

## A REVIEW OF THE RISK FACTORS IN PRIMARY OPEN ANGLE GLAUCOMA

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### ABSTRACT

The aetiology of primary open-angle glaucoma is still uncertain. However certain factors are known or suspected of having an aetiological role. These are known as the risk factors. These include higher intraocular pressures, black race, old age especially after the age of 40 years, the peculiar larger optic disc structure of black people, a positive family history, vascular factors such as systemic hypertension, perfusion pressure, vasospasm, atherosclerosis and acute hypotension which is a risk factor for normal-tension glaucoma. Others are diabetes, which is prone to selection bias, myopia, a history of typical migraine headaches, thinner central corneal thickness and the ability to taste phenylthiourea. If a particular patient is identified as having one or more of these risk factors, that patient is by definition, at greater risk of developing glaucoma than a patient who does not.

Key words: **Glaucoma, risk, factors, aetiology.**

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### INTRODUCTION

If there is any controversial subject in medicine, it is GLAUCOMA. We can't define it; we can't cure it.<sup>1</sup> Most aspects of glaucoma remain a matter of debate and research. The definition, aetiology, diagnostic criteria and choice of therapy in primary open-angle glaucoma are still debatable. This paper will concentrate on the risk factors for the development of glaucoma. Some authors define risk factors broadly to include any characteristic that suggests that a particular patient is at increased risk of developing glaucoma, even if that factor is likely to be an early manifestation of the disease. In this review, its meaning is reserved to parameters associated with glaucoma which are either known or suspected of having an aetiological role.<sup>2</sup>

### Risk Factors

**Intraocular pressure:-** Optic nerve damage and increased intraocular pressure have been inexorably linked in what is generally assumed to be a cause and effect relationship. Even when this relationship has failed to occur, terminologies such as 'low tension glaucoma' for glaucomatous optic nerve damage in the absence of increased intraocular pressure and 'ocular hypertension' for increased intraocular pressure in the absence of glaucomatous optic nerve damage have been used. There are a lot of arguments for and against. However, it has been observed that if one of two eyes has glaucomatous optic nerve

damage, almost invariably, it is the eye with higher intraocular pressure.<sup>3</sup> Practical examples occur in cases of secondary glaucoma.

The Baltimore Eye Survey (BES)<sup>2,4</sup> has helped to confirm that the higher the intraocular pressure, the greater the risk of glaucoma although the relationship is not strictly linear. While 21mmHg has been the traditional cut-off level, when measured by applanation tonometry, with levels above it being regarded as abnormally high, it must be noted the 21mmHg is actually a statistical construct of normality. It was meant to represent 2 standard deviations above the mean intraocular pressure, which is approximately 16mmHg in the normal population.<sup>1</sup> Thus, 21mmHg was chosen because it made the search for glaucomatous optic nerve damage more efficient, not because it defined what was abnormal.<sup>3</sup> Recent population-based studies in different countries and in populations of different racial composition have shown the increased prevalence of glaucoma associated with increasing intraocular pressure.<sup>4,5</sup>

An interesting way to conclude is to consider these statements by Anderson.<sup>6</sup> "We are convinced that intraocular pressure is a causative risk factor, not just a correlating factor. We need not be confused by the occurrence of normal-tension glaucoma or the so-called ocular hypertension. These cases simply exemplify that a small proportion of the population is harmed by normal intraocular pressure (because the risk of damage at normal pressure is not as low as 0%) and that certain proportion of the population is unharmed at high intraocular pressure (because the risk of damage at this pressure is not 100%). It is indeed these non-concordant cases that remind us that intraocular pressure is only one risk factor and not the entire story."

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**Race:-** Several population based studies<sup>7,8</sup> have helped to confirm that the risk of glaucoma is several times higher in black than in white populations despite the fact that intraocular pressures are similar for both population groups and so does not contribute to the racial variation. African-Americans are at three to six times greater risk of developing glaucoma<sup>7</sup> and glaucoma blindness<sup>5</sup> than are white individuals. The exact reason for this is not known. There are however known differences in the organization of the optic nerve and the rates of hypertension in the two groups that may help explain at least some of this racial variation in risk.<sup>2</sup>

**Optic Disc Structure:-** The BES showed that blacks have larger optic discs, larger scleral openings and larger cups than whites.<sup>9,10</sup> Blacks were also more likely to have a smaller neuroretinal rim area per disc area than are whites. Presumably, the larger scleral opening results in the same intrinsic number of optic nerve axons being splayed out over a larger disc periphery, resulting in black individuals having larger cups but the same neuroretinal nerve area as white individuals. As the disc increases in size in normal individuals, the retinal rim area, thought to be the best index of the number of optic nerve axons, increases as well; but the increase is greater in white individuals than in blacks, suggesting blacks may have disproportionately fewer axons, for each size disc than whites.<sup>1</sup> The discs of blacks and whites differ in their relationship to intraocular pressure. Among 'normal' white subjects in the Baltimore Eye Survey, there is a monotonic (almost linear) reduction in neuroretinal rim area with increasing intraocular pressure. Among black subjects, the relationship is more complex, suggesting a threshold effect.<sup>9</sup> This might account for at least part of the increased risk of damage among blacks.

