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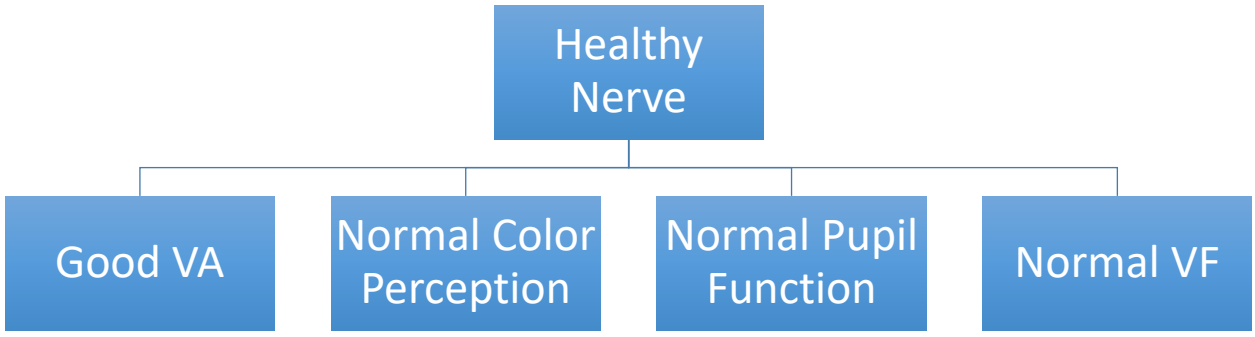
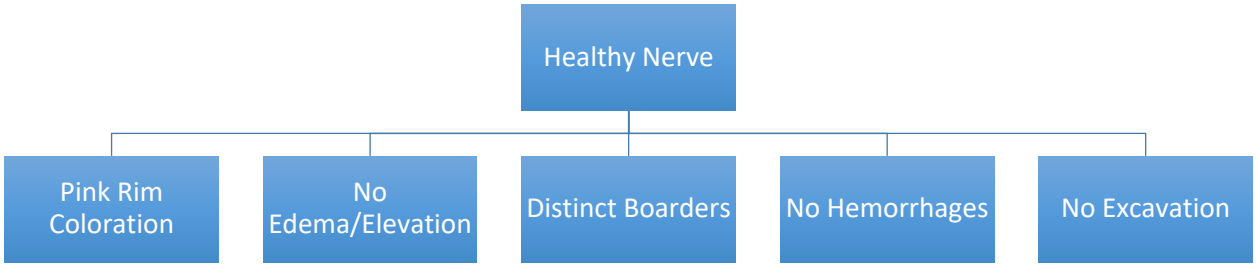
Optic Nerve Assessment

It is important to remember that a healthy nerve will look normally and function appropriately.

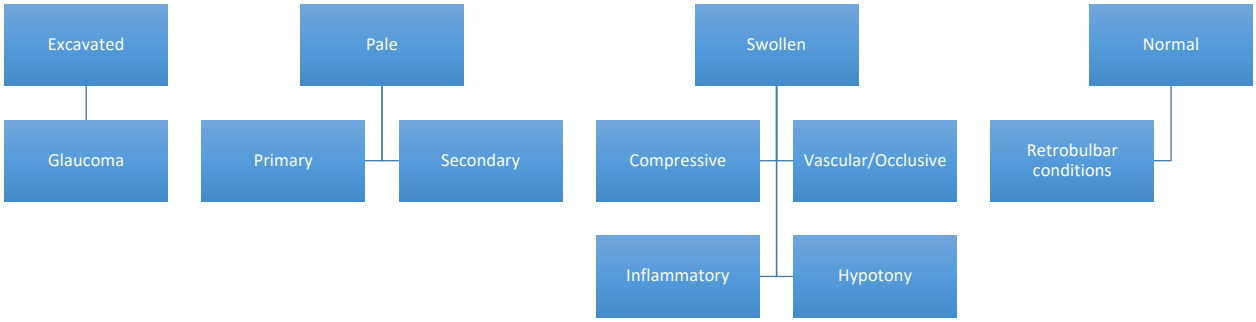
What clinical findings are consistent with a normally functioning optic nerve?



