

# ABOUT THE AUTHOR



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## An Approach to Optic Neuropathies

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Optic neuropathies are varied in their clinical presentations, etiologies, recommended diagnostic investigations, and treatments. This article aims to provide a practical framework to guide the evaluation of a patient suspected of an optic neuropathy (**Figure 1**).

**One should consider whether there is clear optic nerve dysfunction.** Decreased visual acuity, obvious subjective blurring of central or peripheral vision, acquired dyschromatopsia, or a relative afferent pupillary defect (RAPD) in unilateral or asymmetric cases, are clues that suggest an optic neuropathy<sup>1</sup>. Determining whether vision loss is the result of a primary retinal cause (e.g., maculopathy, retinal degeneration, retinal detachment, etc.) or optic nerve damage, can be challenging given the overlapping clinical features<sup>2</sup>. Paying attention to key clinical and optical coherence tomography (OCT) features can be helpful. Clinically, macular disease may produce relative micropsia, macropsia, or metamorphopsia all of

which are very uncommon in optic neuropathies unless there is secondary retinal involvement (e.g., spill over edema into the macula in neuroretinitis, papilledema, hypertensive or diabetic papillopathies). Careful review of an OCT of the macula can reveal whether there are inner retinal abnormalities (e.g., retinal nerve fiber layer [RNFL], or ganglion cell layer [GCC]) versus outer retinal (e.g., ellipsoid zone, or retinal pigment epithelium [RPE]) disruption. For a helpful functional assessment, multifocal electroretinography (mfERG) can aid in distinguishing optic neuropathies exhibiting RNFL or GCC dysfunction from maculopathies (usually outer retinal damage) given that maculopathies will usually demonstrate reductions in amplitude and/or increase in latency, whereas optic neuropathies generally yield normal mfERG findings.

**If optic nerve function is relatively spared**, determine if there are signs or symptoms of raised intracranial pressure (ICP), such as transient visual obscurations, morning

