Case 2. Unilateral Optic Disc Pallor

Case History:
A 56-year-old woman was referred by her GP for recurrent symptoms of tearing, grittiness, and blurred vision in the left eye. The first episode occurred four months prior and had settled with chloramphenicol. Her past ocular history includes childhood left esotropia and strabismus surgery at age 5, with residual esotropia and amblyopia. Her past medical history includes dyslipidaemia, for which she is on a statin and ezetimibe.

Examination:

<table>
<thead>
<tr>
<th></th>
<th>Right eye</th>
<th>Left eye</th>
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<tbody>
<tr>
<td>BCVA</td>
<td>6/6-2</td>
<td>6/12, PH 6/12</td>
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<tr>
<td>Refraction</td>
<td>+2.00/-0.50 x 180</td>
<td>+3.00/-0.25 x 180</td>
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<tr>
<td>Ishihara colour plates</td>
<td>14/14</td>
<td>1/14</td>
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<tr>
<td>Pupils</td>
<td>Normal</td>
<td>Left RAPD</td>
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<tr>
<td>Goldmann IOP</td>
<td>13 mmHg</td>
<td>14 mmHg</td>
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<tr>
<td>Slit lamp examination Anterior segment</td>
<td>Unremarkable</td>
<td>Normal</td>
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<td></td>
<td>Optic nerve (Figure 1)</td>
<td>Small optic nerve with small cup. Well-perfused neuroretinal rim</td>
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<tr>
<td>Retina</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
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<td>Gonioscopy</td>
<td>Open</td>
<td>Open</td>
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**Question 1: What is the significance of unilateral optic disc pallor?**

Answer 1: Disc pallor indicates previous axonal damage. Causes of unilateral optic neuropathy with disc pallor include compressive lesions anterior to the optic chiasm or prior chronic optic nerve head (ONH) swelling. Causes of the latter include previous ischaemic optic neuropathy, central retinal artery/vein occlusion, chronic optic neuritis, chronic papilloedema and traumatic optic neuropathy. Causes of bilateral optic atrophy include tumours or aneurysms affecting the optic tract. The absence of cupping implies non-glaucomatous optic neuropathy.

Further investigations are mandatory, including a brain MRI to rule out compressive optic neuropathy. In a middle-aged woman, optic nerve sheath meningioma is high on the list of differential diagnoses. An urgent MRI brain was performed for our patient, and no evidence of compressive optic neuropathy was identified.

Answer 1 ends
Figure 1. Optic nerve appearance at presentation.

**Question 2: What is the likely diagnosis?**

Answer 2: An optic neuropathy that causes sudden, painless, unilateral vision loss with no associated premonitory visual obscurations in patients 40 to 60 years of age is most likely due to non-arteritic ischaemic optic neuropathy (NAION).

Characteristics of NAION include optic disc swelling in the affected eye, which may be associated with peripapillary splinter haemorrhages; and a contralateral crowded ‘disc at risk’. The swelling typically resolves within 4-6 weeks and is replaced by sectorial or diffuse pallor, as seen in our patient. On further questioning, she had an episode of blurred vision four months prior. This was misdiagnosed by her GP.
An important differential includes arteritic anterior ischaemic optic neuropathy (AAION), caused by occult giant cell arteritis (GCA). As such, an urgent full blood count, ESR and CRP should be requested to rule out GCA. Occult GCA manifests as acute blindness with minimal systemic symptoms. In both conditions, the optic nerve head is swollen with flame-shaped haemorrhages, however only AAION is associated with pallor of the swollen nerve (due to severe infarction).

Answer 2 ends

**Question 3: How do you distinguish a true disc pallor from glaucomatous disc?**

Answer 3: Glaucomatous optic neuropathy is associated with disc cupping and focal thinning of the neuroretinal rim. Cupping typically starts in the superior and inferior regions, leading to vertical enlargement of the cup. Other glaucomatous features include posterior bowing of the lamina cribosa, visible laminar pores (laminar dot sign), bayoneting and nasal shifting of the retinal vessels, disc haemorrhages and increasing peripapillary atrophy. The main feature that distinguishes glaucomatous discs from disc pallor due to atrophy is well-perfused neuroretinal rim in glaucomatous discs.

