GNZ Case 4 - Normal tension glaucoma (NTG)

Learning outcomes:

- To understand the challenges of OCT assessment in patients with myopic optic nerves
- To be familiar with IOP-independent risk factors for glaucoma
- To determine when neuro-imaging is required in a patient with suspected NTG
- To consider tension series and the water drinking test in the assessment of patients with suspected undiagnosed IOP spikes
- To have a basic understanding of the genetics of glaucoma

A 70 year old female presents to you for a glaucoma assessment.

- Past ocular history: Moderate myopia and astigmatism
- Past medical history: Asthma, Migraines – less frequently post-menopause, Raynaud's phenomenon
- Medications: Aspirin, Ventolin Inhaler
- Family history: Mother had glaucoma, diagnosed aged in her 60s, took eye drops

Examination

	Right eye	**Left eye**
BCVA	6/6	6/6
IOP	17 mmHg	14 mmHg
Ishihara colour plates	14/14	14/14
Pupils	No RAPD	
Gonioscopy	D30r	D30r
Corneal Pachymetry	501 µm	503 µm
Fundus examination	See optic nerve photo (Figure 1a). Macula clear. Peripheral retina clear and flat	See optic nerve photo (Figure 1b). Macula clear. Peripheral retina clear and flat
Visual Fields	See visual fields (Figures 2a and 2b)	
OCT	See RNFL analysis (Figure 3) and GCC scan (Figure 4)	

