Risk Factors for Open Angle Glaucoma

COURSE CODE C-17744 O/D

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Glucoma ranks second amongst causes of certification for sight impairment and severe sight impairment in the UK. Early diagnosis is critical to prevent permanent structural damage and irreversible vision loss. Despite extensive research over many years, the causal events leading to chronic open angle glaucoma (COAG) are not fully understood, and this has contributed to the absence of a universally accepted definition of the disease. A clear understanding of risk factors would promote greater awareness amongst the public and healthcare professions regarding the early recognition of this insidious disease. Much research relating to risk factors has been published over the past decade, and some of the research in this area which is relevant to optometrists in their role in the detection of open angle glaucoma (OAG) is reviewed in this article.

Chronic open angle glaucoma

The European Glaucoma Society defines glaucoma as a group of diseases that result in a progressive optic neuropathy that causes characteristic changes in the optic nerve head and retinal nerve fibre layer. Intraocular pressure (IOP) is no longer included in modern definitions of COAG; instead IOP is now regarded as the major risk factor rather than a defining feature (see later). Most cases of OAG are chronic (COAG), typically with gradual onset. COAG is the term used in the NICE guidelines and includes most cases reported in the research literature as primary OAG. In the present article the authors have attempted to use terminology most appropriate to the papers that are being described. OAG is differentiated from angle closure glaucoma (ACG) by the presence of a normal (open) anterior chamber angle. COAG has an adult onset, is usually bilateral though asymmetric in its progression, and causes no noticeable symptoms in most patients until the later stages of the disease when patients lose their central vision. OAG is treatable but because the visual impairment is irreversible, early detection is essential.

Progressive optic neuropathy

An optic neuropathy is characterised by a chronic, slowly progressive loss of retinal ganglion cells and their neurons. Glaucomatous optic neuropathy is associated with remodelling of the optic nerve and retina leading to two characteristic signs encountered in practice: optic nerve head cupping (Figure 1), with a concurrent decrease in the area of the neuro-retinal rim, and visual field defects (Figure 2).

The pathophysiology of glaucomatous neurodegeneration is not fully understood. IOP remains an important primary and prognostic risk factor for OAG but other IOP-independent risk factors may also be involved, especially when optic nerve fibre sensitivity to damage is considered in cases where the IOP is in the ‘normal’ range.

Demographic and genetic risk factors

Age & Race

With increasing age both the incidence and prevalence of OAG also increase. Le et al. reported a significantly higher risk of OAG after 60 years of age and that this risk increased with each subsequent decade of life. The Barbados Eye Study evaluated the risk factors for OAG in a sample of people of African-Caribbean descent and found that the risk more than doubles after the age of 60 years compared with the 40-49 year age group. It has been proposed that optic nerve head damage due to increasing age may reflect the cumulative effects of other factors, making the optic nerve head more vulnerable to IOP, even if IOP is in the ‘normal’ range.

A consistent finding across many studies is that people who are of African-Caribbean descent are more likely to have OAG than people from other ethnic groups. This increased risk may be the result of multiple other contributing factors. Boland and Quigley suggest three main possible factors. Firstly,
the larger optic disc sizes found in those of African-Caribbean origin are theoretically less able to withstand the deformation of the disc in glaucoma that can lead to nerve fibre death. However, there is a potential compensating factor because large optic discs tend to have more optic nerve fibres, giving them some nerve fibres in reserve i.e. more nerve fibres have to be lost before there is significant loss of visual function. But those of African origin with large discs have fewer nerve fibres than Europeans with large discs of the same size. Therefore those of African ethnicity have the biomechanical disadvantage of having a large disc in combination with having a lower reserve number of nerve fibres than those of other ethnicities with large discs. Secondly, there is evidence that the thinner corneas found in people of African-Caribbean origin may also increase their risk of developing glaucoma (see below). Thirdly, Boland and Quigley note that in the United States, people of African descent have less access to eye care and are less aware of the risks of OAG. In the UK, qualitative research among African-Caribbean subjects who were not receiving treatment from the hospital eye service has revealed that although the subjects had positive attitudes to health promotion in general, these positive attitudes did not extend to eye health.17