Answer 3 ends

**Question 4: Discuss the pathophysiology of NAION.**

Answer 4: NAION is caused by partial or complete infarction of the ONH from non-inflammatory small vessel disease. Whilst the mechanism of infarct is controversial, it is thought that the short posterior ciliary arteries are the main vessels affected. The short posterior ciliary arteries divide into superior and inferior distal branches, and the anterior segment of the ONH is a watershed zone between areas supplied by these distal branches. This area is therefore vulnerable to ischaemic injuries during states of hypoperfusion. Hence, any
conditions that can contribute to vascular insufficiency are considered risk factors for NAION and include smoking, diabetes, hypertension, hypercoagulable states (e.g. collagen vascular disease, antiphospholipid antibody syndrome and hyperhomocysteinaemia); and nocturnal fluctuations in blood pressure.

Another important anatomical consideration in the pathogenesis of NAION is a small crowded cup. It is presumed that crowded discs are anatomically susceptible to infarction as even a small amount of axonal oedema can create a compartment syndrome picture, exacerbating pressure rise within the optic nerve. This may accelerate damage to axons and ganglion cell death, and subsequently cause optic nerve dysfunction.

Other risk factors for developing NAION include male gender and the use of phosphodiesterase-5 inhibitors such as sildenafil, presumably by inducing nocturnal hypotension. Furthermore, some surgical procedures, such as cataract surgery, strabismus surgery, LASIK and intravitreal injections have also been associated with NAION for unclear reasons.

Answer 4 ends

**Question 5: Describe the patient’s OCT retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) analysis. How do they compare with glaucomatous loss of RNFL and GCL?**

Answer 5: OCT shows marked asymmetry between the two eyes. The affected left eye shows generalised thinning of both the RNFL and GCL (Figures 2 and 3). The RNFL thinning is pronounced superiorly and inferiorly. The OCT of the unaffected right eye showed a small optic nerve head (disc area 1.47 mm²), with a small, crowded cup. The RNFL and GCL thicknesses were within normal limits in the right eye.

In NAION, the peripapillary RNFL may initially become thick while the disc is swollen. A prospective study of eyes with acute NAION showed that GCL
thinning developed within 1 to 2 months of onset (Kupersmith et al. 2016). As the disc swelling subsided, the RNFL began to lose thickness, but this was not seen until three months after the onset. Progression of RNFL or GCL thinning is rare after six months. Our patient’s RNFL and GCL results are consistent with previous episodes of disc swelling and consequent atrophy.

OCT analysis of NAION patients showed pronounced RNFL thinning in the superior and inferior quadrants, as is the case in our patient (Contreras et al. 2007). The superotemporal quadrant was most frequently affected after an acute episode of NAION. The reason for this is unknown, but several investigators have attributed this to variation in the anatomic location of the vascular watershed, with the superotemporal quadrant being the most common location (Hayreh and Contreras et al. 2005). Others hypothesise that it due to the densely packed superior and inferior arcuate distribution of fibres. In contrast, RNFL loss in glaucoma follows the distribution of retinal nerve fibres, with the superotemporal and inferotemporal zones most commonly affected (Leung et al. 2010a). Unlike NAION, glaucoma is a progressive condition. In a longitudinal study by Leung et al., RNFL progression in glaucoma patients was observed for five years using serial OCT RNFL measurements (Leung et al. 2010b). In this study, glaucoma patients lost an average of 3.3 microns of RNFL thickness per year, and the frequency of progression was highest in the inferotemporal sector, and lowest in the temporal sector. The preservation of the temporal RNFL, or the papillomacular bundle, explains the preserved central vision in glaucoma patients until an advanced stage of glaucoma.

