Ophthalmological Mimickers of Papilledema

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Abstract

Bilateral optic nerve swelling must be investigated with neuroimaging, in the first instance, to exclude papilledema. Subsequent consideration of alternate diagnoses with intracranial normotension should be undertaken to prevent missing sight or life threatening pathology. Papilledema may be indistinguishable from other causes of disc swelling on ophthalmoscopy alone. Therefore, a detailed history, comprehensive assessment of other features on clinical examination, and laboratory testing are important for the successful identification of non-papilledema causes of bilateral optic disc swelling.

Keywords: Papilledema, Bilateral Optic Nerve Swelling, Optic Nerve, Neuro-Ophthalmology

Introduction

Bilateral optic disc edema is a finding that should raise a suspicion of intracranial hypertension although not all cases of bilateral optic disc edema are due to papilledema (the term specifically reserved for optic disc swelling due to raised intracranial pressure). It is crucial then, for a clinician to also consider diagnoses with intracranial normotension in order to avoid missing a sight or life threatening condition. However, papilledema may be indistinguishable from other causes of disc edema on ophthalmoscopy alone. Therefore, it is critical to consider aspects of the history and other features of the clinical examination to assist the clinician to identify non-papilledema causes of bilateral disc swelling. This article reviews commonly encountered causes of bilateral disc edema not associated with intracranial hypertension. We outline ways to clinically separate these diagnoses from that of papilledema. To underscore the importance of testing optic nerve function (by testing visual acuity, color vision, relative afferent pupillary defect, and field of vision) we have separated these diagnoses in to those that are not associated with prominent optic nerve dysfunction and those which are.
Assessment of Optic Nerve Function

Table 1. Summary of optic nerve assessment

<table>
<thead>
<tr>
<th>S. No</th>
<th>Test order</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Visual acuity (VA)</td>
<td>Best corrected visual acuity (BCVA)</td>
</tr>
<tr>
<td>2</td>
<td>Color vision</td>
<td>Ishihara pseudoisochromatic color plates, Farnsworth panel D-15 test, Farnsworth-Munsell 100 hue test</td>
</tr>
<tr>
<td>3</td>
<td>Relative afferent pupillary defect (RAPD)</td>
<td>Swinging flashlight test</td>
</tr>
<tr>
<td>4</td>
<td>Visual field testing</td>
<td>Confrontational visual field testing</td>
</tr>
</tbody>
</table>

The assessment of optic nerve function involves four critical tests: visual acuity, color vision testing, pupil assessment for a relative afferent pupillary defect, and visual field examination.

1. **Visual acuity (VA)** is measured using a Snellen chart. Improvement with pinhole viewing indicates refractive error. Best corrected visual acuity (BCVA) should be obtained with refraction. Eccentric fixation should be noted.

2. **Color vision** should be tested prior to pupillary testing so that bleaching of the retina with bright lights does not interfere with the results. Each eye is tested separately to detect unilateral disease. Ishihara pseudoisochromatic color plate testing is widely available. Originally designed to identify congenital red-green color deficiencies it may identify acquired dyschromatopsia, however, it may miss mild cases. More detailed color testing can be undertaken with the Farnsworth panel D-15 test and the Farnsworth-Munsell 100-hue test that require a patient to arrange 15 and 85 colored discs in order of hue and intensity respectively. Optic nerve disease, in particular demyelinating optic neuritis, may disproportionately affect color vision in comparison to BCVA. In contrast, macular disease will commonly affect VA and color vision equally.

3. **Relative afferent pupillary defect**: A relative afferent pupillary defect (RAPD) is a highly reliable and sensitive indicator of optic nerve dysfunction with the RAPD magnitude correlating to the degree of damage to retinal ganglion cells and their axons. A swinging flashlight test is commonly employed to assess for an RAPD and is performed as follows:

   - Dim lighting is used with the patient asked to look at a distant target (to avoid pupillary constriction secondary to accommodation).

   - Use a bright light and stimulate one eye for 2-3 seconds before quickly moving across the bridge of the nose to stimulate the contralateral eye for 2-3 seconds repeating several times.

   - A dense RAPD will dilate upon stimulation, however, a mild to moderate RAPD is more difficult to detect because the initial movement may still be constriction, albeit less vigorously.

   - The RAPD is graded from 1 - 4+ in increasing severity.

   - When it is difficult to assess an RAPD, such as with dark irides, dilated, miotic, or sluggish pupils, subjective brightness and color intensity can identify and qualitatively grade an RAPD. Brightness testing requires a light source such as an indirect ophthalmoscope with red perception testing requiring a red target such as the top of a cycloplegic bottle. The patient is shown the light or red target individually in each eye at a distance of 30cm. If the eyes are different then the patient is asked to quantify brightness or red color in each eye.

4. **Visual Field Testing**: Evaluation of the visual fields may aid in localising a lesion of the visual pathway with confrontational testing able to be performed easily at the bedside or in clinic. Several confrontation techniques are available. However, the method with the greatest combined sensitivity and specificity is using a kinetic red target. A 5mm red topped pin is moved inward from the far periphery of a patients vision, in a line bisecting the vertical and horizontal meridians. The patient is asked to
report when the red top first appears red \[1\]. It is important to note that confrontation visual fields have limited usefulness to identify mild (and even moderate) visual field defects and patients should undergo formal automated perimetry if there is an index of suspicion of an optic neuropathy.