Interestingly, although the average prevalence of OAG at all ages is higher in African-Caribbean populations than in Caucasian or Asian populations, the rate of increase with age is highest in Caucasian populations, in whom the prevalence of OAG doubles per decade.18

**Gender**

There has been controversy over the question of whether there is a gender difference in the prevalence of COAG.19 Some studies have reported a higher prevalence of OAG in men,19 whilst others have reported a higher prevalence in women;20 and some have found no significant difference between genders.21 Individual studies are most unlikely to have a sufficiently large sample size to detect a statistically significant difference between genders, and this could be one of the reasons for the controversy. In their meta-analysis, Rudnicka et al.18 pooled together data from many different studies, which allowed them to determine any gender effect with greater statistical certainty. They established that COAG prevalence in men was approximately 1.4x higher than in women and this increased prevalence was consistent across all racial groups.

**Family History**

The relative risk of developing OAG has been estimated to be more than 10x higher if a first degree relative is diagnosed with the condition.22 In an African-Caribbean population study, 10% of living relatives of those diagnosed with OAG also had the disease, and a further 13% probably had OAG.23 A positive family history of OAG is a complex risk factor as no single Mendelian mode of inheritance has adequately described the development of glaucoma. The chromosomal locations of several genes, notably optineurin (OPTN) and myocilin (MYOC), that can independently cause the disease have been mapped, indicating that a proportion of cases of glaucoma is caused by single gene defects.10,6 The complexity of glaucoma as a disease makes it likely that in many cases multiple genes may be acting to cause the condition and that interaction between these genes may account for the variations in the condition between individuals (e.g. variation between individuals in the susceptibility of the optic nerve head to damage).24

**Ocular anatomy & physiology**

**Intraocular pressure**

Raised IOP was for many years considered to be a diagnostic feature of OAG, but has now been shown to be a modifiable risk factor.25 It is the only risk factor that is modifiable with medication or surgery.26 Studies have shown that the higher the IOP at presentation, the greater the risk of developing OAG.27 Sommer has stated that there is no single level of IOP above which OAG can be said to always develop and there is no lower level below which OAG never develops.27 The often quoted figure of 21mmHg as being the upper limit of “normal” IOP was derived statistically as being two standard deviations above the population mean of around 16mmHg (in a European population).28 However
OAG frequently occurs at levels of IOP below 21mmHg and is often referred to as normal tension glaucoma (NTG), although Spry and Harper note that this division of COAG into NTG and those with IOPs greater than 21mmHg (sometimes referred to as High Tension Glaucoma) is regarded by many as an arbitrary one, with both types of glaucoma being part of the spectrum of the disease.20 The effectiveness of significant IOP-lowering treatment has been established for NTG, with the Collaborative Normal-Tension Glaucoma Study Group (NTGS) reporting that lowering IOP by 30% from baseline can be effective in decreasing the rate of visual field loss in normal tension glaucoma.30,31,32 The Early Manifest Glaucoma Treatment Study (EMGTS) lowered IOP by an average of 25% in a patient sample that contained patients with baseline pressures of up to 29mmHg. The EMGTS demonstrated that IOP-lowering treatment significantly delayed progression in patients with NTG and in those with higher IOPs.33

Pseudoexfoliation/Exfoliation syndrome & pigment dispersion syndrome

Pseudoexfoliation syndrome and pigment dispersion syndrome (Figure 3) are risk factors for the forms of OAG known as pseudoexfoliative and pigmentary glaucoma, respectively. They are usually classified as secondary glaucomas but the NICE glaucoma guideline includes both these types of glaucoma under their definition of COAG, so they have been considered in this article for completeness.24 In both conditions elevated IOP occurs due to obstruction of aqueous outflow at the trabecular meshwork, caused by an accumulation of abnormal fibrillar extracellular material (pseudoexfoliative glaucoma) or iris pigmented epithelial cells (pigmentary glaucoma).6,25 The probability of converting to pigmentary glaucoma from pigment dispersion syndrome has been estimated at 10% after 5 years rising to 15% at 15 years.26 For those with pseudoexfoliation syndrome approximately 25% of patients will have raised IOP as a result of the syndrome, with around one third of these developing glaucoma.25