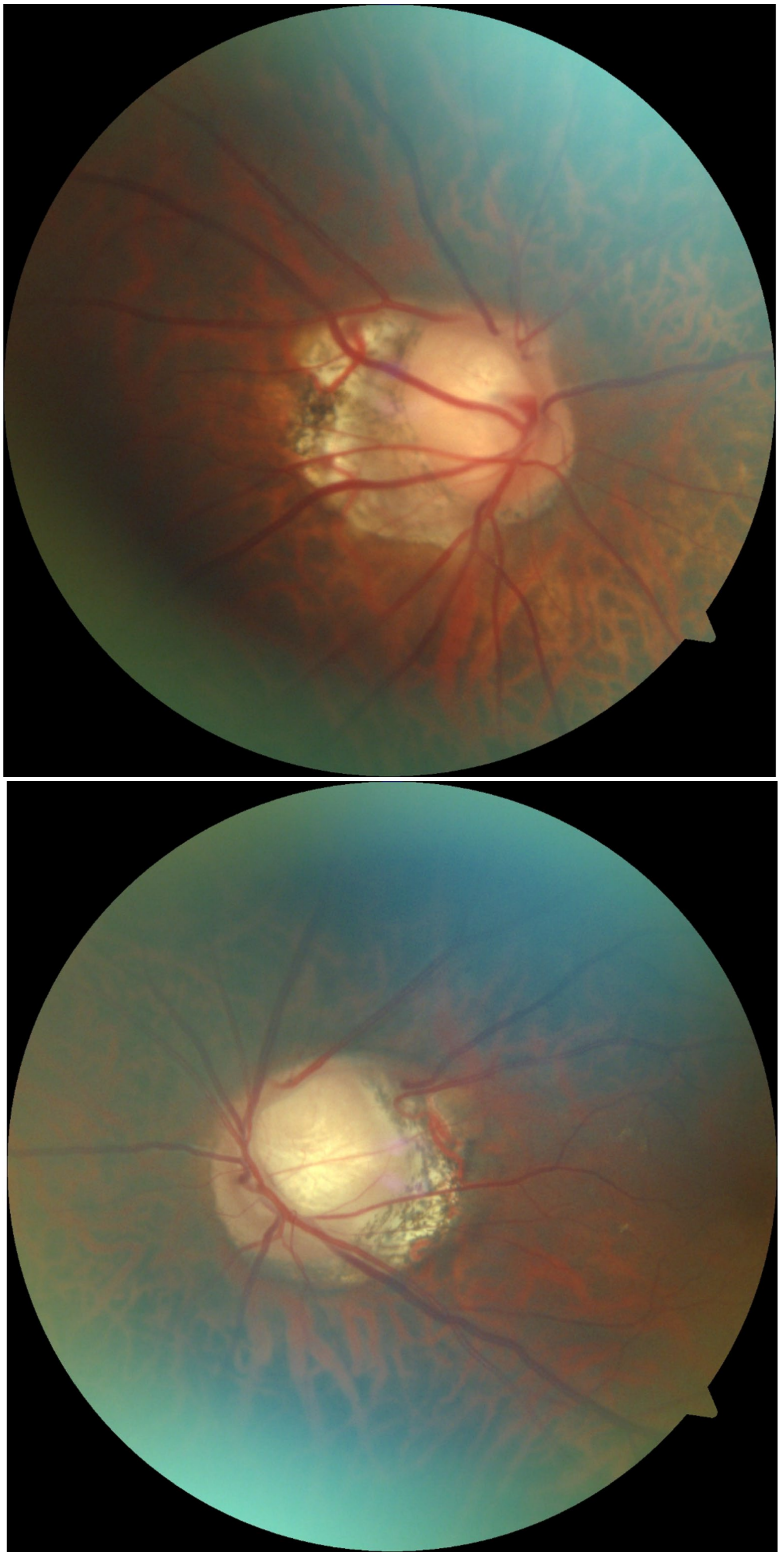


Figure 1: Appearance of right (A) and left (B) optic nerves

Figure 2a – Right visual field

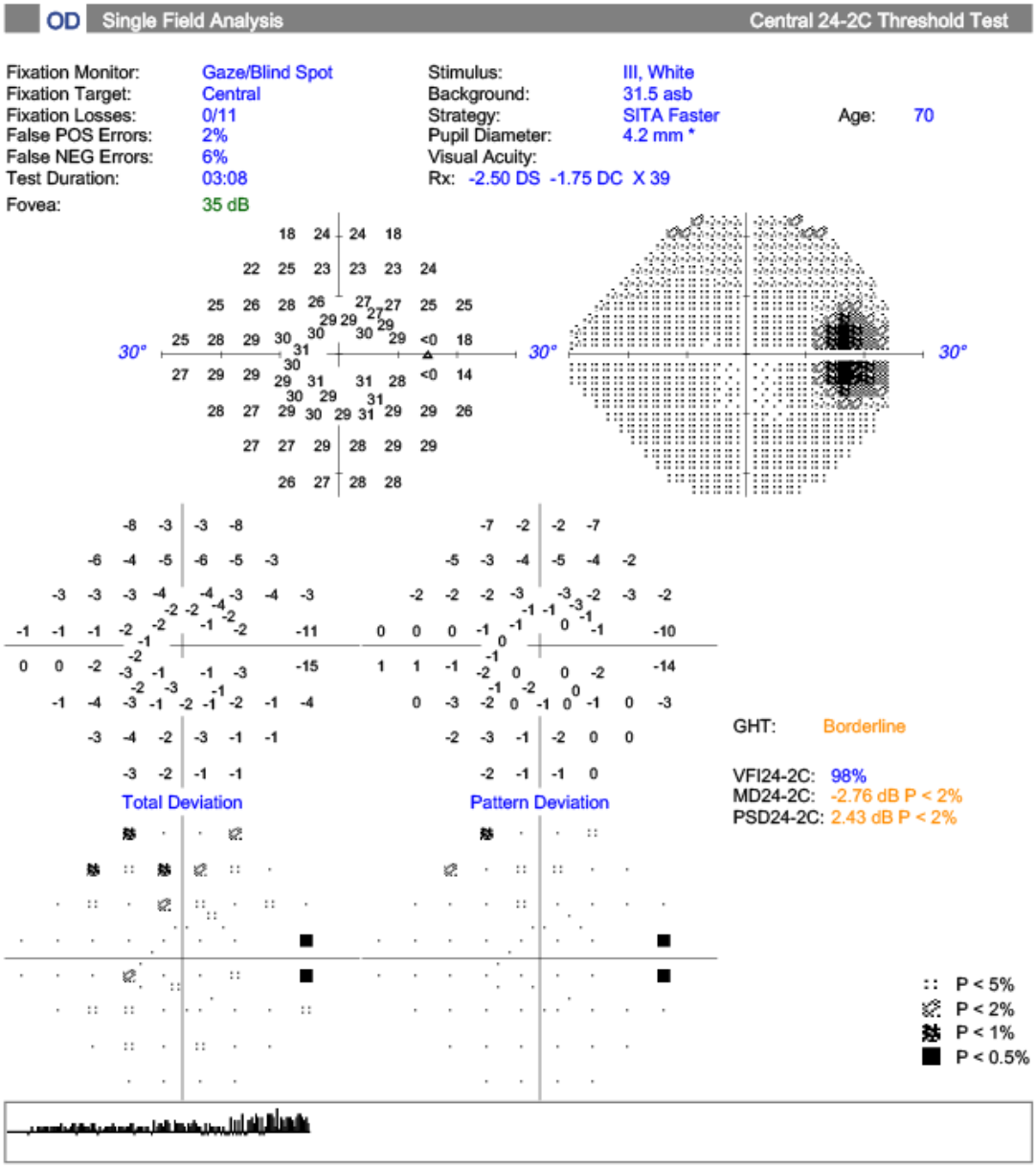
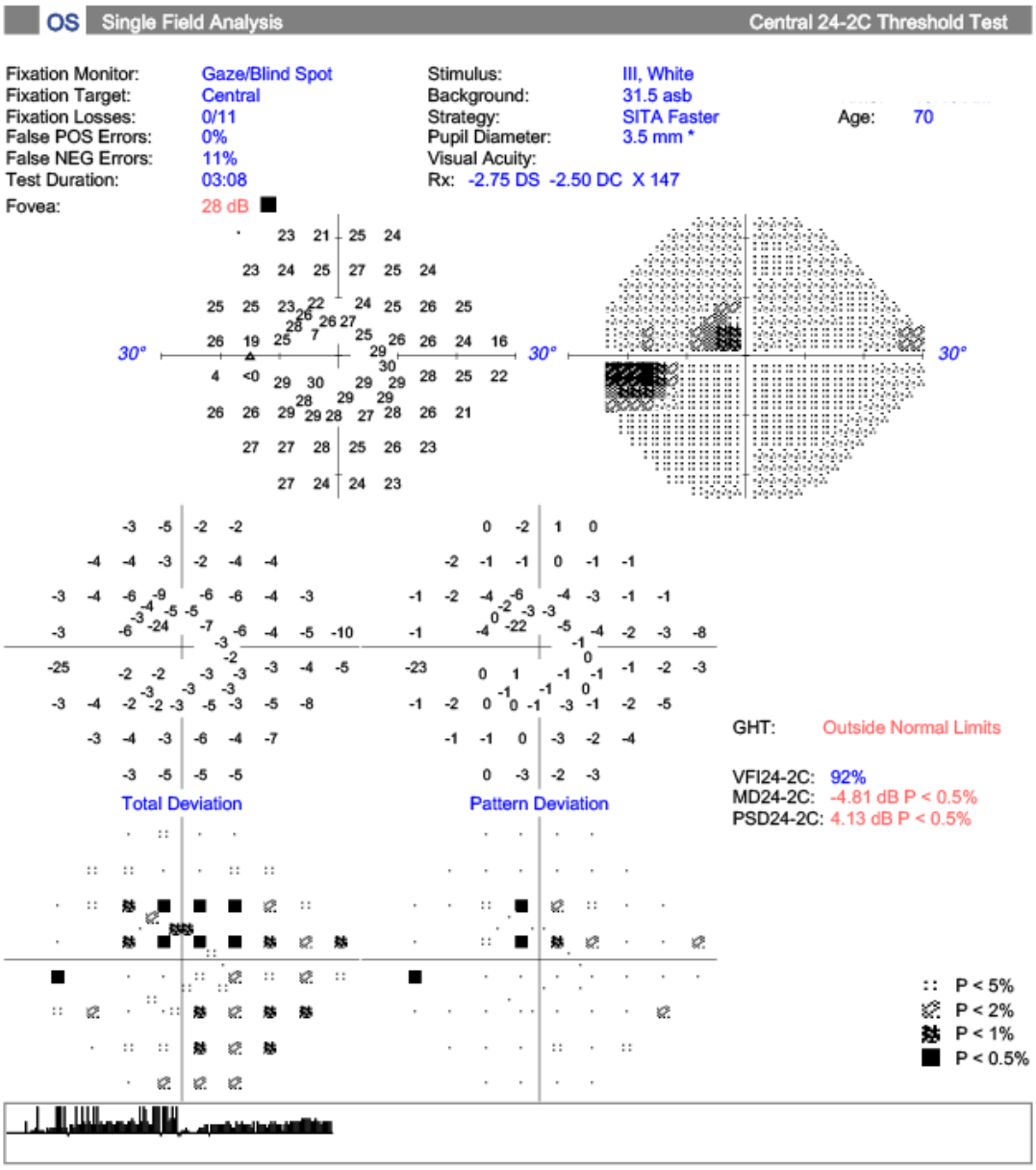