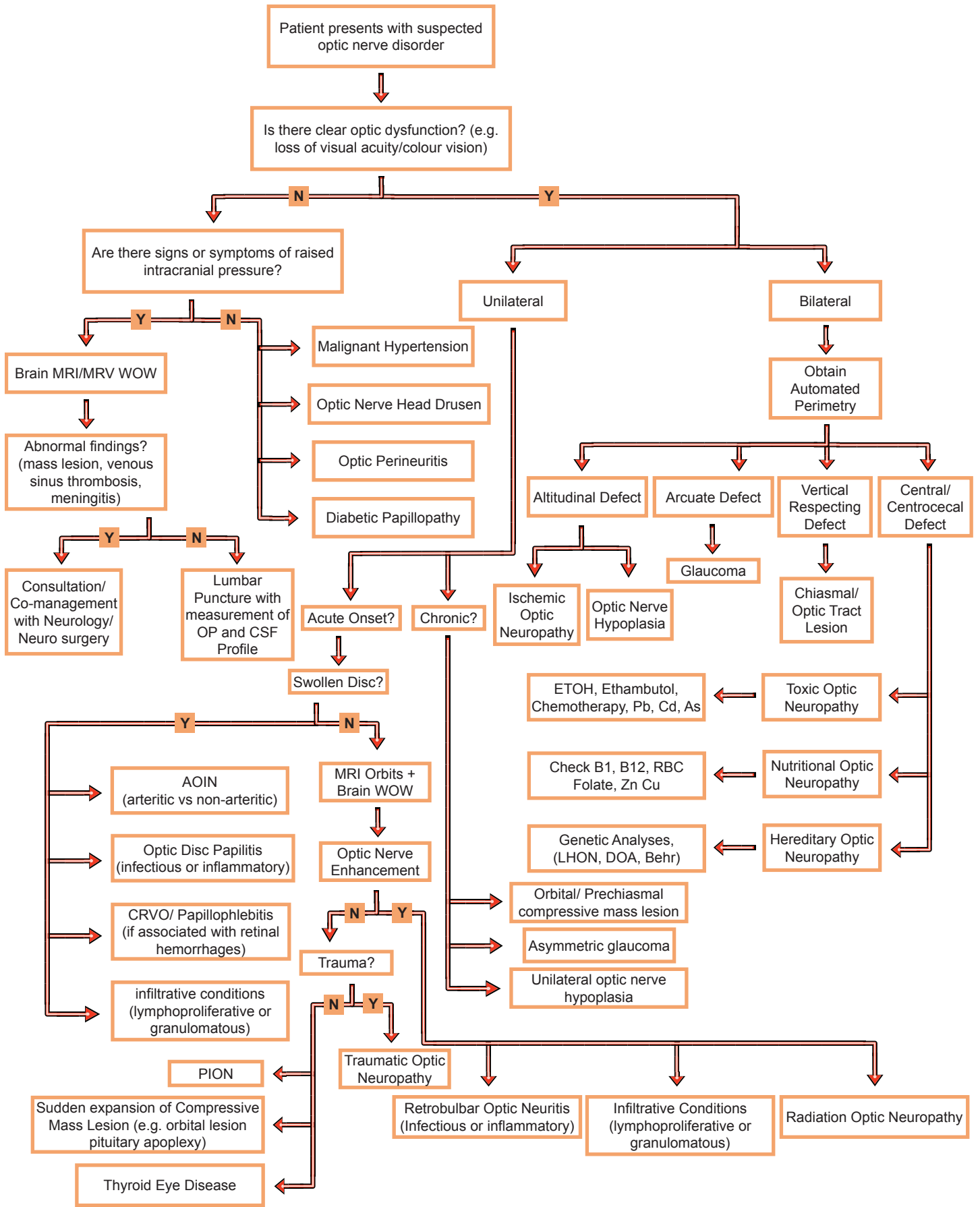


Figure 1. Flow diagram outlining a practical approach for the evaluation of a patient presenting with a potential optic neuropathy.

headaches, pulsatile tinnitus, or new onset abducens palsy. If present, obtain an MRI and magnetic resonance venography (MRV) of the brain with and without contrast (WOW) to look for mass lesions, hydrocephalus, meningitis, or cerebral venous sinus thrombosis<sup>3</sup>. If a structural abnormality is found, coordination and co-management with the relevant service is most appropriate. If neuroimaging does not reveal a structural lesion, obtain a lumbar puncture with opening pressure and cerebrospinal fluid (CSF) profile evaluations to further work up the possibility of idiopathic (IIH) or secondary forms of intracranial hypertension. Even inflammatory etiologies such as meningitis, encephalitis, or autoimmune conditions (e.g., lupus, sarcoidosis) can affect the arachnoid granulations' ability to absorb CSF, leading to elevated intracranial pressure (ICP)<sup>4</sup>. Hence, reviewing the CSF profile is essential before making a diagnosis of IIH. If elevated ICP is not suspected clinically, or a negative work-up as per above, diagnostic possibilities may include malignant hypertension, buried optic nerve head drusen (consider B-scan, fundus autofluorescence or OCT nerve), optic perineuritis where the optic nerve itself is spared but the nerve sheath demonstrates involvement (consider MRI orbits WOW), or diabetic papillopathy<sup>5,6</sup>.

***In patients presenting with unilateral loss of central acuity or dyschromatopsia, determine whether the condition developed acutely (within hours to days) or rather had a more indolent, chronic course (weeks to months).***

In acute cases, if the optic disc appears swollen, anterior ischemic optic neuropathy (AION)<sup>7</sup> and inflammatory optic neuritides<sup>8</sup> should be considered first. Patients >55 years of age should be asked about clinical features of giant cell arteritis (GCA), such as headache, scalp tenderness, jaw claudication, systemic malaise, unintentional loss of weight



**Figure 2.** A patient with leukemic infiltration of the right optic nerve. Note the diffuse elevation of the disc with nodular lesions (arrows) within the substance of the infiltrated optic nerve.

or appetite, and low grade fevers. Acute non-arteritic AION usually presents unilaterally with up to a 15% chance of contralateral eye involvement within 5 years.<sup>9</sup> Risk factors include a small cup-to-disc ratio, obstructive sleep apnea, erectile-dysfunction medication use, and vascular comorbidities. The use of amiodarone should be investigated since a similar form of optic neuropathy can occur in patients even after several months of using this medication<sup>10</sup>. Occasionally, infiltrative conditions like leukemia, lymphoma, or granulomatous disease can produce an acute papillitis (**Figure 2**). A thorough retinal examination may reveal posterior pole venous congestion (papillophlebitis) or wide-spread perivenous hemorrhages (CRVO) in addition to disc edema. Infectious papillitis due to syphilis or toxoplasmosis, among others, should be considered, as well as inflammatory etiologies like myelin oligodendrocyte glycoprotein associated disease (MOGAD), and demyelinating optic disc papillitis, which may be associated with painful eye movements. A recent study from 2020 reported that 86% of patients with MOGAD present with disc edema<sup>11</sup>, in contrast to the landmark Optic Neuritis Treatment Trial (ONTT) which revealed that approximately only one third of demyelinating optic neuritis presents with disc edema (usually non-hemorrhagic)<sup>12</sup>.

***In patients with an acute optic neuropathy without disc edema, obtain an MRI orbits and brain WOW to better evaluate the retrobulbar structures, paying close attention to whether the optic nerve enhances post-contrast.***

If no enhancement is seen, and there is a history of orbital or head trauma, consider traumatic optic neuropathy (TON). TON eventually (usually several weeks after the trauma) leads to pallor and cupping of the optic disc. Acutely, only decreased visual acuity, dyschromatopsia and varied patterns of visual field loss may be present. If a history of trauma is not present, posterior ischemic optic neuropathy (PION) may be a possibility. PION may be further classified as related to GCA, non-arteritic, or post-surgical (e.g., prolonged surgery, significant blood loss, decreased hematocrit, prone position, etc.). The history should point to a particular PION etiology<sup>13</sup>. A rapidly compressive orbital or parasellar lesion (e.g., thyroid eye disease, hemorrhage, vascular malformation which has bled, pituitary apoplexy, etc.) can produce features of an optic neuropathy without disc edema, given the deep retrobulbar location of optic nerve compression. The causative abnormalities will be evident on neuroimaging; MRI is best in this scenario given greater soft tissue detail and resolution than CT.