What clinical findings are characteristic of a healthy optic nerve?



What clinical findings are characteristic of a unilateral sick optic nerve?



Swollen (Edematous)

Optic nerve edema refers to increased fluid within or surrounding CN 2 axons. When identifying optic nerve edema, it is important to utilize the correct terminology, not just in the communication with other providers but it also helps clinicians focus on potential underlying causes of the edema.

Disc edema can be unilateral or bilateral. For our purposes when we refer to **disc edema** (either unilateral or bilateral), we will be referring to **optic nerve swelling due to an underlying cause that is anterior to the chiasm**. When we refer to **papilledema**, we will be referring to **optic nerve swelling in both eyes due to increased intracranial pressure (ICP) and located at the chiasm or posterior to the chiasm** [1].

It is important to remember that the underlying etiology causing disc edema or papilledema typically cannot be determined by clinical presentation alone. Typically to identify the underlying cause of swelling clinicians must rely on history and epidemiology in addition to clinical appearance.

Clinical Findings Consistent with Nerve Swelling

Early on in the course of the swelling there may only be mild obscuration (blurred disc margin) of the nerve fiber. As the condition persists we may see additional findings such as:

- **Early findings**:
  - optic disc hyperemia
  - hemorrhages in the peripapillary nerve fiber layer
  - hard exudates
  - cotton wool spots
  - subretinal fluid
- **Chronic findings**:
  - collateral vessels
  - retinal striae
  - choroidal (Patton's) folds
  - secondary atrophy

Distinguishing Between Bilateral Disc Edema and Papilledema

It is important to distinguish clinically between bilateral disc edema and papilledema because it will help guide subsequent testing and ultimately a diagnosis and treatment that is accurate. First consider that it is very rare to have bilateral disc edema, so when we see two swollen nerves think papilledema first.

Additional clinical characteristics that can be helpful in distinguishing between bilateral disc edema and papilledema include [1] [2]:

- Papilledema
  - Normal visual acuity (VA)
  - Enlarged blind spot on VF testing
  - No relative afferent pupillary defect (RAPD)
- Bilateral disc edema
  - Reduced VA
  - Various VF defects, typically more severe than in papilledema
  - RAPD is likely if swelling is asymmetric

Disc Edema

Again, disc edema refers to the underlying causes as being isolated anterior to the chiasm. Optic disc edema can be unilateral (most common) or bilateral (rare), causes include:

1. **Infectous/Inflammatory** – neuroretinitis, optic neuritis
2. **Compressive** – space occupying lesion
3. **Vascular/Occlusive** – central retinal vein occlusion, anterior ischemic optic neuropathy
4. **Hypotonic** – very low intra ocular pressure following trauma or surgery

Ischemic Optic Neuropathy (ION)

Ischemic optic neuropathy is classified based on the location and underlying etiology of the swelling. **Anterior ION** involves swelling of the optic disc (anterior 1 mm of CN II). Anterior ION is further classified as arteritic (AAION) and non-arteritic (NAION). **Posterior ION** involves swelling of the optic nerve **not including** the optic disc and will not result in disc swelling.

Arteritic Anterior Ischemic Optic Neuropathy (AAION)

Pathophysiology and Demographics

AAION is caused by **inflammation** and **thrombosis** of the **short posterior ciliary arteries** (SPCA's). AAION accounts for approximately **5-10% of all AION**, is most often associated with **giant cell arteritis** (GCA) and in patients **over the age of 70**. If left untreated permanent vision loss occurs in the majority (54-95%) of patients. It is also considered an **ocular emergency** since the second eye can become involved within 24 hours [3] [4].

