Case 1: Glaucoma Mimickers - Multiple Sclerosis

Case History:
A 37 year old Caucasian male presented for ophthalmic examination one day following chiropractic manipulation of his neck. He had a headache and noticed blurred vision in his left eye. He had originally presented to the chiropractor because of numbness in two of the fingers on his left hand. He reported that he was otherwise well and was not taking any medications. There was no significant family ocular history.

The following observations were noted on ophthalmic examination:

<table>
<thead>
<tr>
<th></th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best-corrected Visual Acuity</td>
<td>6/6</td>
<td>Hand Movements</td>
</tr>
<tr>
<td>Ishihara Colour Plates</td>
<td>14/15</td>
<td>Unable to do</td>
</tr>
<tr>
<td>Pupils</td>
<td></td>
<td>Left RAPD</td>
</tr>
<tr>
<td>IOP</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Anterior Segment</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Within normal limits</td>
<td>Swollen</td>
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<tr>
<td>Retina</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
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Question 1: What is the initial management plan for this patient? What other tests would you like to undertake? What is the most likely diagnosis?

Answer 1:

The patient was promptly referred for imaging evaluation, including an MRI. Because of the patient’s history of neck manipulation, the possibility of a carotid artery dissection was also investigated.

Neuro-imaging revealed evidence of demyelinating lesions on the left hand side. There were no vascular abnormalities suggestive of carotid artery dissection on MRA assessment. A diagnosis of optic neuritis, likely due to multiple sclerosis, was made.

The patient was commenced on IV methylprednisolone for three days (1000 mg per day) and then oral prednisone with taper.

Three weeks later, the visual acuity had improved to 6/60+1 in the left eye. There was a left RAPD, and significant colour desaturation in the left eye; none of the Ishihara colour plates were correctly identified. The left optic nerve head was still swollen. The patient had noted episodes of visual blurring following exercise and after a hot shower.
Question 2: What are Uhthoff’s phenomena?

Answer 2:

Uhthoff’s phenomena are a feature of multiple sclerosis and other demyelinating disorders, including neuromyelitis optica. Symptoms are short in duration (less than 24 hours, usually minutes or hours) and are reversible. The changes are linked to an increase in core body temperature (eg. After exercise or a hot shower). Symptoms may include blurring or doubling of vision, and the illusion of environmental movement (oscillopsia).

It is important to differentiate between exacerbation of MS and an episode of Uhthoff’s phenomenon – if Uhthoff’s phenomenon is erroneously diagnosed as exacerbation of MS, the patient may be unnecessarily exposed to corticosteroid treatment, or risk cessation of successful disease-modifying therapy. Differentiating between Uhthoff’s phenomenon and a true MS attack is relatively straightforward, if a thorough history of the event is acquired.

In patients with MS, particularly those who are on treatment, true attacks occur infrequently (generally as little as once every two to three years). However, with Uhthoff’s phenomena, symptoms can occur much more frequently.

Question 3: Taking your most likely diagnosis, what sort of visual field defect would you expect to find?

Answer 3:

Visual field results were mildly unreliable in the right eye due to fixation errors, however the right eye’s visual field was within normal limits. The left eye showed a generalised reduction in sensitivity, most marked inferiorly (see Figure 1 – Right eye initial visual field and Figure 2 – Left eye initial visual field).
Figure 1 – Right eye visual field initial presentation
Figure 2 – Left eye visual field initial consultation
Figure 3 – First OCT scan of RNFL
OCT of the peripapillary RNFL (see Figure 3 – First OCT scan of RNFL) shows thinning of the inferior RNFL in the right eye, with a mild reduction in RNFL thickness (compared to a database of age-matched normals) in the superior and temporal quadrants. The RNFL thickness was above normal limits in the left eye in all regions except the temporal quadrant.

The patient received an initial diagnosis of clinically isolated syndrome with left optic neuritis, probably caused by underlying multiple sclerosis. Three months after the initial presentation, the patient developed tingling in his feet.