Figure 2b – Left visual field



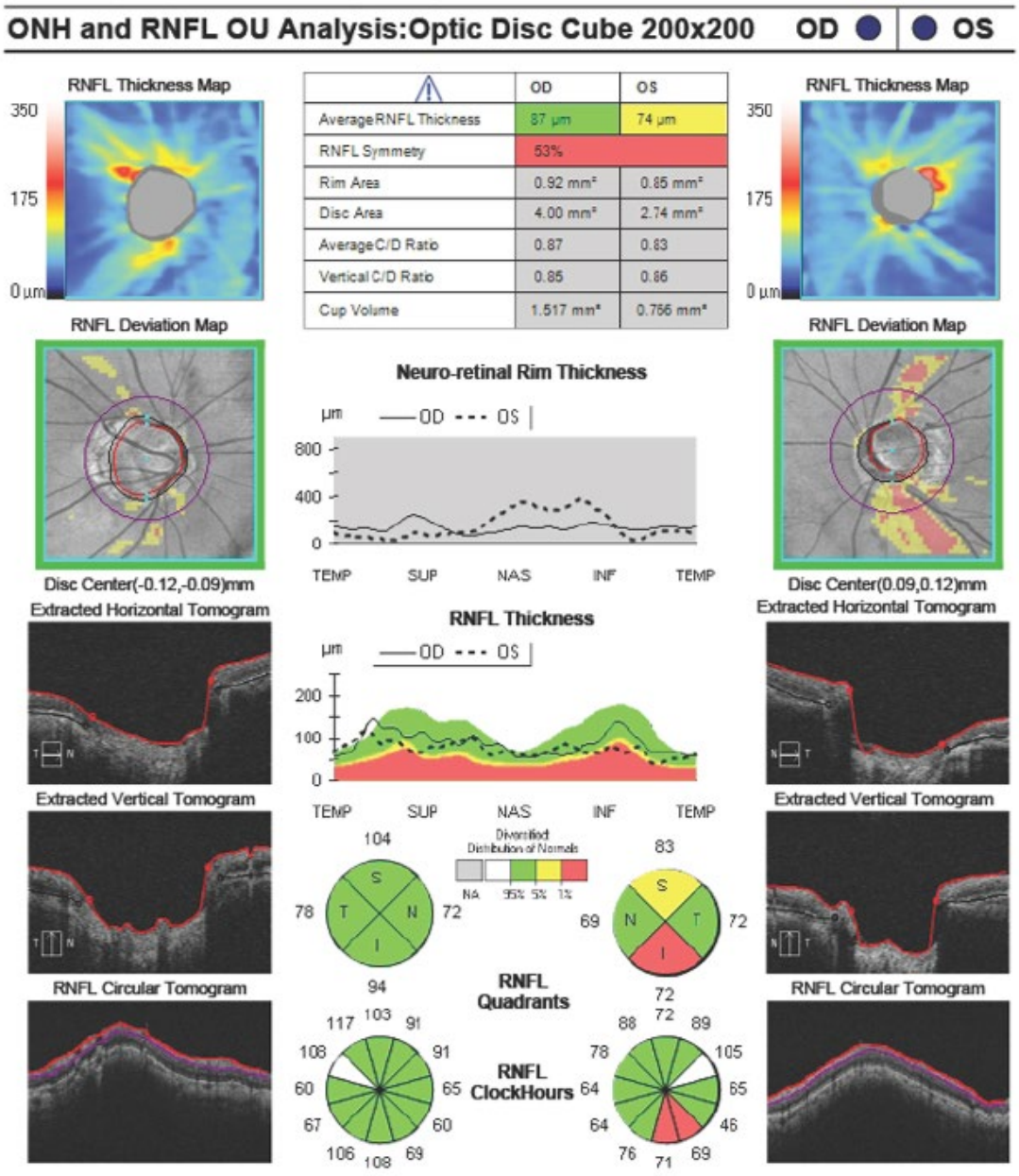


Figure 3 – RNFL thickness analysis

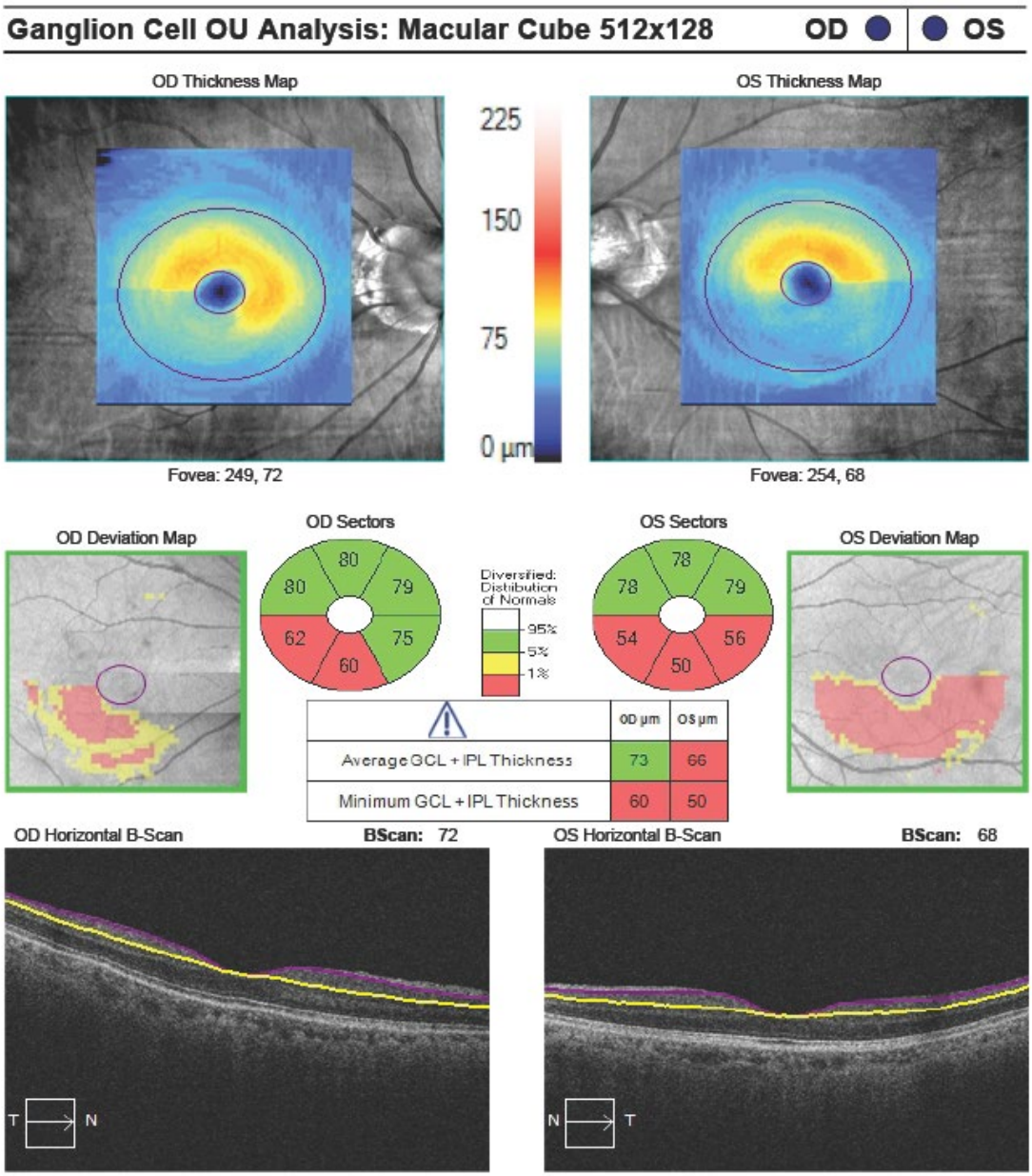


Figure 4 – GCC OCT analysis

Question 1: Describe this patient's optic discs and visual fields

Answer 1

The optic nerve photographs show large, tilted discs with large, deep cups. Both discs have superior thinning of the neuroretinal rim and peripapillary atrophy temporally. The discs have an oval appearance and the optic nerve insertion sites appear to be at an angle. The choroidal vessels appear more prominent due to atrophy of the underlying RPE temporal to the disc. No retinal nerve fibre layer haemorrhages are seen. The cup to disc ratio in both eyes, but particularly in the left, is difficult to determine because of the disc tilt, but also because the

edge of the cup appears to have shallow excavation making it challenging to pinpoint the cup margin.

SITA-Standard 24-2 Humphrey visual fields show reliable tests in both eyes with no fixation losses, and low false positives and false negatives. Gaze tracking shows more movement in the left eye during testing, particularly at the start of the test. In the right eye there is blind spot enlargement and a mean deviation of -2.76 dB. The glaucoma hemifield test is borderline. In the left eyethere is a fairly generalised reduction in sensitivity on the total deviation plot, but on the pattern deviation plot, there is a localised paracentral defect just superior temporal to fixation. The mean deviation is -4.81 dB in the left eye, and the glaucoma hemifield test is outside normal limits.

Answer 1 ends

Question 2: Describe this patient's OCT scans

Answer 2

Both the RNFL and GCC scans are of high signal strength, with few artefacts. On close inspection, the RE RNFL scan shows incorrect segmentation of the optic disc, and you can see that part of the area of peripapillary atrophy is included in the disc and cup margins. It is not uncommon to encounter this in patients with tilted, myopic discs, but it does mean that the RNFL sector and clock hour values in