Symptoms

- **Ocular:** rapid onset of severe, unilateral, painless visual acuity (<20/200 in over 60% of the patients) and visual field (**inferior altitudinal** – most common) loss [5]
- **Systemic: headache** (most common), **scalp** or temporal artery **tenderness**, **jaw claudication** (most specific symptom for GCA), **malaise**, **anorexia**, weight loss, fever, joint and muscle pain, and ear pain

Signs

RAPD, **chalky-white optic disc pallor** is a classic finding, but the nerve can appear with hyperemic edema. **Diffuse swelling** is most common but edema can occasionally be more pronounced

GCA Association

5-10% of patients with GCA will have ocular (AAION) manifestations and up to 20% of all GCA patients with have no systemic symptoms [5].

in one location, disc **flame hemorrhages** can occur as can **narrowing** of the **peripapillary retinal arterioles**. In contrast to NAION, the cup and disc of the fellow eye is normal size [2] [3] [6].

Additional tests that should be evaluated include:

- **Erythrocyte sedimentation rate** (ESR) – STAT – typically elevated up to 70-120 mm/min
- **C reactive protein** (CRP) – STAT
    - The combination of an elevated ESR and CRP has a 97% specificity for GCA
- **Platelets** (CBC w/ diff)
- **Temporal artery biopsy** should be obtained in all cases where GCA is suspected within 1 week of starting treatment
    - False negatives occur in approximately 3-5% of temporal artery biopsies due to the possibility of skip lesions
- Optic nerve OCT can be utilized to assess severity of edema and RNFL thickness/defects and monitor resolution

Traditional Treatment and Management

As mentioned above, early diagnosis and treatment is critical. Classic treatment includes [3]:

- Severe: Pulse **IV methylprednisolone at 1g/day x 3 days** followed by **oral treatment** as below
- Mild-Moderate: **Oral prednisone (60-100mg/day)** for several months with slow

With the steroid treatment:

- VA improvement in the affected eye can occur in 15-34% (higher with IV Tx)
- Progressive VA reduction will occur in 9-17%

Literature Update

How effective is tocilizumab at preventing recurrence of GCA [7]?

- 251 patients with GCA were randomized to receive:
    - subcutaneous tocilizumab **weekly**, combined with a 26-week prednisone taper
    - subcutaneous tocilizumab **every other week**, combined with a 26-week prednisone taper
    - placebo combined with a prednisone taper over a period of **26 weeks**
    - placebo combined with a prednisone taper over a period of **52 weeks**
- Rate of **sustained glucocorticoid-free remission** at week 52 was:
    - Weekly group: 56%
    - Every other week: 53%
    - Placebo w/ 26 week taper: 14%
    - Placebo w/ 52 week taper: 18%
- Serious adverse events
    - Weekly group: 15%
    - Every other week: 14%
    - Placebo w/ 26 week taper: 22%

- Placebo w/ 52 week taper: 25%

Non-arteritic Anterior Ischemic Optic Neuropathy

Pathophysiology and Demographics

The underlying mechanism of NAION is still a source of debate although it is presumed to **result from poor circulation or microvascular infarct** posterior to the lamina cribrosa that obtains its vascular supply from the SPCA's [8] [9].

NAION is the most common cause of acute optic neuropathy in patients over the age of 50, impacting between 2.3-10.3 people per 100,000/year [10]. The sexes are equally impacted and **Caucasians** account for 95% of new cases every year [4]. The majority of patients are between the ages **of 57 and 65**, however it may also occur occasionally (23% of the time) in patients under age 50 [11] [12].

There are additional potential underlying contributors to the development of NAION. These include:

- Sleep Apnea
- Nocturnal hypotension
- Medications
  - **Interferons** – possibly causes the deposition of immune complexes within the optic nerve head
  - **Sildenafil** – unclear if patients with ED are predisposed to blood flow issues in general or from the potentiation of nocturnal hypotension from the medication
- ONH Drusen
- Small optic disc – "disc at risk"
- Autoregulation
- Venous insufficiency
- Microvascular risk factors

Diabetic Papillopathy

Diabetic papillopathy may be a subtype of NAION in patients with diabetes causing minimal vision loss [37].