Central corneal thickness

It is well known that central corneal thickness (CCT) affects the estimate of IOP using an applanation tonometer. In a patient with a thicker than average CCT, applanation tonometry will overestimate the true IOP while, conversely, in a patient with a thinner than average CCT, applanation tonometry will underestimate the true IOP.25 It has been postulated that patients with thinner than average CCTs are more likely to develop optic nerve damage before it is detected.6 The European Glaucoma Society report notes that CCT measurements are required for the management of ocular hypertension (OHT).7 and CCT measurement is an integral part of the NICE Clinical Guideline for diagnosis and monitoring of OHT.7 The Ocular Hypertension Treatment Study identified CCT as the best predictor for conversion of their subjects to OAG.25 All these findings strongly suggest that pachymetry has an important role to play in glaucoma case finding in community optometric practice. CCT is subject to racial variations and is thinner in African-derived populations.36

Optic disc features & myopia

Optic disc diameter was identified as a risk factor for OAG in two population studies involving those of both Caucasian39 and African descent.40 A large study involving over 3000 subjects compared optic disc size in the eyes of those classified as normal to those with OAG, OHT, or pseudoexfoliation syndrome. The mean optic disc diameter in glaucomatous eyes was significantly larger than in normal eyes, eyes with OHT, and eyes with pseudoexfoliation syndrome, leading to the conclusion that patients with glaucoma have larger optic discs than non-glaucomatous subjects.41 Eyes with large optic disc diameters tend to have high C/D ratios and several studies have suggested that a vertical C/D ratio of greater than 0.6 and/or asymmetry between right and left eyes in optic disc cupping gives an increased risk for developing glaucomatosus visual field loss.42,43 The large optic disc sizes found in myopia might be explained, in part, by stretching of the eye, and therefore a deformation of the lamina cribrosa. It can be hypothesized that the deformation and thinning of the lamina cribrosa in highly myopic eyes is similar to that which occurs in the lamina cribrosa in OAG.44 How this influences the risk of developing OAG is still unclear. Jonas and Budde45 suggested that there may be a higher susceptibility for optic nerve fibre loss in highly myopic glaucomatous eyes (eyes with more than 8.00D of
myopia) than in non-highly myopic eyes with glaucoma. The two groups had been adjusted for optic disc area and there was no significant IOP difference between the two groups. Population-based studies, including the Blue Mountains Eye Study and the Barbados Eye Study, have found an association between myopia and OAG. A recent meta-analysis showed that individuals with myopia have approximately twice the risk of developing OAG in comparison to individuals without myopia.44

Hypertension, diabetes, thyroid disease, and vascular regulatory disorders (e.g. cold extremities, migraine and Raynaud’s phenomenon - discolouration of fingers and toes after exposure to heat or cold) are common presentations in optometric practice and all have been linked to OAG development in some studies, although the research evidence is often contradictory.31 The effects of these systemic diseases on glaucoma relate mainly to the vascular theory of development of OAG. In the vascular theory, low blood pressure particularly when combined with elevated IOP can reduce the perfusion pressure at the optic nerve head. This can result in ischaemic damage to the retinal ganglion cells. However, there is also a risk of OAG from chronically elevated blood pressure because increased peripheral resistance and small-vessel disease can also reduce perfusion of the optic nerve head.44 Clearly, the relationship between vascular hypertension and glaucoma is complex, and some studies of vascular hypertension have suggested that there is no increased risk of OAG50 but others have shown that years of exposure to vascular hypertension is an important consideration for OAG development.6

There is increasing evidence that low blood pressure and reduced ocular perfusion pressure at the optic nerve head does increase the risk of OAG.6,49 The relationship between diabetes and OAG is also far from clear. A recent review by Wong et al. tabulated the outcome of 18 epidemiological trials that have investigated a possible association between the two diseases.52 There was an association between OAG and diabetes in 7 trials and no association in 11. The authors noted that this lack of agreement was not surprising given the varied definitions of glaucoma, different methods of classifying subjects as diabetic, varying statistical analyses, and inadequate sample sizes in some studies. While the epidemiological evidence for an association between OAG and diabetes remains controversial, this paper concluded that laboratory research provides good evidence for an association between diabetes and glaucoma. Based on this evidence it seems prudent for optometrists to have an increased suspicion of glaucoma in patients with diabetes.

