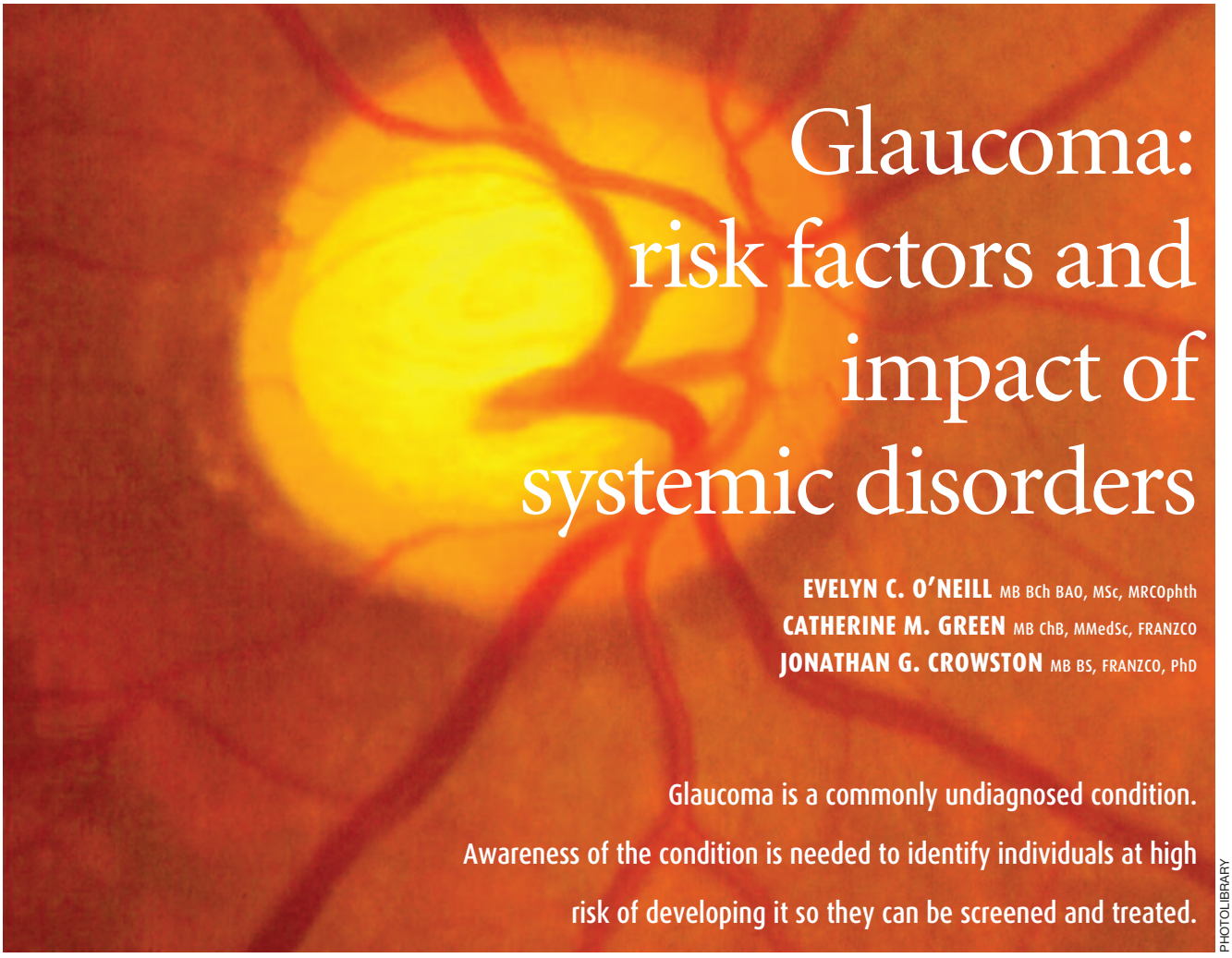

Glaucoma: risk factors and impact of systemic disorders

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Glaucoma is a commonly undiagnosed condition. Awareness of the condition is needed to identify individuals at high risk of developing it so they can be screened and treated.

PHOTOLIBRARY

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Glaucoma is the most prevalent optic neuropathy, affecting an estimated 70 million people worldwide.[1] The most common form of glaucoma is primary open-angle glaucoma (POAG),[1] which is an asymptomatic chronic condition that progresses silently until it affects central vision in the advanced stages of the disease. At least 50% of patients with glaucoma in Europe, the USA and Australia remain undiagnosed, with rates approaching 90% in developing countries.[2-4] Widespread population-based screening for glaucoma is not thought to be cost-effective or efficient. However, improved awareness of the condition and case detection through screening of high-risk individuals has been shown to be beneficial.[5,6]

Increased awareness of the disease and the risk factors associated with its development and progression are needed to enable the identification of people at risk who require screening. The aim of this review is to highlight the features that may alert physicians to the patients at higher risk of POAG and the systemic considerations that should be taken into account in patients with glaucoma.