Symptoms

Rapid onset (usually upon awakening) of **unilateral**, painless vision loss and often described as "clouded" or "blurred" (**20/64 or better in 49%** and 20/200 or better in 66%) and visual field (**inferior altitudinal** – most common) loss [13].

- It is atypical for patients to report pain, 8-12% of patients with NAION do have symptoms of headache or pain around the eye [14].

Signs

RAPD, segmented or diffuse hyperemic **disc edema**, **flame hemorrhages**, focal **narrowing** of the peripapillary retinal **arterioles**.

Perform the same lab tests and biopsy as described in AAION to ensure the patient is not at risk for further vision loss. Routine neuroimaging is not required but MRI w/ and w/o contrast should be strongly considered in patients with pain on eye movement, persistent edema and progressive vision loss.

- Vision can worsen over the first 2 week period but should stabilize by 2 months

Traditional Treatment and Management

There is no standard treatment for NAION although the following has been proposed:

- Aspirin +/-
- Ocular hypotensive medications +/-
- ~~Optic nerve decompression surgery~~ [15]

Flame Hemorrhages

75% of patients with NAION will present with peripapillary hemorrhages while only 5-15% of patients with optic neuritis will present with peripapillary hemorrhages [13] [36]. **If hemes are present and the clinical picture is not clear think NAION first.**

Literature Update

Are early oral steroids effective at improving VA and VF in patients with NAION [16]?

In a study on 613 consecutive NAION patients (within 2 weeks of onset) with no randomization, placebo control or masking, patients were given the option of being treated with **oral prednisone** (80 mg/day x 2 weeks with long taper) or **monitoring alone** and they found the following:

- Median time to resolution of edema:
  - Steroids: 6.8 weeks
  - Monitor: 8.2 weeks
- After 6 months, patients with an initial visual acuity of **20/70** or worse had visual acuity improvement in:
  - Steroids: 69.8%
  - Monitor: 40.5%
- Improvement in VF defect:
  - Steroids: 40%
  - Monitor: 24.5%
- In patients with NAION and VA of 20/70 or worse neuro-ophthalmology consult may be appropriate to consider high does steroids

Optic Neuritis

Pathophysiology and Demographics

Optic neuritis is an immune-mediated inflammatory process that leads to demyelination of the optic nerve. The prevalence estimated to be 1-5/100,000 and is more common in young (20-45 yo) females (3:2) and more common in patients with multiple sclerosis (MS).

Symptoms

Patients can present with:

- Reduced vision
- Optic nerve dysfunction including decreased peripheral vision, decreased color vision, decreased contrast/brightness sense, RAPD
- **Periocular pain** (92%) may precede the visual loss by a few days and is precipitated or made **worse upon eye movement** (87%) [17]
- Altered motion perception (Pulfrich phenomenon)
- VA worsening with rises in body temperature (Uhthoff's phenomenon)

Signs

Clinical signs include: **RAPD**, VF defects, disc edema (but 65% can have **retrobulbar** optic neuritis), retinal vascular sheathing, pars planitis

In patients suspected of optic neuritis, **MRI** imaging helps rule-out potential other masqueraders of optic neuritis (such as tumors and neuroretinitis) and also aids in understanding the likely prognosis (discussed below).

