
- Poor diet due to excessive alcohol use may be main contributor of nutritional optic neuropathy in developed world

Toxic Optic Neuropathy

- Many antibiotics don't differentiate between mitochondria of the PMB and bacteria
- Be careful in older patients who may weigh less and/or have poor kidney function
- Some drugs have a shorter half-life which affects how fast optic neuropathy develops and also how long drug stays in the system

Common Toxins

- Medications
  - Ethambutol, Rifampin, Isoniazid, Streptomycin
  - Chloramphenicol
  - Amiodarone
  - Isoretinoin
  - Cyclosporine
  - Linezolid

Common Toxins

- Acute Toxins
  - Methanol: by-product of moonshine and present in some cleaning agents
  - Ethylene Glycol: main ingredient in anti-freeze and hydraulic brake fluid
- Vaccines
  - Influenza, HPV, Hep A and B, MMR
- Vaccination associated with retrobulbar optic neuropathy due to rare type 3 hypersensitivity reaction throughout body
- Small blood vessels become blocked by immune complexes
Optimal Workup

- BCVA: patients may describe visual loss as central haze or dark cloud
- Color vision: washout of color across whole spectrum, but most often affects color red
- Visual fields: central field defect with sparing of the periphery is hallmark
- Pupils: RAPD usually not seen since disease is bilaterally symmetrical

Optimal Workup

- Fundus exam: Optic nerve pallor occurs over time, but may appear normal at first
- Wedge-shaped defect may be seen on temporal side of nerve fiber layer
- Blood tests appropriate for nutritional deficiency
- If medication is suspected cause, then only real test is to stop the drug