General risk factors

The most important risk factors for developing glaucoma are increasing age,[7-10] increased intraocular pressure (IOP),[8-10] a

positive family history of glaucoma[8-10,11,12] and race.[9,13,14]

Advancing age is a well-known risk factor for all forms of glaucoma and the prevalence of glaucoma increases significantly with increasing age.[7-9,15-19] The pathophysiology that predisposes the ageing optic nerve to glaucoma is not fully understood. However, increased vulnerability to injury through mitochondrial dysfunction,[20,21] alterations in optic nerve head biomechanics and impaired autoregulation of optic nerve head blood flow may all contribute in certain individuals. It has also been shown that independent of other factors IOP increases with age.[22] Owing to a rapidly ageing population, the number of patients with POAG is expected to rise considerably over the coming decades.

Raised IOP is a well-known risk factor for glaucoma development and progression. A 1 mmHg increase in IOP at baseline compared with the average for the general population confers a 10 to 14% increased risk across a population for developing POAG.[8,10,17,21] Increased IOP remains the most important modifiable risk factor for POAG.

A positive family history of glaucoma increases the overall risk of a first-degree relative developing POAG by three to ninefold, highlighting the need for first-degree relatives of patients with glaucoma to seek regular optic nerve assessment.[11,12,23,24] Multiple genes associated with glaucoma have now been identified. The first of these was the *myocilin* (*MYOC*) gene; however, the full genetic component of POAG remains to be determined.

Race plays an important role in the development of glaucoma, with African, Caribbean and Hispanic/Latino descendants having significantly higher prevalences of POAG.[9,13,14] It is becoming increasingly apparent that POAG is, in most cases, inherited as a complex trait, where the disease results from the interaction of multiple genes and environmental factors.[23]

Comorbidities and systemic considerations

Multiple common systemic conditions and medications have been associated with an increased risk of glaucoma development and progression. However, in some circumstances the relation remains unclear. It is important for physicians to be aware of which patients may be at increased risk of developing glaucoma and therefore warrant screening.

Cardiovascular disease

Generalised cardiovascular disease and systemic hypertension have been shown to be associated with an increased risk of glaucoma development and progression.[7,17,25-35] The pathogenesis is postulated to be due to both increased IOP secondary to systemic hypertension and increased vascular resistance as a result of the hypertension. However, studies continue to show conflicting evidence and the progression of glaucoma may be due to nocturnal hypotension and reduced ocular perfusion pressure in patients with treated hypertension.[31,33,36]

Systemic hypotension, due to the resultant reduced ocular perfusion pressure, significantly increases the risk of glaucoma development and progression, particularly normal-tension glaucoma,[9,26,31,37,38] which is thought to be due to a reduced ocular perfusion pressure. Ocular perfusion pressure (systolic/diastolic) is calculated as blood pressure minus IOP.

Both systolic and diastolic ocular perfusion pressures have been implicated in the onset and progression of normal-tension glaucoma. Earlier studies found that when diastolic perfusion pressure was below 55 mmHg the risk of glaucoma development and progression was significantly increased.[17,27,32,33] More recently, systolic perfusion pressure has been shown to significantly affect the progression of glaucoma, suggesting that in patients with lower baseline systolic perfusion pressures the condition progresses more rapidly than in their counterparts with normal pressures.[26]

The significance of large noctural dips in blood pressure remains to be elucidated but it is thought to be a cause of glaucoma in some cases.[38] As such, it is important for GPs to consider the potential effect that antihypertensive drugs will have on the ocular perfusion pressures of patients with glaucoma or suspected glaucoma. Close monitoring of blood pressure-lowering agents is needed in these patients to ensure blood pressure is not reduced excessively.

Vasospastic tendencies such as migraine headaches, peripheral vasospasm, Raynaud's phenomenon and cold hands and feet have also been implicated in increasing the incidence and prevalence of certain subgroups of patients with glaucoma.[25,39,40] These tendencies play a greater role in patients with normal-tension glaucoma than in those with POAG. Previous haemodynamic shock or substantial blood loss requiring transfusion is an important risk factor for the progression of glaucoma, particularly in patients with normal-tension glaucoma.