**Differentiating Optic Nerve Swelling from Pseudo-Swelling**

The clinician’s first step in managing suspected papilledema is to rule out pseudopapilledema. Acute and chronic papilledema (Fig. 1) have unique ophthalmoscopic findings. Acute papilledema produces a hyperemic optic disc with dilation of the surface capillary net. The swollen part of the disc shows a grayish white appearance with obscuration of the disc edge and vessels that course through it (Fig. 1). With papilledema there is absence of spontaneous venous pulsations. However, 20% of the general population does not have spontaneous venous pulsations. In early papilledema optic nerve function is preserved. In the late stages of papilledema the disc may appear pale and swollen (Fig. 1). This is an ominous feature of impending demise in visual function.

Features that help differentiate true disc swelling from pseudo-disc swelling are disc hyperemia, peripapillary cotton-wool spots, exudates, hemorrhage, and opacification of the retinal nerve fibre layer. Most cases of pseudopapilledema result from optic disc drusen. Other causes of an elevated disc appearance mimicking papilledema include small congenitally anomalous optic nerves often seen in hyperopes, hyaloid remnants, and glial tissue on the disc surface. Obscuration of disc margins can occur without disc elevation from myelination of the nerve fibres. Myelination appears as a dense, white opacity compared with the partially translucent, grayish white appearance of true edema.

![Fig. 1. Optic disc photos of early papilledema (a,b) and late papilledema (c,d) in patients with idiopathic intracranial hypertension. Note that late papilledema is associated with more pallor in the disc and fewer hemorrhages. The pallor is because many of the retinal nerve fibres have died.](image)

Table 2. Causes of optic nerve swelling associated and not associated with optic nerve dysfunction

<table>
<thead>
<tr>
<th>Associated With Optic Nerve Dysfunction</th>
<th>Not Associated With Prominent Optic Nerve Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory (giant cell arteritis, non-arteritic anterior ischemic optic neuropathy, central retinal vein occlusion, Behçet’s disease, and sarcoidosis)</td>
<td>Optic nerve head drusen</td>
</tr>
<tr>
<td>Infective (syphilis, ocular toxoplasmosis, and cat scratch disease)</td>
<td>Tilted optic discs</td>
</tr>
<tr>
<td>Other multifocal inflammatory conditions associated with optic nerve edema – see Table 3</td>
<td>Ocular hypotony</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>Vogt-Koyanagi-Harada disease</td>
</tr>
<tr>
<td>Leber’s hereditary optic neuropathy</td>
<td>Posterior scleritis</td>
</tr>
<tr>
<td>Amiodarone optic neuropathy</td>
<td>Hypertensive retinopathy</td>
</tr>
<tr>
<td>Infiltrative</td>
<td></td>
</tr>
</tbody>
</table>

Causes not associated with prominent Optic Nerve Dysfunction

Optic Nerve Head Drusen

Optic nerve head drusen (ONHD) are calcific deposits found in the anterior portion of the optic nerve. They are present in approximately 0.3-2% of individuals and are bilateral in 65-90% [2]. Buried ONHD represent a diagnostic challenge as their clinical appearance can easily be mistaken for optic nerve swelling and papilledema. Patients are predominantly asymptomatic and have preserved visual acuity (VA) with mild visual field defects. These visual defects tend to progress slowly during adulthood with an average interval of change of approximately nine years [3]. There are no effective treatments available for ONHD [2]. A variety of diagnostic techniques have been evaluated for the identification of optic nerve head drusen from true swelling of the optic nerve. B-scan echography is an ocular specific ultrasound in which drusen appear as highly reflective rounded shadows at the optic nerve head (Fig. 2) [4].

ONHD are autofluorescent and hence fundus photography with fluorescent filters can reveal buried ONHD not obvious on fundoscopy (Fig. 2) [2]. CT scans in patients with suspected papilledema may also identify ONHD, however, this is greatly dependent on the thickness of the scanning slices and the orientation of the nerve head [2]. Optical Coherence Tomography (OCT) is a reliable and sensitive measure of retinal nerve fibre layer (RNFL) thickness in optic neuropathies. However, its usefulness in the differentiation of ONHD is controversial.

Tilted Optic Discs

A tilted optic disc refers to the fundoscopic appearance of an oblique entrance to the optic nerve. Angulation of the optic nerve head gives an elevated appearance to one side of the disc and hence in bilateral cases can be mistaken for bilateral disc edema [5]. A clue to the diagnosis of tilted optic discs can be the presence of myopia. Multiple studies have reported a positive relationship between increasing myopia (and hence increased axial length) and the presence of tilted discs [6]. The diagnosis of a tilted optic disc is made clinically.

Fig. 2. Optic disc photo (a) and optic disc autofluorescence (b) of a patient’s right optic disc drusen.