the affected regions will be less accurate. Wherever possible, scans should be repeated at the same visit, with the aim of better segmentation. However, in this case, the same issue was encountered, even after multiple scans of the RE. The LE optic nerve head and cup appear appropriately demarcated. The RNFL scan shows significant inter-eye asymmetry, with average thickness 87 μm in the right eye and 74 μm in the left. The right eye RNFL scan appears within normal limits with all quadrants. The left eye RNFL scan confirms thinning of the superior and inferior RNFL, particularly in the inferior portion. When assessing the absolute values of the RNFL clock hour thickness one is able to see a reduction of thickness in the left disc at the 6 o'clock position (value of 71). This is at the lowest end of the distribution of normal (lowest 1% of age-normal values) and is significantly different from the right eye 6 o'clock position (value of 108). There is corresponding thinning of the neuroretinal rim in both the superior and inferior quadrants.

The right eye has GCC thinning in the inferior and inferotemporal sectors. The left eye has significant GCC thinning inferiorly. Myopic patients tend to have thinner macular GCC values. In glaucoma, there is often localised thinning of the GCC with corresponding visual field and RNFL defects. The pattern of GCC thinning tends to respect the horizontal meridian. In this case, the inferior GCC thinning in the left eye, corresponds with the observed superior paracentral defect on visual field testing.

Answer 1 ends

Question 3: What are the proposed IOP-independent mechanisms thought to be involved in NTG and what are the recognised risk factors?

Answer 3

Proposed IOP-independent mechanisms include vascular insufficiency at the optic nerve head, metabolic and neurodegenerative disorders, oxidative stress, and abnormal biomechanics of the lamina cribrosa. Genetics is known to play a role because of the strong association with family history and variation in prevalence in different ethnicities that persists after migration.