Important Pearls from the Optic Neuritis Treatment Trial [17] [18]

In a prospective, randomized, multi-center trial, 457 patients (85% Caucasian, 18-60 years old with symptoms of decreased vision **8 days or less** without prior episodes, not taking prednisone, and without any significant systemic diseases were randomized to treatment in the below groups and followed for at least 6 months:

1. oral placebo
2. 250mg IV solumedrol q6hrs for 3 days then 1mg/kg of prednisone for 11 days
3. 1mg/kg of PO prednisone alone for 14 days

They found:

- Patients treated with **IV steroids recovered faster** (within first 4-6 weeks), but after 6 months there was no statistical difference in final visual outcome
- Patients treated with oral steroids alone had a higher rate of recurrence – **oral steroids alone are contraindicated**
- Most patients return to normal or near normal vision (1-6 months) but reduced contrast sensitivity typically persists
    - 94% recover 20/40 or better
    - Only 3% of patients will have VA of 20/200 or worse
- Prolonged pain with eye movement, lack of recovery, recurrence within 2 months should prompt consideration and evaluation of other conditions
- Patients **without any** demyelinating lesions on initial MRI have the following risk of developing clinically definite MS (CDMS) is:
    - 16% in 5 years
    - 22% in 10 years
    - 25% in 15 years
- Patients with **1 or more** demyelinating lesions on initial MRI have the following risk of developing CDMS:
    - 56% in 10 years
    - 72% in 15 years

Papillophlebitis

Papillophlebitis has the clinical presentation of a central retinal vein occlusion in young (younger than 50) patients without a history of vascular disease [19].

Clinical findings include: **painless unilateral disc edema** and hyperemia, **retinal venous engorgement**, and a variable extent of **intraretinal hemorrhage** and **macular edema**.

Clinical Note

Think about papillophlebitis as a CRVO in a you healthy patient without any microvascular risk factors.

Compressive Optic Neuropathy

It is important to remember that in addition to **disc edema**, compressive optic neuropathy, can also appear as **normal**, **atrophic** (chronic) and also contain optociliary shunt vessels. Anything that can produce a mechanical mass effect can lead to this type of optic neuropathy. These conditions include [20]:

- Retrobulbar hemorrhage
- Aneurysm
- Mucocele
- Meningioma
- Glioma
- Pituitary adenoma
- Craniopharyngioma
- Metastases

It can be challenging to know when to consider compressive optic neuropathy from other more common conditions that can cause disc edema, atrophy, VA and VF loss. The following clinical findings should raise suspicion of a compressive etiology of an optic neuropathy [21]:

- VA reduction is 20/100 or worse
- IOP is not elevated
- Ipsilateral proptosis
- Resistance to retropulsion
- EOM restriction
- Choroidal folds
- Central/cecocentral VF defects
- Pallor in the absence of excavation
- Significant asymmetry in VA, RAPD or VF with minimal difference in nerve appearance

Grave's Disease (Thyroid Eye Disease)

Clinicians can consider thyroid eye disease (TED) as a type of compressive optic neuropathy.

Pathophysiology and Demographics

TED occurs due to **inflammation and infiltration of the extraocular muscles** that results in compression of the optic nerve. It is typically associated with hyperthyroidism but can also occur with an immune mediated hypothyroidism. The onset tends to be in the 40-60's and smoking seems to exacerbate the condition.

Symptoms

Depending on the severity of the condition, symptoms include; **pain**, **photophobia**, **lacrimation**, **foreign body sensation**, **diplopia** and a **reduction in VA**.

Signs

Disc edema (late finding), swelling and redness of soft tissues, **eyelid retraction**, lid lag, Von Graefe's sign, chemosis, exposure keratopathy, **proptosis**, choroidal folds, restrictive myopathy [22]

The clinical diagnosis can be made in patients with [23]:

- Abnormal TSH, T4, Thyroid stimulating immunoglobulin
- Exophthalmos
- Optic neuropathy
- EOM restriction

DDx

TED can be distinguished from orbital pseudotumor with neuroimaging. **Patients with orbital pseudotumor will have an enlargement of the muscle tendon while patients with TED will not** [22].

MRI, CT and ultrasound will show an asymmetric enlargement of the muscle belly **without impacting the muscle tendons**.