Optic disc photographs taken six months following the initial presentation show mild temporal rim pallor in the right eye. The neuroretinal rim in the inferior, superior and nasal quadrants looks healthy in the photograph (See Figure 4 – RE optic nerve). The photograph of the left optic nerve shows a pale neuro-retinal rim, particularly temporally (See Figure 5 – LE Optic Nerve). There is no evidence of optic nerve head swelling. Visual field testing revealed normal visual fields in both eyes (See Figures 6 and 7 – Right and Left Visual Fields six months after initial presentation).
Figure 4 – Right optic nerve
Figure 5 – Left optic nerve
Figure 6 – Right eye visual field six months after presentation
Figure 7 – Left eye visual field six months after presentation
Question 4: Is optic disc pallor normally a feature of glaucomatous optic neuropathy?

Answer 4:

Optic disc pallor is normally a feature of non-glaucomatous optic neuropathies. Temporal pallor is seen in conditions that selectively affect the papillomacular bundle (the temporal quadrant of the peripapillary RNFL). Conditions that can lead to temporal pallor include hereditary optic neuropathies (eg. Leber’s hereditary optic neuropathy), toxic/nutritional optic neuropathies, compressive optic neuropathies and multiple sclerosis.

OCT scans acquired at the most recent visit, 20 months after the initial presentation, show no progression in RNFL thinning in the right eye compared with baseline (See Figure 8 – RNFL Progression RE). The RNFL swelling in the left eye (observed at initial presentation) has resolved, and this can be seen in the serial OCT scan analysis (See Figure 9 – RNFL Progression LE). However, the RNFL layer has atrophied in the superior, inferior and temporal quadrants of the left eye (See Figure 10 – RNFL both eyes – 20 months). The global RNFL thickness has decreased gradually over time, compared with the second baseline scan. Although the superior and inferior RNFL quadrants are also affected in the left eye of this patient, there is significant loss of the temporal RNFL, corresponding to the nerve fibres originating at the macula. Interestingly, despite this dramatic reduction in temporal RNFL thickness, visual acuity was well preserved at 20 months, at 6/4.8 in the left eye.

The right eye Ganglion cell complex thickness was mildly reduced in the inferior-nasal region of the right macula. There was generalised reduction in ganglion cell complex thickness in the left eye (See Figure 11 – Ganglion Cell complex analysis). Visual fields at this visit were normal in both eyes, with good reliability indices.
Figure 8 – RNFL progression analysis right eye
Figure 9 – RNFL progression analysis left eye
Figure 10 – RNFL scan both eyes at 20 months
Question 5: Would you expect to see recovery of colour vision in this patient?
Answer 5:

At initial presentation, this patient was unable to do colour vision testing due to poor vision in the affected left eye. Most patients with an acquired optic neuropathy will have dyschromatopsia. Following resolution of visual acuity, colour vision was re-checked with Ishihara pseudoisochromatic plates, and although he was able to correctly identify 12/14 plates in the left eye (all plates were correctly identified in the right eye), he reported a significant subjective difference between the two eyes. When assessing colour vision it is important to assess the speed of plate recognition, as well as the number of correctly identified plates. A patient may correctly identify all plates with the affected eye, but may take longer on each page. Red saturation testing (eg. With the cap of a bottle of tropicamide) may also be useful.

Question 6: The patient commenced fingolimod therapy. What macular changes do you need to be aware of?

Answer 6:

The patient commenced fingolimod therapy approximately 12 months prior to his most recent examination. Fingolimod is the first FDA approved oral agent for the treatment of relapsing remitting multiple sclerosis. The medication can cause macular oedema in a small percentage (0.5%) of patients. The incidence of fingolimod macular oedema is daily dose-dependent (patients on higher daily doses of fingolimod are more likely to experience this adverse effect). Patients about to start therapy should have a baseline macular OCT scan, and then a follow-up OCT scan 3-4 months after starting therapy, as the majority of cases of fingolimod-associated macular oedema occur within this time-frame. The recommendation is for a third examination six months after the second, and then annual fundus examinations (and OCT scans) thereafter. OCT scans of patients with macular oedema associated with fingolimod therapy will show cystic changes at the fovea, and central vision will be affected. There may be a yellow-ish discolouration of the fovea visible on clinical examination. Fundus fluorescein angiography shows leakage at the macula. Discontinuation of fingolimod therapy is a joint decision between the patient, their neurologist and the ophthalmologist. Macular oedema can resolve following discontinuation of fingolimod.