There is emerging evidence of a moderate association between vascular deregulation (or vasospasm) and OAG.52 Vascular deregulation can be defined as a situation where blood flow to specific body tissues is insufficient. It is associated with a number of conditions, including migraine, and Raynaud’s phenomenon. More research is needed to make this association definitive but again the presence of migraine in a patient should alert the practitioner to the possibility that this patient could be at increased risk of OAG. There may also be an increased risk of glaucoma in patients with thyroid disease. The association is well-known if the thyroid disease leads to orbital compression but is much less clear cut otherwise.6 A population based study has identified thyroid eye disease as a possible risk factor, having found an association between glaucoma and thyroid disease, especially in people receiving thyroxine treatment for hypothyroidism.53 However, the researchers noted that further evaluation of this possible association was required.

**Lifestyle**

Exercise has been shown to lower IOP by an average of 20% in a study on a small sample of sedentary adults with OHT.54 Although maintaining a healthy body mass index (BMI) is important for general health, a large retrospective study found that the incidence of OAG was significantly lower in women with a higher BMI.55 This finding was confirmed in recent research in which women with high BMIs had higher IOPs, yet were less likely to develop glaucoma than those with lower BMIs.56 Smoking, alcohol and caffeine consumption have no clear associations with OAG.50, 57, 58, 59

**Conclusion**

The most important risk factors for OAG are elevated IOP, increasing age, family history, race and myopia. For the community optometrist involved in the difficult decision of whether to refer a patient for suspect glaucoma (or whether to repeat measurements of IOP or perimetry to inform the decision of whether to refer) the consideration of risk factors can play a crucial role in the decision-making process. Risk factors should, of course, always be considered alongside the clinical examination for signs of OAG, which has traditionally focussed on assessment of the optic nerve head, IOP measurement, and perimetry. Recent innovations in diagnostic technology, such as optical coherence tomography (OCT) and dynamic contour tonometry, bring exciting prospects of improved detection of glaucoma within reach of the community optometrist. Further research into glaucoma risk factors will increase our knowledge of an individual patient’s personal risk profile for the disease.
Improved technology for glaucoma detection, in combination with better risk profiling of the patient and a better understanding of the disease process, should aid optometrists in the crucial role they play in glaucoma detection.

### About the Authors
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### References
See http://www.optometry.co.uk clinical/index. Click on the article title and then download “references”.

### Module questions Course code: C-17744 O/D

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1. The rate of increase in prevalence of OAG with age:
   - a) Is highest in Caucasians
   - b) Is highest in African-Caribbeans
   - c) Is not dependent on ethnicity
   - d) Is a purely coincidental finding

2. Regarding the influence of gender on the prevalence of OAG:
   - a) Most research studies have reported similar findings
   - b) There is no difference between males and females
   - c) Females are 1.4x more likely to develop OAG than males
   - d) Males are 1.4x more likely to develop OAG than females

3. Goldmann tonometry:
   - a) Underestimates true IOP in thinner than average corneas
   - b) Underestimates true IOP in thicker than average corneas
   - c) Overestimates true IOP in thinner than average corneas
   - d) Is not dependent on central corneal thickness

4. The incidence of OAG:
   - a) Is lower in women with a low BMI
   - b) Is lower in women with a high BMI
   - c) Is higher in women with a high BMI
   - d) Is not related to BMI

5. Considering the ocular and systemic risk factors for OAG:
   - a) There is no association with diabetes
   - b) There is no association with migraine
   - c) Myopes have moderately increased risk compared with hyperopes
   - d) There is a moderately reduced risk in smokers

6. With regards to OAG:
   - a) It is the most common cause of severe sight impairment registration in the UK
   - b) Inheritance is likely to involve one gene in most cases
   - c) Eyes with larger than average optic disc diameters are at greater risk
   - d) Increased ocular perfusion pressure at the optic nerve head increases OAG risk