Ocular Hypotony

Low intraocular pressure (IOP) can induce disc swelling by decreasing the pressure gradient across the optic nerve head (translaminar pressure). Ocular hypotony does not occur until IOP is lower than 5mmHg, but has been documented with IOPs as high as 9mmHg [7]. Ocular hypotony most commonly occurs following intraocular surgery (such as glaucoma surgery or cataract surgery) or trauma. A detailed history should be acquired to explore these causes of optic nerve swelling. Adjuncts such as OCT of the macula (to detect macula edema, which is often present in ocular hypotony) and fluorescein angiography (to detect chorioretinal folds) may be useful in equivocal cases [7]. If IOP is normalized, changes in the ocular structures (including disc swelling) should also normalize, however, visual recovery often depends on the duration of hypotony [7].
Vogt-Koyanagi-Harada Disease

Vogt-Koyanagi-Harada Disease (VKH) is an autoimmune, bilateral uveitis that is associated with skin, auditory, and neurological changes. Its etiology is a T-lymphocyte mediated immune process against an antigen in melanocytes [8]. Hence the disease has a predilection for pigmented peoples such as those of Asian, Indian, Middle Eastern, Native American, Hispanic, Maori, or Pacific Island descent [9]. It is uncommon in patients of Caucasian or sub-Saharan African descent [9]. Age of onset is typically between 20 and 50 years and females are more commonly affected in a ratio of 2:1 [10]. VKH can be separated into distinct clinical phases. Initially a prodromal phase may mimic a viral illness with symptoms of headache, photophobia, and tinnitus lasting days. This is followed by a uveitic phase in which 70% of patients describe a visual blur [11]. On ophthalmological exam optic nerve edema is common (occurring in around 43%) [12] and together with the preceding systemic symptoms can easily be mistaken for intracranial hypertension. Further fundus examination also reveals a bilateral posterior granulomatous uveitis [13]. Choroiditis with multifocal areas of subretinal fluid are readily visible on OCT and fluorescein angiography [13]. If not sufficiently treated by this stage the disease can progress to a convalescent phase characterized by depigmentation of the skin (vitiligo), eyebrows, and eyelashes (poliosis) over months to years. While optic nerve function tends to be spared early in the disease process, deficiencies in color vision, field of vision, and VA have been reported in VKH. It is likely that these are a result of both retinal and optic nerve disease [14].

Posterior Scleritis

Posterior scleritis refers to inflammation of the sclera posterior to the insertion of the rectus muscles. Approximately 13-18% of patients have associated disc edema and in bilateral cases this may be difficult to distinguish from papilledema [15]. Typically patients are in their fourth decade and there is preponderance for females over males. Posterior scleritis can be associated with systemic inflammatory conditions such as rheumatoid arthritis, ANCA associated vasculitis, and systemic lupus erythematosus (SLE). Up to 40% of posterior scleritis cases are associated with a systemic disease [16].

Prominent features of the clinical presentation are periorcular pain, blurred vision, and headaches [16]. Only a minority of patients have visible anterior segment inflammation (25.8-36.4%) and hence the history, intraocular examination, and examination adjuncts are crucial [15]. B-scan echography is a key adjunct, showing thickening of the sclera and fluid in the subtenons space, which, when around the optic nerve, is often referred to as the ‘T-sign’ [15].
Hypertensive Retinopathy

Signs of hypertensive retinopathy are relatively common and correlated with systemic hypertension [17]. Signs may include intraretinal exudates, hemorrhages, cotton wool spots, retinal edema, macula star formation, and retinal arterial and venous narrowing and obstruction [18]. Choroidal manifestations include vascular hypoperfusion resulting in subsequent focal and diffuse retinal pigment epithelium (RPE) atrophy and serous retinal detachment [18]. Optic nerve findings are those of optic disc edema and hemorrhages [18]. Optic disc edema secondary to systemic hypertension may resolve following medical treatment. However, it can progress into optic atrophy with variable levels of visual compromise [19].

In patients with severe systemic hypertension and bilateral optic disc edema treatment is with systemic blood pressure lowering medications with a good visual outcome achieved commonly following resolution of disc edema [19].

Fig. 6. A patient with hypertensive retinopathy with optic disc edema, cotton wool spots, and a flame-shaped hemorrhage.

Causes associated with Optic Nerve Dysfunction

Giant Cell Arteritis

Giant cell arteritis (GCA), also known as temporal arteritis, is a life and sight threatening vascular inflammatory condition. Arteritic anterior ischemic optic neuropathy is the most common cause of visual loss and presents with pallid disc edema in a majority of patients [20]. Bilateral ocular involvement is not uncommon and this often presents as sequential vascular events, but can be simultaneous [20]. Unilateral arteritic anterior ischemic optic neuropathy may rapidly progress to bilateral involvement and therefore the diagnosis needs to be considered and managed expeditiously.

GCA occurs in patients over the age of 50 with an increasing incidence with age. Typical symptoms include a new onset headache, scalp tenderness, fevers, and weight loss. Jaw claudication, often described as a cramping pain increasing with continued mastication or speech, is highly specific for GCA [21].

Vision loss in GCA is often profound with between 60-80% having a VA worse than 20/200 [21]. Color vision and visual fields are severely compromised in eyes with visual loss [23]. In patients with arteritic anterior ischemic optic neuropathy a ‘chalky white or pallid’ edema of the optic disc is often described and is not typically associated with disc haemorrhages [21]. Other fundoscopic findings can include attenuated retinal vessels, whitening of the retina, and a cherry red spot at the macula due to a central retinal artery occlusion (CRAO) or cilioretinal artery occlusion.