This patient had no evidence of macular oedema in either eye after one year on fingolimod therapy. As the patient is continuing to take this medication, they have been placed on an annual review.

Question 7: What other retinal changes could you see in a patient with multiple sclerosis?

Answer 7:
In approximately 5 – 10% of patients with multiple sclerosis, microcysts in the inner nuclear layer can be observed on high definition OCT scans. These microcysts are not associated with disease modifying multiple sclerosis therapies, but have been found to predict the recurrence of optic neuritis, and they are associated with increasing disease severity and poorer visual acuity. In patients with these microcysts, there is thickening of the inner nuclear layer, and corresponding thinning of the RNFL, ganglion cell layer and inner plexiform layer. The microcysts can be bilateral, but are more likely to be found in one eye. Similar findings have been documented in other conditions affecting the optic nerve including neuromyelitis optica, glaucoma, dominant optic atrophy and Leber’s hereditary optic neuropathy. The cause of the macular microcysts is not known.

Patients with multiple sclerosis tend to have reduced macular volume compared with healthy individuals, even in eyes with no history of optic neuritis. In patients who have had optic neuritis, the loss of macular volume (and a reduction in thickness of the individual retinal layers) is more extensive.

Question 8: Do patients with multiple sclerosis and no history of optic neuritis have RNFL thinning on OCT scans?

Answer 8:

Multiple sclerosis eyes with a history of optic neuritis demonstrate the greatest reduction in RNFL thickness. However, more subtle thinning in the eyes of patients with multiple sclerosis but no history of optic neuritis has been demonstrated in several studies. Both the eyes of multiple sclerosis patients with no history of optic neuritis and the unaffected fellow eye of patients with previous unilateral optic neuritis have a significant reduction in RNFL thickness compared with healthy control eyes.

Question 9: What are the similarities and differences in the patterns of RNFL loss in MS vs. glaucoma?

Answer 9:

In patients with multiple sclerosis and a history of optic neuritis, the most predictable RNFL finding is thinning of the temporal quadrant. However, as seen in the patient outlined in this case, thinning of the superior and inferior quadrants may also be observed. As mentioned above, patients with multiple sclerosis but no history of optic neuritis also have thinning of the RNFL, although it is much more subtle, and the RNFL values may still fall within the ‘normal range’ when compared to the normative database.

In glaucoma, there is generally thinning of the superior and inferior neuroretinal rim, so there is corresponding RNFL loss in these two quadrants. The temporal RNFL is usually spared in glaucoma until the very advanced stages. In glaucoma there is likely to be more severe visual field loss with less extensive RNFL
thinning. For example, this patient with multiple sclerosis has a well-preserved visual field despite a significantly reduced RNFL with global thickness of 59 µm papillomacular bundle thinning.

References and Reading List:

Case 1 – Test

Question 1
Which of the following is not one of the potential differential diagnoses in cases of unilateral optic disc swelling?

A. Non-arteritic anterior ischaemic optic neuropathy
B. Optic Neuritis
C. Anterior uveitis
D. Optic nerve sheath meningioma
E. Sarcoidosis

Question 2
Which of the following features is suggestive of a non-glaucomatous optic neuropathy?

A. Impaired colour vision
B. Relative afferent pupillary defect
C. Visual field loss
D. Pallor of the neuro-retinal rim
E. All of the above

Question 3
Which of the following is false regarding Uhthoff’s phenomena?