Answer 5 ends
Figure 2. ONH RNFL analysis
Figure 3. OCT GCL analysis
Figure 4. Left eye visual field test. Top: at presentation. Middle: 4 months after presentation. Bottom: 10 months after presentation.
**Question 6: See Figure 4. Her visual field loss worsened at the four months-follow up then improved at 10 month-follow up. This is not typical of NAION. Interpret this finding.**

Answer 6: The four month follow up test has a low-test reliability and requires caution in interpretation. Her fixation loss, represented as the number of positive responses during retesting of the blind spot was 14/17 (82%). False negatives are failed responses to a stimulus 9 dB more intense than one previously seen at that location. False positives are responses to a pause during a sequence of stimulus presentations. Her false negative rate was 10% and false positive 2%. For a visual field test to be reliable, fixation loss must be under 20%, and false negative and positive errors under 33%. Wandering eyes and misalignment of the eyes at the beginning of visual field tests are usually responsible for high fixation loss. The patchy peripheral depressed areas also suggest a component of fatigue. The test at four months is unreliable and should not carry high weighting in assessing her clinical progress. In her 10 month follow-up visual field follow-up, fixation losses are also high (5/5 before fixation monitoring was turned off), indicating that this result should also be interpreted with caution.

Answer 6 ends

**Question 7: Describe the natural course of NAION.**

Answer 7: In the majority of cases, visual acuity and visual field stabilise within two weeks of sudden loss of vision. Rarely, NAION can progress over days to weeks until the disc swelling resolves. Progression of disease past two months is unusual and should raise questions about the initial diagnosis of NAION. About 40% of patients will show some improvement in visual acuity by six months, but visual field defects usually persist. Prognosis is poor if the presenting visual acuity is worse than 6/60.

Our patient’s visual acuity at presentation was 6/12. This slightly worsened at the two week follow-up, but stabilised at 6/15 at four and 10 months follow-
The inferonasal visual field defect remained stable. RNFL and GCL thinning showed no further progression after the initial presentation.

Rate of recurrence in the affected eye ranges from 3-8%. There is approximately 10% risk of the event to the fellow eye after two years and 15-25% after five years. The rate of recurrence tends to be higher if the presenting visual acuity is poor or if the patient has diabetes.

Answer 7 ends

**Question 8: Summarise the current evidence regarding treatment of NAION.**

Answer 8: There is as yet no medical or surgical intervention that has shown conclusive benefit in the treatment or prevention of NAION. The Ischaemic Optic Neuropathy Decompression Trial is a randomised, single-blind study, which investigated the effectiveness of optic nerve sheath fenestration (a surgical technique to create openings within the optic nerve sheath to reduce the hydrostatic pressure within the subarachnoid space of the optic nerve). This trial demonstrated no benefit of optic nerve sheath fenestration in acute NAION. Optic nerve sheath fenestration is therefore no longer offered as a treatment option. Similarly, systemic corticosteroids and intravitreal injection of anti-VEGF antibodies have both been tested in clinical trials, but neither treatment significantly altered the course of NAION.

Currently, referral to a physician for the management of cardiovascular risk factors is the mainstay of treatment. The goal of treatment is to reduce the chance of fellow eye involvement. Aspirin may be considered if there are no contraindications. Obstructive sleep apnoea is thought to cause nocturnal hypoxaemia during episodes of apnoea and is therefore considered to be a risk factor. Patients should be referred to respiratory service for assessment if expressing symptoms of sleep apnoea. Young patients under 40 should be further investigated for underlying coagulopathy. Unfortunately, none of these strategies are evidence-based; they are based on the presumed pathogenetic mechanism of NAION.
**Question 9: What is appropriate management plan for this patient?**

Answer 9: She was assessed two weeks after her initial examination, and then at four and ten months. Her visual acuity and field remained stable, so she was discharged from neuro-ophthalmology follow-up.

She has been referred to her physician for cardiovascular optimisation. She started working on her lifestyle and exercise regime and was started on aspirin. Due to symptoms of sleep apnoea, she was referred for a sleep study. If there are any symptoms in her right eye, she will need to present to the emergency eye clinic immediately. Lastly, one of her initial complaints of watery eyes is unrelated to NAION, and, following a comprehensive anterior segment examination, she was referred to oculoplastics for further workup of epiphora.