Blood inflammatory markers such as an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are useful for ruling out GCA, and when they are used together have a reported sensitivity of 99% [24]. Temporal artery biopsy (TAB) is the gold standard for diagnosis of GCA [21]. Arranging a TAB should not delay treatment in cases with a high clinical suspicion of GCA. Studies have shown no difference in biopsy positivity rates within two weeks of starting steroid therapy [25].

Classification criteria for GCA developed by the American College of Rheumatology (ACR) in 1990 were derived from differences between GCA and other vasculitides [26]. A prospective study by Murchison et al [27] has shown that these have a limited clinical utility when it comes to diagnosing GCA in a broader clinical setting. They found that approximately a quarter of patients with biopsy proven GCA did not make the ACR criteria, and a quarter of those with negative biopsies would have been diagnosed with GCA [27].
Systemic corticosteroids are the treatment of choice to prevent ongoing ischemic complications and should be initiated if the patient is suspected of having GCA [21]. Despite treatment with steroids visual prognosis is often poor in the affected eye. The purpose of treatment is to prevent further visual deterioration rather than rescuing vision loss.

Non-Arteritic Ischemic Optic Neuropathy

Non-arteritic ischemic optic neuropathy (NAION) is the most common cause of an acute optic neuropathy in patients over the age of 50. The exact pathogenesis of this has not been fully elucidated, however, nocturnal hypotension, impaired autoregulation, vasculopathic occlusion, and venous insufficiency are all proposed mechanisms [22]. The most recognized risk factors for NAION occurring are diabetes mellitus and hypertension. Median age at presentation is around 60 years but unlike GCA patients can present as young as 40 [21, 28]. Visual acuity at presentation is variable, however, up to 50% of patients may have a normal VA (better than 20/30) [28]. A majority of patients have a moderate to severe visual field defect and color vision is likely to be impaired [28, 29]. Approximately 75% of eyes affected by NAION will have either diffuse or focal disc swelling, and unlike GCA, are often associated with disc hemorrhage (72%). Typically NAION is unilateral and very rarely can be sequential. Bilateral simultaneous NAION is uncommon apart from in instances related to systemic hypotension during surgery or medications such as phosphodiesterase inhibitors and interferon alpha [22, 30].

A small optic disc size and a small or absent physiological cup are suggestive of NAION as this crowded appearance to the optic disc is a known risk factor [31]. There is currently no effective treatment for NAION.

Central Retinal Vein Occlusion

Retinal vascular occlusions such as a central retinal vein occlusion (CRVO) often present with concomitant disc edema. Most often these vascular events are unilateral, however, systemic hypercoagulable states can present with bilateral simultaneous disc edema [32, 33]. Patients with bilateral CRVOs should be investigated for systemic causes such as SLE, antiphospholipid antibody syndrome, Waldenstrom macroglobulinemia, multiple myeloma, and hyperhomocystinemia [34].

In CRVO retinal changes such as widespread hemorrhages, dilated vessels, macular edema, and occasional cotton wool spots are obvious on dilated retinal examination [35].

In CRVO optic nerve function is markedly different based on whether the event is classified as ischemic or non-ischemic and this distinction can be made on ophthalmological exam often with the aid of fluorescein angiography. In ischemic CRVO, VA at presentation is
often poor, 99% are worse than 20/200 compared to only 22% of non-ischemic eyes.

Fig. 9. Optic disc edema in a patient with CRVO. Hemorrhages are seen in all four quadrants.

**Inflammatory and Infective optic Neuropathies**

Several systemic inflammatory or infective diseases can present with bilateral optic nerve head swelling which mimics papilledema. In order to diagnose these conditions there must be a certain level of suspicion which can be determined on the basis of an adequate history and appropriate investigations.

**Behçet's Disease**

Behçet's disease (BD) is a multi-system inflammatory condition with ocular involvement in 60-70% of patients [36]. Ocular inflammation is often in the form of posterior or panuveitis and is often bilateral [37, 38]. The incidence of optic nerve head swelling is reported to be as high as 67.3% [38]. The most common age at presentation is between 30 and 40 years and there is a slight male preponderance [37, 38]. Systemic features are most commonly aphthous ulcers, genital ulcers, and skin manifestations (such as erythema nodosum). However, arthritis, occlusive vascular disorders, and neurological involvement are also documented [39]. There is an increased prevalence of BD in populations located on the ancient silk road in the Middle East, Mediterranean, and East Asia [40].

Genetic testing suggests that BD has an association with the gene locus HLA-B51.

Although the classic description is of a white eye with a mobile hypopyon (leukocytic exudate visible in the anterior chamber), ocular inflammation in BD is more likely to present with inflammation visible only on examination of the posterior pole [37, 38]. In two large series of patients with BD, vitritis, retinal vasculitis, and retinitis were all more common findings than hypopyon [37, 38]. Optic neuropathy in BD can be related to neurological BD, intraocular inflammation, or can occur in isolation. A recent review of 20 cases of BD related optic neuropathy found 4 cases (20%) who had bilateral synchronous disc swelling and these cases can be potentially mistaken for papilledema [41, 42].