A. Symptoms generally last up to a few hours
B. Uhthoff’s phenomena occur as a result of an increase in core body temperature
C. It is necessary to take a thorough history to determine whether the symptoms are Uhthoff’s phenomena or exacerbation of multiple sclerosis
D. Patients on disease-modifying agents for multiple sclerosis should cease taking their medication in order to determine the cause of the symptoms
E. Uhthoff’s phenomena can include blurred vision, double vision and loss of depth perception

Question 4
Which of the following is false regarding optic disc pallor?

A. Pallor affecting the temporal retinal nerve fibre layer is often associated with reduced visual acuity
B. In compressive optic neuropathies, pallor of the neuroretinal rim may be visible on clinical examination
C. Temporal pallor is seen in conditions that selectively affect the papillomacular bundle
D. A pale optic disc indicates a long-standing optic neuropathy or as a sequel to an acute inflammatory or ischaemic optic neuropathy
E. Pallor of the neuroretinal rim is not associated with optic disc cupping
Question 5:
The retinal nerve fibre layer is comprised of photoreceptor axons
TRUE or FALSE?

Question 6:
Which of the following is true regarding non-glaucomatous optic neuropathies?

A. Retinal nerve fibre loss may be out of proportion to the reduction in visual acuity
B. Patients with a suspected non-glaucomatous optic neuropathy do not require further imaging investigation
C. Non-glaucomatous optic neuropathy is always associated with reduced visual acuity
D. Non-glaucomatous optic neuropathy is never bilateral
E. Optical coherence tomography is not useful in the assessment of patients with non-glaucomatous optic neuropathy

Question 7:
Microcystic macular oedema....

A. Is associated with the use of fingolimod therapy in multiple sclerosis
B. Is observed in the inner nuclear layer
C. Does not change over time
D. Is observed in 25% of patients with multiple sclerosis
E. Is always bilateral

Question 8:
Which of the following is false regarding microcystic macular oedema?

A. Microcystic changes have been found in patients with glaucoma, Leber’s hereditary optic neuropathy and dominant optic atrophy
B. Microcystic macular oedema is less likely to occur in eyes with a history of optic neuritis
C. Microcystic changes are associated with thinning of the inner plexiform layer
D. Microcystic changes are associated with more advanced disability in multiple sclerosis
E. The cause of the macular microcysts is not yet known

Question 9:
Which of the following is false regarding fingolimod therapy in multiple sclerosis

A. A small percentage of patients taking fingolimod will develop cystic macular oedema
B. All patients should have a baseline high-definition OCT scan of the macula prior to commencing fingolimod therapy
C. Patients on higher daily doses of fingolimod are more likely to develop macular oedema
D. If the OCT scan is normal at six months then no further ophthalmic follow-up is required
E. A patient is most likely to develop fingolimod-associated macular oedema within 3-4 months of starting the medication

Question 10:
30-35% of retinal thickness at the macula is composed of retinal ganglion cells and their axons
TRUE or FALSE?

Question 11:
You have a patient who has macular oedema associated with fingolimod therapy for multiple sclerosis. What should you do?

A. Advise the patient to discontinue fingolimod therapy immediately
B. Monitor them in six months to check for any progression
C. Write a letter to their neurologist advising them of your findings
D. Commence treatment with non-steroidal anti-inflammatory eye drops
E. Reduce their medication dose in consultation with their general practitioner

Question 12:
Which of the following statements about colour vision is true?

A. Patients with optic neuritis are most likely to develop blue-yellow colour vision defects
B. Red saturation testing is not useful in patients with suspected optic neuritis
C. If all Ishihara plates are correctly identified, the speed of plate recognition does not need to be taken into account
D. Patients with acquired colour vision defects will always have reduced visual acuity
E. A patient with optic neuritis may experience partial recovery of colour vision as visual acuity improves
Question 13:
What is the role of corticosteroids in the treatment of optic neuritis?

A. Intravenous methylprednisolone followed by oral prednisone speeds the recovery of visual loss due to optic neuritis
B. Oral prednisone alone is useful in the treatment of optic neuritis
C. Oral prednisone alone reduces the risk of developing multiple sclerosis within 24 months after an episode of optic neuritis
D. Body weight is not taken into account when determining the dose of oral prednisone
E. Topical prednisolone acetate 1% is used as an adjunctive treatment for patients with optic neuritis

Question 14:
Neuromyelitis optica....