Answer 9 ends

**References and recommended reading**


Kardon R. The Role of the Macula OCT Scan in Neuro-ophthalmology. J
Neuroophthalmol. 2011. 31(4): 353-361


Question number: 1
Question text: Which of the following is a risk factor for non-arteritic anterior ischaemic optic neuropathy (NAION)?
Answer A: Nocturnal hypotension
Answer B: Diabetes mellitus
Answer C: Cataract surgery
Answer D: Sleep apnoea syndrome
Answer E: All of the above

Question number: 2
Question text: Which of the following is true about NAION?
Answer A: Biopsy of the affected artery shows granulomatous inflammation, proliferation of the intima and gross narrowing of the lumen.
Answer B: Patients commonly present with scalp tenderness, jaw claudication and polymyalgia rheumatica.
Answer C: The risk factors for fellow eye involvement are poor visual acuity in the first eye and diabetes.
Answer D: The use of sildenafil has not been linked with NAION.
Answer E: Most people make a complete vision recovery over time.

Question number: 3
Question text: What are you least likely to see during the fundus exam of a patient with NAION?
Answer A: Diffuse hyperaemic disc swelling
Answer B: Normal cup-disc-ratio in the fellow eye
Answer C: Disc pallor
Answer D: Peripapillary splinter haemorrhages
Answer E: Optic disc drusen

Question number: 4
Question text: In patients with NAION, involvement of the fellow eye occurs in what percentage of patients after 5 years?
Answer A: 0%
Answer B: 5%
Answer C: 20%
Question number: 5
Question text: Diagnosis of NAION can only be made in retrospect, after observing the course of vision loss over time. True or False?

Question number: 6
Question text: Choose a possible cause of artefacts that can arise during visual field testing.
Answer A: Eyelid and brow ptosis
Answer B: Miosis
Answer C: Incorrect refractive correction
Answer D: Fatigue
Answer E: All of the above

Question number: 7
Question text: Non-glaucomatous optic nerve dysfunction typically leads to which following acquired colour vision defects?
Answer A: Blue/yellow
Answer B: Blue/green
Answer C: Red/green
Answer D: Red/blue
Answer E: Rod monochromacy

Question number: 8
Question text: What is not an appropriate immediate management plan for suspected NAION?
Answer A: Neuroimaging if optic atrophy is present.
Answer B: Urgent full blood count, CRP and ESR in elderly patients.
Answer C: Testing for hypercoagulable states in patients under the age of 50
Answer D: Obtain baseline visual field test, OCT and disc photos.
Answer E: Arrange a temporal artery biopsy.
Question number: 9
Question text: Choose the correct statement about NAION.
Answer A: All patients should be started on aspirin immediately in order to improve the visual prognosis of the affected eye.
Answer B: NAION mostly occurs in females.
Answer C: Early optic nerve fenestration has shown benefit.
Answer D: Sleep apnoea has a protective effect against NAION.
Answer E: Onset is usually not associated with headaches.

Question number: 10
Question text: A patient with a pale disc with mild cupping has significant loss in central visual acuity, RAPD in the ipsilateral eye and a red/green colour vision defect. This patient likely has glaucoma. True or False?

Question number: 11
Question text: Which of the following is not a feature of a glaucomatous disc?
Answer A: Sectoral pallor in the absence of cupping
Answer B: Splinter haemorrhage
Answer C: Optociliary shunt vessels
Answer D: Laminar dot sign
Answer E: Pink neuroretinal rim

Question number: 12
Question text: What is the main source of blood supply to the optic nerve head?
Answer A: Short posterior ciliary artery
Answer B: Central retinal artery
Answer C: Anterior ciliary artery
Answer D: Posterior ethmoidal artery
Answer E: Supratrochlear artery