VA was worse than 20/200 in 7 of 17 (41%) patients, however, a majority (67%) of all cases reported a return to normal VA after treatment. Central scotomas on visual field testing were a common finding [41]. Rapid treatment with systemic corticosteroids or biologic agents to induce remission of inflammation is necessary to minimise the chance of vision loss [43].

**Sarcoidosis**

Sarcoidosis is a multisystem granulomatous disorder with ocular involvement in around 22% of cases [44]. There are two mechanisms of disc swelling in sarcoidosis not involving intracranial hypertension: granulomatous infiltration of the nerve and inflammation at the optic nerve [45]. Patients tend to present with signs of compromised optic nerve function. Complete ocular examination can reveal either active inflammation or evidence of previous uveitis in 42% of cases [46]. Inflammation can be in the form of an anterior, intermediate, posterior, or panuveitis.

Diagnostic workup for a suspected sarcoidosis should include a chest X-ray for hilar lymphadenopathy and serum ACE level. It should be noted that the incidence of an elevated serum ACE in neuro-ophthalmic sarcoidosis is variable (reported between 33-73%) and in sarcoidosis related uveitis it is highly specific for sarcoidosis (95%) but not as sensitive (reported between 58-84%) [46, 47].

A tissue diagnosis is ideal but often not feasible in neuro-ophthalmic sarcoidosis. Instead, neuroimaging showing leptomeningeal or optic nerve enhancement, and lumbar
puncture demonstrating lymphocytic pleiocytosis or raised protein may be indicative of neurosarcoidosis [46, 48]. Corticosteroids are the mainstay of treatment for all forms of sarcoidosis and steroid sparing therapies are often initiated for long term management [48].

![Fig. 10. Optic disc edema in a patient with sarcoidosis.](image)

**Syphilis**

Syphilis is a sexually transmitted infection caused by the spirochete Treponema Pallidum. In the past decade there has been a resurgence in the incidence of syphilis and other sexually transmitted infections worldwide [49]. Systemic symptoms of syphilis depend on disease stage. Optic nerve involvement can occur in secondary syphilis when it is associated with uveitis. Bilateral optic perineuritis (swelling of the optic nerve sheath but preserved optic nerve function) mimicking papilledema has been described as a presenting feature of syphilis in several case reports [50, 51].

Neurosyphilis can present with bilateral optic nerve swelling and progressive loss of visual function [52]. All cases of ocular syphilis should raise suspicion for neurosyphilis, which is confirmed by CSF analysis including CSF VDRL (venereal disease research laboratory test for syphilis) and clinical examination [53].

Treatment is with a course of intramuscular or intravenous Penicillin G for between 2-3 weeks dependent on the stage of syphilis encountered [53]. All patients with positive syphilis serology should also have HIV testing as co-infection is common and seems to have a synergistic effect; increasing the rate of progression to neurosyphilis, worsening disease severity, and worsening response to treatment [54].

![Fig. 11. Optic disc edema in a patient with syphilis (this has no distinctive features).](image)

**Ocular Toxoplasmosis**

Ocular toxoplasmosis is the most common cause of posterior uveitis worldwide [55]. It is due to infection by the protozoan Toxoplasma Gondii. Studies have shown that this pathogen is present in 25-30% of the population, however, it is largely asymptomatic [55]. Age, immune status, and genetic factors contribute to the risk of developing ocular toxoplasmosis which commonly manifests as a necrotising chorioretinitis [55]. Cases presenting with bilateral disc swelling mimicking papilledema are uncommon but have been reported [56]. Approximately 5-13% of patients with ocular toxoplasmosis develop disc swelling [56, 57]. Other findings on an ophthalmological exam can include vitritis and neuroretinitis (disc swelling associated with macular swelling and exudate) [55]. The diagnosis of ocular toxoplasmosis is often made clinically and confirmed with serological testing. Positive serology for IgM or IgA antibodies against Toxoplasma Gondii indicates an acute infection. Positive IgG antibodies indicate a previous exposure, however, high IgG levels are also associated with active lesions or recurrences [55].

Although treatment is not necessary in all cases of ocular toxoplasmosis, those involving the optic disc do require treatment. This usually comprises of a systemic corticosteroid paired with an antiprotozoal such as pyrimethamine with sulfadiazine, co-trimoxazole.
(sulfamethoxazole with trimethoprim), or clindamycin alone [55]. With treatment, between 70-85% of patients will show an improvement in VA [56].

![Fig. 12. Optic disc involvement in a patient with ocular toxoplasmosis.](image)

**Cat Scratch Disease**

Cat scratch disease (CSD) is a systemic illness caused by the bacteria Bartonella henselae. Inoculation occurs as a result of a bite or scratch from an infected cat leading to fevers and lymphadenopathy [58]. CSD is the most common cause of neuroretinitis (optic disc edema associated with a macular star), however, isolated optic disc edema can also occur [59]. When the optic nerve head is involved, CSD is bilateral in 17% of patients and cases misdiagnosed with intracranial hypertension are reported [60].