A. Is a demyelinating inflammatory disease of the central nervous system
B. Is associated with recurrent episodes of optic neuritis with poor visual recovery
C. Was previously considered to be a variant of multiple sclerosis
D. Symptoms may include intractable vomiting
E. All of the above

Question 15:
The most common presenting visual field defect in optic neuritis is a diffuse reduction in sensitivity

TRUE or FALSE?

Question 16:
With regard to baseline visual fields in optic neuritis, which of the following is true?

A. The most common type of initial visual field presentation in optic neuritis is a nasal step
B. The visual field in the affected eye at presentation can present as almost any type of visual field defect
C. The visual field defect tends not to resolve over time
D. In 25% of patients with optic neuritis, their visual field is normal at presentation
E. At baseline, the visual field of the fellow eye is always normal

Question 17:
A patient with a diagnosis of multiple sclerosis (and no history of optic neuritis) presents to your practice for a routine eye examination, what is the most likely finding?

A. Generalised, severe thinning of the retinal nerve fibre layer on OCT examination
B. Temporal disc pallor on optic nerve examination
C. Subtle thinning of the retinal nerve fibre layer and macular layers on OCT examination
D. Loss of red saturation in one eye compared with the other
E. Raised intraocular pressure

Question 18:
In the management of a patient with optic neuritis, which of the following is false?

A. Fingolimod therapy is likely to be initiated immediately
B. The patient should be promptly referred for ophthalmological assessment
C. Further imaging, including MRI, may be undertaken
D. The patient may ultimately be managed by a multidisciplinary team including neurologists and ophthalmologists
E. A baseline visual field examination is important

Question 19:
When assessing RNFL loss in glaucoma vs. multiple sclerosis which of the following is false?

A. In both conditions, patients may have RNFL values that lie within the normal range
B. In glaucoma there is thinning of the superior and inferior RNFL
C. The temporal RNFL is more likely to be affected in multiple sclerosis
D. The papillomacular bundle is preferentially affected in glaucoma
E. In glaucoma, visual field loss is likely to be more severe than in multiple sclerosis with comparable RNFL loss

Question 20:
A patient with suspected optic neuritis may have normal optic nerve appearance on fundus examination

TRUE or FALSE?

Question 21:
In a patient with a history of optic neuritis and multiple sclerosis, what might you expect to find on macular OCT examination with retinal layer segmentation?

A. Preferential thinning of the inner retinal layers
B. Increased thickness in the outer plexiform layer
C. No difference compared with healthy controls
D. Gliosis at the fovea
E. Isolated thinning of the outer nuclear layer

Question 22:
What is the role of OCT examination in multiple sclerosis?

A. It can be used as a standalone tool to diagnose optic neuritis
B. Serial OCT examinations of the peripapillary RNFL and macula may be useful in the monitoring of multiple sclerosis patients over time
C. Macular scans may detect microcystic changes which can be associated with poorer visual acuity
D. A, B and C
E. B and C

Question 23:
Which of the following is not a possible presenting symptom of optic neuritis

A. Reduced visual acuity
B. Pain on eye movement
C. Visual field loss
D. Watery discharge
E. Reduced colour saturation

Question 24:
Which of the following is false?

A. Patients with multiple sclerosis but no history of optic neuritis tend to have thinner RNFL values compared with age-matched controls
B. Time domain OCT provides more accurate retinal layer segmentation than spectral domain OCT
C. Patients with optic neuritis in one eye may have subclinical thinning of the RNFL and macula in the fellow eye
D. The ganglion cell complex thickness is reduced in patients with a history of optic neuritis
E. With subsequent repeat episodes of optic neuritis, there will be progressive loss of RNFL thickness

Question 25:
Visual recovery is more likely in optic neuritis associated with neuromyelitis optica compared with optic neuritis associated with multiple sclerosis

TRUE or FALSE?