Question number: 13
Question text: Bilateral sequential NAION can give rise to unilateral disc swelling with contralateral optic atrophy. In the absence of a compressive intracranial lesion, this phenomenon is called:
Answer A: Morning glory anomaly
Answer B: Neuromyelitis optica
Answer C: CHARGE syndrome
Answer D: Pseudo Foster-Kennedy syndrome
Answer E: Giant cell arteritis

Question number: 14
Question text: You are seeing a patient with progressive vision loss and noticed a pale cupped disc during examination. Which of the following is not an appropriate next step?
Answer A: Complete neuro-ophthalmic evaluation.
Answer B: Perform a visual field test.
Answer C: Start medical therapy to lower intraocular pressure.
Answer D: Consider neuroimaging and laboratory work-up if features atypical of glaucoma are present.
Answer E: Ensure the degree of cupping is closely correlated with the amount of visual dysfunction.

Question number: 15
Question text: A patient with glaucoma will have low pattern standard deviation on automated perimetry.
True or False?

Question number: 16
Question text: Choose a false statement regarding OCT.
Answer A: RNFL thickness is measured with circular scans of 3.4mm diameter centered around the optic nerve head.
Answer B: OCT can provide high-resolution up to few microns.
Answer C: OCT can be used to construct a three-dimensional image of the retina.
Answer D: Macular GCL thickness is not influenced by the degree of optic atrophy following resolution of disc swelling.
Answer E: OCT uses near-infrared light to obtain the retinal image.

Question number: 17
A 65-year-old man wakes up with painless loss of vision in the left eye. He has no significant medical history and takes no regular medication apart from Viagra. His visual acuity is 6/24 in the left eye and 6/6 in the right eye. He has left disc swelling. His visual field shows an inferior altitudinal defect. His CRP is 0.6 and ESR 3.

Based on the above information, what is the most likely diagnosis?

Answer A: Optic neuritis
Answer B: Giant cell arteritis
Answer C: Hypertensive retinopathy
Answer D: Chronic glaucoma
Answer E: NAION

Which of the following statement best describes the peripapillary RNFL change in NAION?

Answer A: RNFL initially becomes thick due to disc swelling. Thinning begins after three months of onset. No further progression is seen after six months.
Answer B: RNFL initially becomes thick, then progressively thins.
Answer C: Thinning of RNFL starts immediately after onset due to ischaemic axon loss.
Answer D: The temporal RNFL is the most vulnerable.
Answer E: None of the above.

Choose a medical therapy that has been shown to improve visual recovery in patients with NAION.

Answer A: Aspirin
Answer B: Corticosteroid
Answer C: Anti-VEGF
Answer D: Dietary supplements
Answer E: None of the above

Absence of disc swelling rules out NAION.
True or False?
Question number: 21
Question text: Which of the following statements regarding the RNFL is false?
Answer A: Average RNFL thickness in a normal eye is >80 microns.
Answer B: A graphic plot of peripapillary RNFL thickness shows double hump due to the superior and inferior poles being the thickest RNFL.
Answer C: Average RNFL thickness is usually greater in individuals with very large optic discs.
Answer D: The RNFL is formed by ganglion cell axons.
Answer E: >80% of RNFL loss is required to produce a visual field defect

Question number: 22
Question text: Which of the following conditions gives rise to a visual field defect clearly distinguishable from glaucoma?
Answer A: Myelinated nerve fibre layer
Answer B: Pituitary adenoma
Answer C: NAION
Answer D: Retinal vein occlusion
Answer E: Optic disc drusen

Question number: 23
Question text: Six months after an episode of NAION, which of the following is often present:
Answer A: Marcus-Gunn pupil
Answer B: Cystoid macula oedema
Answer C: Progression of visual field defect
Answer D: Thickened RNFL
Answer E: Optic disc drusen

Question number: 24
Question text: The mechanism of infarct in NAION is controversial, but least likely to be caused by:
Answer A: Vascular insufficiency
Answer B: Coagulopathy
Answer C: Inflammation of blood vessels
Answer D: Crowded disc
Answer E: Nocturnal hypoxemia

Question number: 25
Question text: Optic atrophy will not occur with tumours posterior to the lateral geniculate nuclei.
True or False?