In patients with CSD optic disc edema, initial VA is often poor. Serological testing for IgM and IgG antibodies against Bartonella has a 90-100% specificity and a 50-80% sensitivity [60]. As IgM titres drop after an acute infection there may be a delay in the rise of IgG antibodies and thus a false negative result. To prevent this, a convalescent titre is recommended two weeks after the initial reading in patients where there is a high level of suspicion [61].

CSD tends to follow a benign and self-limiting course. At final follow up 68% of the patients had a VA of 20/40 or better, and only 5.7% had VA worse than 20/200 [59].

There are no definitive treatment recommendations for management of CSD in an immunocompetent individual [59]. There have been no prospective trials for the treatment of ocular CSD, however, there is some retrospective evidence for benefit with antibiotic therapy such as Doxycycline [60, 62].

![Fig. 13. Disc edema with neuroretinitis in cat scratch disease.](image)

**Other Multifocal Inflammatory conditions associated with Optic Nerve Edema**

There are a heterogeneous group of inflammatory eye conditions that can present with multifocal yellow-white lesions at various levels of the retina and choroid and may be associated with optic nerve edema. These conditions include multiple evanescent white dot syndrome (MEWDS) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE). These typically affect young healthy adults and are characterized by rapid onset of blur, visual field defects, and photopsia. Blind spot enlargement is common and abnormalities at the level of outer retina and choriocapillaris may be seen on OCT.

Birdshot chorioretinopathy and multifocal choroiditis and panuveitis (MCP) also cause multifocal chorioretinal lesions and can also lead to mild optic nerve swelling and disc leak seen angiographically. They tend to present in middle age and older adults and have a more indolent presentation with floaters, blur, and photopsias. These conditions are progressive and require immunosuppressive therapy.
### Table 3. Other multifocal inflammatory conditions associated with optic nerve edema

<table>
<thead>
<tr>
<th></th>
<th>MEWDS</th>
<th>APMPPE</th>
<th>MCP</th>
<th>Birdshot retinochroidopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Female &gt; Male [63]</td>
<td>Female = Male [64]</td>
<td>Female &gt; Male [64]</td>
<td>Female &gt; Male [64]</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Young adults (20-45) [63]</td>
<td>Young adults (20-30) [64]</td>
<td>20 to 60 years old [64]</td>
<td>40 to 60 years old [64]</td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td>Most often unilateral [63]</td>
<td>Bilateral (second eye often affected several days to weeks after first) [63, 64]</td>
<td>Most commonly bilateral but can present asymmetrically with delay of development of disease in the contralateral eye [63]</td>
<td>Bilateral [63, 64]</td>
</tr>
<tr>
<td><strong>Viral prodrome</strong></td>
<td>30-50% of cases [63, 64]</td>
<td>30% of cases [63, 66] May include meningeal symptoms [64]</td>
<td>Variable</td>
<td>None</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Acute</td>
<td>Acute</td>
<td>Insidious</td>
<td>Insidious</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Weeks to months</td>
<td>Weeks to months</td>
<td>Chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>Rare</td>
<td>Rare</td>
<td>Recurrent</td>
<td>Recurrent</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Visual blurring, paracentral and temporal scotomas, dyschromatopsia, and photopsia [63, 64, 65]</td>
<td>Antecedent viral illness that may include meningeal symptoms [64], bilateral asymmetric visual loss with central and paracentral scotomas, and photopsia [63, 64]</td>
<td>Photopsia, reduced visual acuity, and an enlarged blind spot [64]</td>
<td>Poor vision out of proportion to their measured visual acuity along with nyctalopia, paracentral scotomas, floaters, photopsia, and reduced color vision [67]</td>
</tr>
<tr>
<td><strong>Findings</strong></td>
<td>RAPD may be present, multiple discrete white dots at level of RPE or outer retina, pathognomonic granular appearance of the fovea [65]</td>
<td>Multifocal yellow-white placoid lesions at level of outer retina, RPE and choriocapillaris less than 1 disc diameter in size. Improve within 1-2 weeks [64]</td>
<td>Active yellow-white outer retinal and choroidal lesions at the macula replaced by punched out scars. CME may be present with CNV [64]</td>
<td>Bilateral symmetrical distribution of multiple choroidal lesions of a cream color with indistinct borders, less than one disc diameter in size, often appearing to radiate out from the optic nerve and sparing the macula [68]. Lesions tend to be more prominent in nasal retina and there may be arterial narrowing [63]</td>
</tr>
<tr>
<td></td>
<td>Variable [63]</td>
<td>Usually quiet [64]</td>
<td>50% [64]</td>
<td>Absent or minimal</td>
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<td>----------</td>
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<tr>
<td>Anterior chamber cells</td>
<td>Mild [63]</td>
<td>Mild [64]</td>
<td>Moderate [64]</td>
<td>Moderate (present in all cases to some degree) [69]</td>
</tr>
<tr>
<td>Vitreous cells</td>
<td>May be hyperemic and edematous [63, 64]</td>
<td>May have disc swelling [63, 64]</td>
<td>May have disc swelling [63, 64]</td>
<td>May have disc swelling [63, 64]</td>
</tr>
<tr>
<td>Optic nerve appearance</td>
<td>Early hyperfluorescence with punctuate lesions with “wreath-like” configuration on late staining [63, 64]</td>
<td>Characteristically demonstrates early hypofluorescence and late hyperfluorescence [64]</td>
<td>Acute phase of disease: early block and late staining. Later stages of disease: window defects [63, 64]</td>
<td>Can be normal. May have CME or vascular leakage [63, 64]</td>
</tr>
<tr>
<td>Fluorescein</td>
<td>RPE depigmentation and possible CNS vasculitis [63, 64]</td>
<td>CNV and punched out scars</td>
<td>CME or rarely CNV [63, 64]</td>
<td></td>
</tr>
<tr>
<td>Sequelae</td>
<td>Observation [64]</td>
<td>Ocular: observation [63, 64] CNS: consider corticosteroids [63, 64]</td>
<td>Treatment of early stages is with corticosteroids with late disease requiring the use of immunosuppressive agents with laser photocoagulation, photodynamic therapy, and anti-VEGF treatment useful for CNV [63, 64]</td>
<td>Corticosteroids, methotrexate, mycophenolate, cyclosporine [64]</td>
</tr>
<tr>
<td>Treatment</td>
<td>Good. Most cases resolve spontaneously with vision returning to baseline [65]</td>
<td>Good. Without treatment majority of cases achieve VA of 20/40 or better [63, 64]</td>
<td>Often poor</td>
<td>Guarded</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Viral [64]</td>
<td>Viral [64]</td>
<td>Unknown, ? viral [63]</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Etiology</td>
<td>HLA-B7, HLA-DR2</td>
<td>None</td>
<td>None</td>
<td>90% positive for HLA-A29 [67]</td>
</tr>
<tr>
<td>HLA association</td>
<td>None</td>
<td></td>
<td></td>
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Neuromyelitis Optica (NMO)