Treatment and Management

Treatment of patients with TED is typically supportive and can include [24]:

- Artificial tears
- Cool compresses
- Nocturnal head elevation
- Thyroid control

Some patients with acute flare ups will require **oral steroids for 4-6 weeks** and severe cases may require IV steroids. Occasionally orbital radiation is beneficial in addition to steroid treatment in an effort to spare patients from orbital decompression surgery, however, about **20% of patients with TED will require orbital decompression surgery**.

Neuroretinitis

Neuroretinitis is a combined inflammation of the optic nerve and neuroretina which is seen clinically as a patient with **disc edema** and a **macular star** (radial hard exudates in the macula). Neuroretinitis can be idiopathic but a common causative agent is *bartonella* species (cat scratch) [25].

Papilledema

Papilledema refers to swollen nerves in **BOTH eyes** secondary to **increased intracranial pressure** (ICP) and the underlying etiology lies at the **chiasm or posterior to the chiasm. It is important to remember that papilledema does not mean benign (idiopathic) intracranial hypertension (IIH), which is a diagnosis of exclusion.**

Symptoms

Early papilledema has few symptoms. **Headache** (worse when straining, coughing, bending and in the morning), **transient visual obscurations** (short periods of vision loss when standing or changing position), **hearing vascular sounds** (whooshing), **double vision**.

Opening Pressure

Normal CSF pressure is 250 mm of water.

Signs

Bilateral optic nerve swelling, **loss of spontaneous venous pulsation** (SVP), **dilated disc capillaries**, RNFL edema and opacification, **obscured retinal vessels**, dilated veins, **flame hemes** at the disc, **cotton wool spots**, **hard exudates**, macular edema, Paton's folds, and as it becomes chronic pallor occurs with possible optociliary shunt vessels. Early VF can show enlarged blind spot, later fields can show peripheral defects.

When grading severity of papilledema the following (Frisen) scale has been used [26]:

- **Stage 0** - **Normal Optic Disc** with possible blurred nasal, superior and inferior disc margin
  - Rare obscuration of a major blood vessel, usually on the superior rim
- **Stage 1** -**Very Early Papilledema**
  - Obscuration of the nasal border of the disc
  - No elevation of the disc borders
  - Disruption of the NFL arrangement with grayish opacity accentuating nerve fiber layer bundles
  - Normal temporal disc margin.
  - Subtle grayish halo with temporal gap (best seen with indirect ophthalmoscopy)
  - Concentric or radial retrochoroidal folds
- **Stage 2 - Early Papilledema**
  - Obscuration of all borders
  - Elevation of the nasal border
  - Complete peripapillary halo
- **Stage 3 - Moderate Papilledema**
  - Obscurations of all borders
  - Increased diameter of optic nerve head. Obscuration of one or more segments of major blood vessels leaving the disc
  - Peripapillary halo-irregular outer fringe with finger-like extensions
- **Stage 4 - Marked Papilledema**
  - Elevation of the entire nerve head
  - Obscuration of all borders
  - Peripapillary halo
  - Total obscuration on the disc of a segment of a major blood vessel
- **Stage 5 - Severe Papilledema**
  - Dome-shaped protrusions representing anterior expansion of the optic nerve head
  - Peripapillary halo is narrow and smoothly demarcated
  - Total obscuration of a segment of a major blood vessel may or may not be present
  - Obliteration of the optic cup

Underlying Causes

When considering underlying causes of papilledema it is important to evaluate the patient for the following:

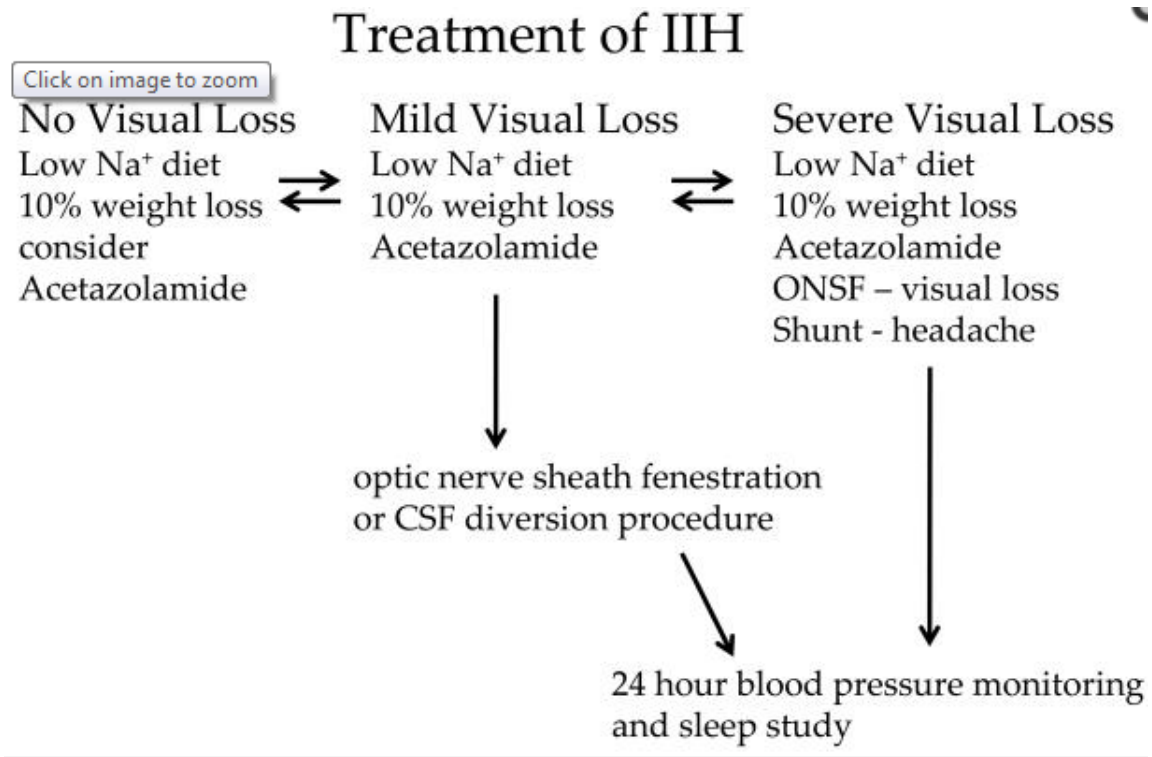
1. Malignant hypertension → take **blood pressure**
2. Space occupying lesions → order **MRI/CT**
3. Infectious/Inflammatory → obtain a lumbar puncture **(LP)**
4. Obstructed arachnoid villi → order **MRV**
5. Idiopathic → All the above are normal

Idiopathic Intracranial Hypertension (IIH)

IIH, often called benign intracranial hypertension or pseudotumor cerebri, is a condition that causes an increase in CSF pressure in the absence of other identifiable pathology. **The diagnosis of IIH is made when number 1-4 above are performed the only abnormal finding is an elevated opening pressure on LP and the only localizing defect is CN 6 (and/or CN 7 palsy)**. Risk factors include [27]:

- **Medications:** oral contraceptives, steroids, vitamin A, Isotretinoin, lithium, growth hormone, nitrofurantoin, phenytoin, sulfa drugs, Tamoxifen, naladixic acid, thyroid replacement, tetracycline/minocycline, and some chemotherapeutic drugs
- **Increased BMI**
- **Female**

Depending on severity of vision loss, treatments includes low sodium diet, weight loss, medications (acetazolamide, furosemide, topiramate), CSF shunting procedures [28].



Pallor

Optic nerve pallor/atrophy can be classified as either primary or secondary.

- **Primary pallor** means that the nerve went from looking normal to pale without any intermediate stage.
- **Secondary pallor** means that the nerve went from looking normal → swollen → pale, so any condition that will cause edema can ultimately cause pallor.

Since we have covered most conditions above that can cause secondary pallor and some (compressive lesions) that can cause primary pallor, it is important to understand a few other conditions that can cause a nerve to appear pale.