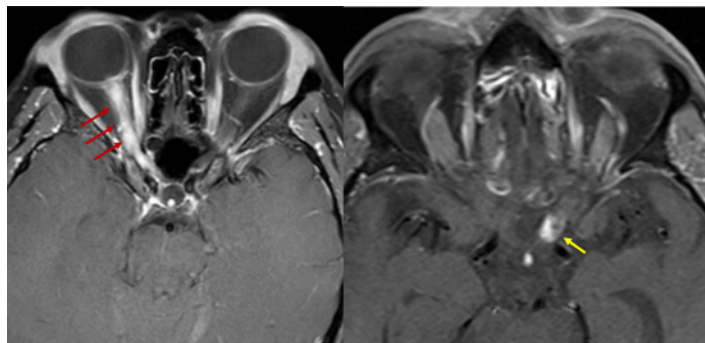
If the MRI reveals optic nerve enhancement, retrobulbar optic neuritis -- both inflammatory and infectious forms -- are the most common etiologies (e.g., MOGAD, MS, neuromyelitis optica spectrum disorder [NMOSD], tuberculosis, herpes simplex virus, syphilis, fungal disease, etc.). Radiation optic neuropathy typically demonstrates avid enhancement of the pre-chiasmal region of the optic nerve(s), 12 to 18 months after high



dose radiation treatment (>50 Gy) to the retrobulbar or parasellar regions (**Figure 3**).

Chronic unilateral optic neuropathies warrant consideration of a retrobulbar compressive mass lesion, asymmetric glaucoma, or unilateral optic nerve hypoplasia. Imaging (MRI orbits and brain WOW) is imperative in these cases.

Evaluation of a bilateral optic neuropathy should begin with a careful, thorough history, followed by automated perimetry. The pattern of visual field loss can be very informative and help narrow down the diagnostic possibilities. As mentioned above, approximately 15% of non-arteritic AION may become sequentially bilateral; hence, clinicians should consider this possibility if bilateral altitudinal defects are seen. Central/centrocecal defects are classically associated with toxic/nutritional/metabolic/hereditary optic neuropathies<sup>14</sup>. In such cases, there may be subtle optic disc swelling in the acute or subacute phases, with distinct ganglion cell loss present even in the acute phase, with the latter structural finding correlating better with the clinical picture of central vision and



**Figure 3.** On the left is a T1 post-gadolinium MRI axial image demonstrating avid, homogeneous enhancement of the entire left optic nerve in a patient with MOGAD. On the right is a post-gadolinium MRI axial image of a patient with radiation of optic neuropathy exhibiting focal enhancement (arrow) at the junction of the left optic nerve and chiasm, 18 months following high dose radiation to the parasellar region.



dyschromatopsia than the seemingly “normal” RNFL measurements. There may also be a sharp, distinct demarcation between the preferentially affected papillomacular bundle (higher metabolic demand hence more susceptible) and the adjacent arcuate bundles (**Figure 4**).

Glaucoma remains the most common bilateral optic neuropathy (e.g., nasal steps, arcuate, nerve-fiber bundle type visual field defects, etc.) with chronic, often subclinical field loss, and superior and inferior RNFL thinning on OCT; however, if the field loss respects the vertical meridian, a chiasmal or optic tract lesion must be considered. Inflammatory optic neuropathies such as MOGAD<sup>15</sup>, NMOSD<sup>16</sup>, infectious, autoimmune or paraneoplastic optic neuropathies, can also present bilaterally and may have a predilection for the chiasm. MRI brain and orbits WOW can be informative, looking for optic nerve enhancement in inflammatory and infectious forms of optic neuropathies, followed by the relevant serological and systemic evaluations such as bloodwork, chest and abdominal imaging, and CSF analysis.

The evaluation of a patient suspected of having an optic neuropathy requires attention to the major tenets of clinical medicine: thorough yet poignant history-taking, careful clinical examination, and thoughtful, directed use of ancillary investigations. While the optimal approach is far from algorithmic, maintaining a logical, sequential framework from which to evaluate the individual patient, can aid in improving diagnostic accuracy. When determination of a specific diagnosis is not possible, categorization of the condition such as ischemic, infiltrative, inflammatory, etc. can be very helpful in guiding management. Careful follow up is key, allowing the clinician to reassess as necessary.



**Figure 4.** Prominent thickening of the interface between the papillomacular and arcuate bundles bilaterally in a patient with chronic heavy alcohol consumption, leading to a bilateral toxic optic neuropathy.

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