Endocrine disease

Both diabetes and thyroid dysfunction have been implicated in the development and progression of glaucoma. The relation between diabetes and POAG is unclear. Diabetes, particularly late-onset type 2 diabetes and poorly controlled diabetes, is thought to increase the risk of POAG.[41,42] It has also been shown that patients with glaucoma and diabetes tend to have slightly higher IOP, even when treated, when compared with those without diabetes.[42] However, the evidence is inconclusive with other studies disputing the association.[43] In contrast, it is well known that diabetes, particularly poorly controlled diabetes and diabetes of longer duration, cause retinal ischaemia and neovascularisation, which can result in neovascular glaucoma. The incidence and prevalence of diabetes is rapidly increasing and therefore the incidence of neovascular glaucoma is expected to increase concurrently.

Thyroid dysfunction, both hypothyroidism and Graves' disease with its associated hyperthyroidism and thyroid eye disease, have been linked to the development of glaucoma. However, the evidence is conflicting. Studies have shown hypothyroidism increases the risk of developing POAG,[44,45] but other studies have disputed this.[46] Additionally, a significant relation has been demonstrated between POAG and Graves' disease and its associated thyroid eye disease, with a higher prevalence of POAG and ocular hypertension in patients with thyroid eye disease secondary to Graves' disease.[47] It is also thought that the longer the duration of active thyroid eye disease then the greater the risk of developing POAG.

Medications

Current and previous medication use should be reviewed in any patient with a potential risk of developing glaucoma. Medications can be subdivided into those that may increase a patient's risk of developing glaucoma and those that may mask an elevated IOP in an at-risk individual. It is well recognised that local ocular (topical and intravitreal), inhalant and systemic corticosteroid use increases the risk of ocular hypertension and glaucoma development.[48-50]

Estimates suggest that between 18 and 36% of the general population are responsive to corticosteroids and this increases significantly in those with known POAG (between 46 and 92%). Elevation in IOP usually occurs within two to four weeks of commencing corticosteroids; however, late onset increases in IOP and prolonged increases in IOP following discontinuation have been reported. The mechanism is thought to be due to impaired aqueous drainage.[50,51]

Less commonly used but important to note are the anticancer drugs docetaxel and paclitaxel, which have both been reported to induce glaucomatous optic neuropathies in patients.[50] Drugs such as systemic beta-blockers (e.g. propranolol) may mask an elevated IOP and their use must always be reviewed.

Several medications are known to increase the risk of acute angle-closure glaucoma (such as adrenergic agonists, cholinergic and anticholinergic agents, sulfa-based drugs, selective serotonin reuptake inhibitors and both histamine H1 and H2 receptor antagonists). However, a detailed discussion of these medications is outside the scope of this review.[50]

Lifestyle

Several lifestyle factors have been associated with the potential to increase IOP and therefore the risk of glaucomatous optic nerve damage. These include:

- large volume rapid fluid intake, which has been shown to increase IOP
- playing high- and low-resistance wind instruments, which causes transient increases in IOP, that over time can cause visual field loss and glaucomatous optic nerve damage[52]
- certain exercises, particularly head down yoga postures, which have been shown to double IOP.[53]

It is important to note that other factors such as dehydration and acidosis following exercise and use of alcohol and marijuana can transiently decrease IOP. Finally, factors such as smoking must also be considered. It is thought that current smoking may increase the risk of developing POAG; however, the evidence is still conflicting.

Miscellaneous systemic considerations

Although not causal of glaucoma, conditions such as asthma, chronic obstructive airways disease, heart block and heart failure must be taken into account in a patient with glaucoma or suspected glaucoma because they will limit the use of topical beta-blockers (e.g. betaxolol, timolol) in treatment. Use of antidepressant medications (e.g. the monoamine oxidase inhibitors) must also be considered because they preclude alpha-agonist (e.g. apraclonidine, brimonidine) use.

In subjects with visual field defects but lacking other features of glaucomatous optic neuropathy, causes such as pituitary tumours and medication-induced visual field defects (e.g. from anticonvulsants, vigabatrin) must be considered and excluded. Finally, a previous history of stroke, tumours of the central nervous system, head injuries, neurosurgery, dementia and/or depression must always be noted because they may affect the patients' monitoring of the condition and compliance with treatment.

Conclusion

POAG is a chronic, generally asymptomatic condition. Although screening is not justified on a wide scale, screening of those at higher risk is almost certainly beneficial. Some of the well-known risk factors and some of the less established risk factors have been discussed. Patients at high risk should be referred to an eye care professional (optometrist or ophthalmologist) for screening. Close collaboration between optometrists and ophthalmologists is essential to provide an optimal environment for the diagnosis of glaucoma. There is no published data regarding management of patients with glaucoma by optometrists beyond the initial diagnosis and commencement of medical therapy beyond which care should be with an ophthalmologist. Co-existent or previous medical conditions often make long-term assessment of these patients difficult. MT

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A list of references is available on request to the editorial office.

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