Neuromyelitis optica is an idiopathic, relapsing, demyelinating disease, which preferentially affects the optic nerve and spinal cord and typically spares the brain. The optic neuritis can be simultaneously bilateral. The most recent international consensus for the diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) are as follows: [70]

Diagnostic criteria for NMOSD with aquaporin-4 IgG (AQP4-IgG):
- At least one core clinical characteristic
- Positive test for AQP4-IgG using best available detection method (cell based assay strongly recommended)
- Exclusion of alternative diagnoses

Diagnostic criteria for NMOSD with negative or unknown AQP4-IgG status
1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis, or area postrema syndrome
   b. Dissemination in space (two or more different core clinical characteristics)
   c. Fulfilment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

Table 4. Diagnostic criteria for NMO: core clinical characteristics

<table>
<thead>
<tr>
<th>Core clinical characteristics [70]</th>
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<tbody>
<tr>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Acute myelitis</td>
</tr>
<tr>
<td>Area postrema syndrome: episode of unexplained nausea and vomiting or hiccups</td>
</tr>
<tr>
<td>Acute brainstem syndrome</td>
</tr>
<tr>
<td>Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions</td>
</tr>
<tr>
<td>Symptomatic cerebral syndrome with NMOSD-typical brain lesions</td>
</tr>
</tbody>
</table>

Table 5. Diagnostic criteria for NMO: additional MRI requirements for NMOSD with negative or unknown AQP4-IgG status

<table>
<thead>
<tr>
<th>Additional MRI requirements for NMOSD with negative or unknown AQP4-IgG status [70]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute optic neuritis requires brain MRI showing:</td>
</tr>
<tr>
<td>a. normal findings or only non-specific white matter lesions OR</td>
</tr>
<tr>
<td>b. optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over &gt;1/2 optic nerve length or involving optic chiasm</td>
</tr>
<tr>
<td>2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (longitudinally extensive transverse myelitis) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis</td>
</tr>
<tr>
<td>3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions</td>
</tr>
<tr>
<td>4. Acute brainstem syndrome: requires associated periependymal brainstem lesions</td>
</tr>
</tbody>
</table>
Technological advances in the testing of AQP4-IgG assays have allowed for improved sensitivity without compromising specificity [70]. The current recommendation is for cell-based serum assays (microscopy or flow cytometry-based detection) so as to optimise autoantibody detection. This is reported as a mean sensitivity of 76.7% in a pooled analysis with 0.1% false positive rate in a multiple sclerosis cohort [70].

Indirect immunofluorescence assays and ELISAs are noted to have a lower sensitivity of 63-64%. False-positive results reported as 0.5-1.3% for ELISA [70].

Initial treatment for acute attacks of optic neuritis or myelitis is commonly with intravenous corticosteroid therapy. Patients who do not respond promptly or were refractory to corticosteroid treatment may benefit from plasmapheresis [71, 72].

Systemic immunosuppression is used for prevention of recurrent attacks. There is some limited data to suggest that treatment initially with intravenous glucocorticoids and therapeutic plasma exchange is associated with improved outcomes in comparison to intravenous glucocorticoid treatment alone [73]. Seronegative and seropositive NMO are treated identically with the mainstay of treatment consisting of systemic immunosuppressive agents.