**Age:-** Several population based studies show a rapid rise in prevalence of glaucoma for both black and white races after the age of 40 years.<sup>5,7,8</sup> What is not clear however is whether older individuals have more vulnerable optic nerves or they have simply suffered more frequent and prolonged insults over their lifetime. Both mechanisms may however play a role.<sup>12</sup> It may reflect cumulative damage to the optic nerve that fails to become clinically apparent until such a time as a critical proportion of axons have been lost (variously estimated at 30% to 50%).

**Family History:-** Positive family histories have been reported in 13% to 25% of glaucoma cases.<sup>11,12</sup> This is 5 to 20 times higher than population prevalence rates. The BES has helped to confirm that family history is an important risk factor for open angle glaucoma.<sup>13</sup> Autosomal recessive, autosomal dominant and sex-linked pedigrees have been described.<sup>14</sup> Oligogenic, polygenic or multifactorial mechanisms have also been proposed.<sup>14</sup>

The juvenile primary open-angle glaucoma gene on chromosome 1q has been identified, while loci for adult primary open-angle glaucoma have been described in chromosomes 1,2 and 3 and termed GLC1A, GLC1B and GLC1C.<sup>14</sup>

**Systemic Hypertension and Perfusion Pressure:** Systemic hypertension, vasospasm, atherosclerosis, and acute hypotension have all been listed as potential factors that may affect the risk of glaucoma.<sup>15,16,17</sup> Despite the biologic rationale for a causal link between these vascular risk factors and glaucoma, the epidemiologic evidence is inconsistent and difficult to interpret. Most of the earlier studies have been clinic based and may suffer from problems of selection bias. Considerable attention has been paid to haemodynamic crises and related, dramatic drops in blood pressure, particularly as a potential causative factor in normal tension glaucoma. Like many studies before it, the BES only showed a modest positive association between systolic and diastolic blood pressure on one hand and primary open angle glaucoma on the other.<sup>18</sup> When age was corrected for, a stronger association was found among older people. Lower perfusion pressure (blood pressure-intraocular pressure) was strongly associated with an increased prevalence of primary open-angle glaucoma.<sup>18</sup> In addition, the risk of glaucoma rose with increasing (diastolic or systolic) hypertension.

**Diabetes:-** Diabetes has been a recognized risk factor for primary open-angle glaucoma patients.<sup>19</sup> There are a number of studies that show no association as well.<sup>20</sup> The Beaver Dam Study concluded that primary open-angle glaucoma was twice as common among older-onset diabetes than among non diabetic patients.<sup>19</sup> The BES on the other hand failed to provide confirmation that diabetes was a risk factor for glaucoma but provided clues as to how this belief may have arisen.<sup>20</sup> In their study, diabetes was not associated with primary open-angle glaucoma but patients whose glaucoma had been diagnosed before the examination showed a positive association with diabetes indicating that selection bias could explain the positive results of previous clinic-based studies. selection bias could explain the positive results of previous clinic-based studies. Both diabetes and glaucoma are commonly underdiagnosed, a situation that offers the potential for significant selection bias if ascertainment is based only on self-presentation to a clinical facility. The BES relied on the presence of visual field defects for definitive diagnosis unlike the Beaver Dam Study, which diagnosed glaucoma on the basis of an elevated intraocular pressure associated with either disc or visual field criteria. Studies, which include elevated intraocular pressure as part of the diagnosis of glaucoma, make it difficult to separate an association of diabetes with ocular hypertension from an association of diabetes with glaucomatous optic nerve damage.

**Myopia:-** Myopia has been identified as a risk factor for primary open angle glaucoma.<sup>21</sup> Evidence suggests that patients with ocular hypertension and myopia are more likely to develop glaucomatous visual field defects than patients with ocular hypertension and no myopia.<sup>21</sup>

**Phenylthiourea tasting:** Primary open-angle glaucoma has been shown to be associated with genetically determined traits such as phenylthiourea tasting.<sup>22</sup>

**Migraine:** The association between typical migraine headache and open-angle glaucoma has been suggested by several studies.<sup>16,23</sup> The Blue Mountains Eye Study<sup>23</sup> suggested the possibility of an association between a history of typical migraine headache and glaucoma, which could be modified by age. This may be related to the vasospasm, which occurs in migraine.

**Central corneal thickness:** The Ocular Hypertension Treatment Study,<sup>24</sup> using multivariate analyses identified the following prognostic factors leading to glaucoma as follows: increasing age, larger cup-to-disc ratios, higher intraocular pressures, greater pattern standard deviation with Humphrey perimetry, and thinner central corneal thickness. For the first time central corneal thickness was recognized as a risk factor. In conclusion, patients identified as having one or more of these risk factors, are by definition, at greater risk of developing glaucoma than patients who do not.

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