- Age
- Family history
- Female gender
- Thin central corneal thickness
- Systemic hypertension
- Nocturnal hypotension
- Migraine
- Raynaud's phenomenon
- Obstructive sleep apnea

Answer 3 ends

Question 4: Name six conditions that will be in the differential diagnosis of a patient with normal tension glaucoma?

- Compressive optic neuropathy
- Previous IOP spikes that caused glaucomatous optic neuropathy but have now resolved – past iritis or steroid-induced glaucoma
- Wide diurnal fluctuation
- Dominant optic atrophy
- Past history of trauma, surgery, haemodynamic crisis
- Primary open angle glaucoma with falsely low IOP due to thin cornea: previous LASIK or keratoconus

Answer 4 ends

Question 5: Describe two in-office methods for identifying IOP variations.

Answer 5

IOP may fluctuate over a 24-hour period and often patients with 'normal tension glaucoma' have undiagnosed spikes of higher IOP.

Most IOP measurements are undertaken during office hours at a single point in a day. It is therefore possible that this measurement is not at a time of a patient's peak IOP.

Two methods of identifying IOP variations are:

1. The water drinking test. The patient consumes 1 litre of water over a 15 minute period and IOP is measured at baseline and every 15 minutes for 1 hour. This method has been shown to correlate with diurnal IOP variations.
2. Multiple measurements of a patient's IOP over the course of a day to give a better idea of the diurnal IOP variation. This does not include supine or nighttime measurements and therefore IOP spikes may be missed.

Answer 5 ends

Question 6: Please describe the significance of optic nerve head haemorrhage in patients with glaucoma.

Answer 6

The presence of a RNFL haemorrhage at the optic disc, also known as a Drance haemorrhage, has been classically associated with normal tension glaucoma, however, this finding can be present in any form of glaucoma.

The presence of an optic disc haemorrhage is a negative prognostic indicator.
The Collaborative Normal Tension Glaucoma Study group found that the risk of glaucomatous visual field progression was higher in patients with optic disc haemorrhage who were not on intraocular pressure lowering therapy. Anderson *et al* reported the presence of optic disc haemorrhages at the time of diagnosis of NTG as an unfavourable prognostic marker for likely visual field progression.

The Collaborative Normal Tension Glaucoma Study (CNTGS) used the presence of a disc haemorrhage as one criteria for initiation of treatment in patients with NTG. It should be noted that the CNTGS was undertaken prior to the advent of OCT testing in glaucoma.

Answer 6 ends

Question 7: Describe the role of neuroimaging in glaucoma

Answer 7

The appearance of glaucomatous change in the optic nerve head does not necessitate imaging if other features such as raised IOP, visual field changes that match the optic disc appearance, and absence of other focal afferent visual system dysfunction are present.

Neuroimaging should be undertaken in any patient suspected of having NTG with the following signs:

- Optic nerve pallor in excess of cupping
- Visual field defects not corresponding to optic nerve damage
- Unexplained visual acuity loss
- Acquired colour vision deficit
- Atypical neurological symptoms for glaucoma
- Age less than 50 years
- Marked asymmetry of optic nerves without clear history of secondary glaucoma (such as trauma)

Answer 7 ends

Question 8: How does the family history of glaucoma influence clinical management?

Answer 8

A positive family history is a strong risk factor for POAG. In a Dutch cohort, glaucoma was identified in 10.4% of the siblings of glaucoma patients, while 0.7% of the siblings of control subjects had glaucoma (Wolfs et al. 1998). The first-degree relatives of glaucoma patients in this study showed significantly higher lifetime risk of elevated IOP (42.5% vs 6.7%), large CDR (62.2% vs 16.6%) and developing glaucoma (22% vs 2.3%), compared to the first-degree relatives of control subjects. In an Australasian study, more than half of patients with advanced POAG had a positive family history, and those with a family history presented at a significantly younger age compared to those without (mean age at presentation 54.7 years vs 63 years) (Souzeau *et al.* 2012).