**Leber’s Hereditary Optic Neuropathy (LHON)**

LHON is a maternally inherited disease of acute or subacute visual loss with variable penetrance that predominantly affects young men. Approximately 95% of LHON cases are caused by one of three primary mitochondrial DNA mutations (G3460A/ND1, G11778A/ND4 or T14484C/ND6) affecting respiratory complex I [74] resulting in reduced efficiency of adenosine triphosphate (ATP) synthesis [75]. Penetrance is much higher in males compared to females with penetrance also varying significantly within the same pedigree. Factors affecting penetrance include heteroplasmy, environmental factors, and nuclear modifying genes [75].

Presentation is with subacute, painless loss of vision in one eye followed weeks to months later with a similar loss of vision in the contralateral eye. Visual acuity is usually less than 20/400 with a dense central or cecocentral scotoma. Telangiectatic capillaries and optic disc pseudoedema with swelling of the surrounding RNFL is seen on fundus examination. As time progresses there is loss of the papillomacular bundle with corresponding atrophy of the temporal optic disc with eventual progression to diffuse atrophy [76].

LHON currently has no proven treatment. Idebenone is a second generation short-chain benzoquinone related to Coenzyme Q10 and EPI-743, a para-benzoquinone reported to have a higher level of antioxidant activity than Idebenone, have had some variable success [77, 78].

![Fig. 14. Optic disc edema in a patient with Leber’s hereditary optic neuropathy.](image)

**Infiltrative**

Infiltrative tumours rarely mimic papilledema as they are uncommonly bilateral. Optic nerve gliomas (ONG) and optic nerve sheath meningiomas (ONSM) are benign tumours that can lead to blindness due to compression of the anterior visual pathway. Bilateral occurrences are often related to genetic conditions such as neurofibromatosis 1 (associated with ONG) and neurofibromatosis 2 (associated with ONSM) [79, 80, 81].

Patients often present in childhood with optic atrophy and possibly optic nerve swelling. Visual field defects are common and proptosis may be present [79]. Neuroimaging often reveals diffuse enlargement of the optic nerves, however, kinking of the optic nerve is a unique feature to ONG and not ONSM. Both tumours are slow growing and often management is conservative [79]. Infiltrative malignancies represent a rare but life threatening cause of bilateral optic nerve head swelling.
Lymphoma and leukaemia are the two most common malignancies responsible. Infiltration of the ONH in lymphoma occurs in around 0.5% of patients but this increases to 20-25% in primary CNS lymphoma [82]. Around 80% of cases are bilateral and can present with diffuse swelling of the optic nerves [79, 83]. Ophthalmological examination may reveal vitreous cells (lymphocytic infiltration) and patients often report symptoms of increased floaters [79]. Optic nerve function is dependent on the extent of involvement but can be profoundly reduced [83]. In suspected cases often a vitreous biopsy can establish the diagnosis [79].

Leukemic infiltration at the optic nerve can present with bilateral disc edema mimicking intracranial hypertension [83, 84]. Retinal examination may reveal peripapillary and peripheral hemorrhages, leukemic deposits at the optic nerve head, and subretinal fluid [79]. Early and aggressive radiotherapy is the treatment of choice in most cases [83, 84].

Amiodarone optic neuropathy usually presents with insidious gradual visual loss and bilateral optic disc edema which is present for months. The main differential diagnoses are papilledema and bilateral arteritic anterior ischemic optic neuropathy, although the latter is more likely to be associated with significant visual dysfunction. Unilateral disc swelling should be differentiated from non-arteritic anterior ischemic optic neuropathy. The presence of systemic symptoms consistent with amiodarone toxicity increases the suspicion of this diagnosis. Cessation of amiodarone usually, but not always, results in resolution of the disc edema [87].

Fig. 15. Optic nerve edema secondary to an optic nerve sheath meningioma.

**Amiodarone Optic Neuropathy**

Since amiodarone optic neuropathy was first reported in 1987 it has been established that the clinical picture is variable [85]. The diagnosis of amiodarone optic neuropathy is a clinical one. Most cases present with bilateral optic nerve swelling with mild optic nerve dysfunction. The mechanism of amiodarone neuropathy is not completely understood but a histopathologic study of the optic nerve demonstrated multiple lamellar inclusion bodies within large axons [86]. Amiodarone optic neuropathy usually presents with insidious gradual visual loss and bilateral optic disc edema which is present for months. The main differential diagnoses are papilledema and bilateral arteritic anterior ischemic optic neuropathy, although the latter is more likely to be associated with significant visual dysfunction. Unilateral disc swelling should be differentiated from non-arteritic anterior ischemic optic neuropathy. The presence of systemic symptoms consistent with amiodarone toxicity increases the suspicion of this diagnosis. Cessation of amiodarone usually, but not always, results in resolution of the disc edema [87].

Fig. 16. Amiodarone optic neuropathy with flame-shaped hemorrhage at 7 o’clock position.

**Conclusion and Important Points**

Bilateral optic nerve swelling must be considered to be papilledema and investigated with neuroimaging. However, it is important to consider other causes of optic nerve head swelling that may mimic papilledema. A detailed history, clinical examination, and laboratory tests should allow for the successful differentiation of the causes of bilateral optic nerve head edema. Measurement of optic nerve function is an important component of early assessment for those patients with bilateral disc edema and can significantly reduce the number of potential diagnoses. Early review by an ophthalmologist is essential for diagnosis of vision or life threatening pathology with this also allowing for early treatment to be commenced.
References