Autosomal Dominant Optic Atrophy

Dominant optic atrophy typically has a gradual onset early in life (**first-second decade**), when VA loss occurs it is usually **bilateral and mild** (80% of patients maintain 20/200 or better) [29]. It is transmitted through mitochondrial DNA and the optic atrophy typically **shows focal, wedged-shaped temporal optic atrophy** with RNFL defects in the papillomacular bundle, but diffuse pallor may occur as well. VF defects include central, centrocecal and paracentral scotomas [30].

Leber's Hereditary Optic Atrophy (LHON)

LHON typically has an onset between the ages of **10 and 30 years** and starts with symptoms of mild blur but can also be asymptomatic early on in the course but can **ultimately lead to vision loss that is usually worse than 20/200**. The condition has a predilection in males and is also transmitted via mitochondrial DNA. **Early on in the condition optic nerves can appear normal or even mildly edematous** (although it is not true edema) followed by pallor and atrophy. VF defects include central or cecocentral scotoma [31].

Excavation

The most common cause of acquired optic nerve excavation is glaucoma, however, other congenital anomalies of the optic nerve can also cause localized pallor and excavation.

Glaucoma

As a general overview, clinical findings in glaucoma include: **Increased C/D ratios**, **cupping**, asymmetry of more than 0.2, **RNFL defects**, thinning/**notching** of the neuroretinal rim tissue, **vessel kinking**, saucerization, **vessel bayonetting**, **vessel baring** (where a vessel that was abutted up against the edge of the cup now has space between it and the cup), Splinter (drance) hemorrhages, zone beta atrophy.

VF defects include: nasal steps, arcuate, paracentral and wedge.

Does lowering IOP help slow progression in patients with low tension glaucoma [32]?

- 140 patient eyes, 61 - treatment group, 79 - untreated controls.
- **Twenty-eight (35%) of the control eyes and 7 (12%) of the treated eyes reached end points**
  - (specifically defined criteria of glaucomatous optic disk progression or visual field loss).

Does it matter what medications we use to treat patients with low tension glaucoma [33]?

- 99 - brimonidine, 79 - timolol

- **Statistically fewer brimonidine-treated patients (9, 9.1%) had visual field progression by pointwise linear regression than timolol-treated patients (31, 39.2%, log-rank 12.4, P=.001)**.
- **Mean treated IOP was similar for brimonidine- and timolol-treated patients at all time points.**

How much IOP reduction can we expect after cataract surgery alone [34]?

- The study comprised 124 eyes.
- The final mean IOP reduction was 8.5 mm Hg (34%) in the 29 to 23 mm Hg group, 4.6 mm Hg (22%) in the 22 to 20 mm Hg group, **3.4 mm Hg (18%) in the 19 to 18 mm Hg group**, and 1.1 mm Hg (10%) in the 17 to 15 mm Hg group. In the 14 to 5 mm Hg group, IOP increased by 1.7 mm Hg (15%).

How much IOP reduction can we expect after combined cataract surgery plus iStent [35]?

- Overall, the mean IOP was stable between 12 months and 24 months (17.0 mm Hg ± 2.8 [SD] and 17.1 ± 2.9 mm Hg, respectively) in the stent group but increased (17.0 ± 3.1 mm Hg to 17.8 ± 3.3 mm Hg, respectively) in the control group.
- **Ocular hypotensive medication need was statistically significantly lower in the stent group at 12 months; it was also lower at 24 months, although the difference was no longer statistically significant.**

Optic Nerve Pits

Optic nerve pits are approximatly 1/3 DD, typically unilateral and present as small, grayish, round or oval hypopigmented **excavated depressions in the optic nerve head**. They are most commonly located at the **inferior temporal** aspect of the optic nerve. They can be asymptomatic but can become symptomatic when they are associated with **macular edema**, **schesis** and **serous detachments**.

VF defects can mimic glaucomatous defects.

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