Common adult-onset types of glaucoma, namely POAG and NTG, exhibit a complex inheritance pattern that does not obey Mendelian laws of inheritance. Interaction of multiple genes and environmental factors likely determines the glaucoma phenotype. Recent genome-wide association studies in European and Asian populations identified 16 genes that are significantly associated with POAG and NTG (Wiggs *et al.* 2017). In genome-wide association studies, the entire genome of a patient is screened for small variations called single nucleotide polymorphisms (SNPs). The SNPs that occur more frequently in patients with glaucoma compared to those without glaucoma are mapped to specific gene loci. The genes found to be associated with POAG so far are thought to play roles in cytokine signalling (*CDKN2BAS, TGFBR2, FNDC3B*), lipid metabolism (*ABCA1, CAV1/CAV2, ARHGEF12*), membrane biology (*CAV1/CAV2*), extracellular matrix (*AFAP1*), fructose and mannose metabolism (*GMDS, PMM2*), cell division (*CDKN2BAS, TMCO1, GAS7*) and ocular development (*SIX6*, *FOXC1*). It is unknown how these genes contribute to the pathogenesis of glaucoma.

It is worth noting, however, that negative family history is less helpful in risk prediction. Family members may have undiagnosed glaucoma, or may not always inform the family that they have glaucoma.

Answer 8 ends

Question 9: What is the most commonly recommended treatment for normal tension glaucoma and the mechanism of action?

Answer 9

Prostaglandin analogues are the most commonly used because of their efficacy, minimal side-effects and once a day dosing.

Prostaglandin analogues increase uveoscleral outflow. There is some evidence to support re-modelling of the extracellular matrix of the ciliary muscle causing widening of the connective tissue filled spaces.

Side effects include:

a. Conjunctival hyperemia (reversible) and ocular irritation
b. Peri-orbital pigmentation and darkening of skin (reversible)
c. Periorbital fat atrophy
d. Change of iris colour. In particular green/hazel eyes tend to go brown with time (irreversible). Blue eyes are not affected, and dark brown eyes will not change colour
e. Increase in eyelash growth and thickness
f. Inflammatory effects- should be used with caution in uveitis or complicated cataract surgery as it may worsen the inflammation. It may also increase the incidence of cystoid macular oedema

Question 9 ends

Question 10: Discuss the relationship between corneal thickness and NTG

Answer 10

Corneal pachymetry is used to measure the central corneal thickness (CCT). Reduced CCT is associated with progression risk. Thinner corneas are associated with the underestimation of intraocular pressure using applanation tonometry. However, other factors such as corneal hysteresis also contribute to measurement error in applanation tonometry. There is not a simple conversion calculation to determine IOP at corneal thickness values above or below average.

Answer 10 ends

Question 11: What is the relationship between myopia and glaucoma?

Answer 11

Multiple large-scale epidemiological studies have consistently established myopia as an independent risk factor for POAG (see Marcus *et al.* 2012 for meta-analysis). The risk of developing POAG generally increases with increasing degrees of myopia.

Although the reason for increased risk of glaucoma in myopes is unclear, a prevailing theory concerns a myopic deformation of the lamina cribrosa. Axial elongation causes thinning of lamina cribrosa, greater pore areas, horizontal lamina cribrosa tilting and a range of lamina cribrosa defects, such as surface irregularity, holes, and disinsertions (Sugiyama et al. Chapter 3 Section 2). The lamina cribrosa defects were highly prevalent, and larger in myopic glaucoma patients, compared to those with myopia only (Han et al. 2016). It has been proposed that highly myopic eyes with deformed lamina cribrosa, thin scleral walls and altered elasticity may render them intolerant of IOP fluctuations and prone to glaucomatous damage at any given IOP.

The relationship between myopia and IOP is still controversial. Elevated IOP is a well-known risk factor for glaucoma, but there is no consensus regarding high IOP in myopia. Some studies found a significant correlation between IOP and myopic refraction, while others did not (for review, see Hsu *et al.* 2015).

Answer 11 ends

Required Reading

- Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. American Journal of Ophthalmology, 126(4), 487-497.

Selected References

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