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Laura M. Gianelli
Pacific University

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Abstract

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PRIMARY OPEN-ANGLE GLAUCOMA AND THE ROLE OF OCULAR HYPERTENSION IN EARLY DIAGNOSIS: A LITERATURE REVIEW

By

LAURA M. GIANELLI

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TABLE OF CONTENTS

INTRODUCTION: INCIDENCE AND PREVALENCE

The various forms of glaucoma, statistics reveal, is one of the most common causes of legal blindness and permanent visual impairment. It has been estimated that the prevalence of glaucoma accounts for approximately 14% of all cases of visual impairment in the United States, with over 67,000 individuals legally blind from the disease and about 1 million individuals with permanent visual impairment.[1] There are 5000-6000 new cases of legal blindness reported each year due to glaucoma, and it is estimated that 1.5 million cases remain undiagnosed.[2] Although prevalence studies within general populations differ considerably, primary open-angle glaucoma (POAG) is cleary the most common single form of glaucoma, accounting for about 85% of those individuals diagnosed with some form of glaucoma.[2,6,7]

Early diagnosis is the key to effective management of POAG which can prevent permanent visual impairment. Primary open-angle glaucoma is an insidious disease, and since it doesn't follow a predictable course of symptoms or signs, it can remain undiagnosed. In addition, POAG has been referred to as a "silent disease" because most patients are asymptomatic. Problems with diagnosing this tricky disease include the fact that positive results with many glaucoma detection procedures only indicate the increased suspicion of glaucoma while negative results do not free the patient from suspicion completely.[17] Also, the definition of glaucoma has changed historically as new knowledge of the disease has come forth,

though the etiology is still unknown. The result of this has led to lack of uniformity and confusion in the diagnosis of glaucoma and inherent chaos in the literature on glaucoma.

POAG AND OCULAR HYPERTENSION DEFINED

The definition of glaucoma varies from practitioner to practitioner, but Ajamian suggests a useful working definition: Glaucoma is present in any patient with intraocular pressures (IOPs) that the eye cannot tolerate, causing damage to the optic nerve head and subsequent loss of visual field.[3] Primary glaucomas are not associated with obvious systemic or other ocular disorders that might account for the alteration in the IOP. Primary open-angle glaucoma is typically defined by these three criteria: 1) an IOP consistently above 21 mm Hg in at least one eye; 2) an open, normal appearing anterior chamber angle with no apparent ocular or systemic abnormality that might account for the elevated IOP; and 3) optic nerve head damage with subsequent glaucomatous visual field loss.[20]

Ocular hypertension refers to the condition when the IOP is elevated greater than 21 mm Hg, but there is no damage to the optic nerve or visual field loss. While the use of 21 mm Hg is the clinically accepted upper limit of normal, Colton and Ederer stress the arbitrary nature of specifying upper limits of normality since there is no IOP that can distinguish between normal eyes and those that will become glaucomatous.[5] Ocular hypertensive individuals are termed "glaucoma

suspects" because they are at greater risk for developing glaucoma, since there is a definite correlation between increased IOP and the incidence of glaucoma. Other factors that may indicate glaucoma that relate to the IOP include abnormal difference (asymmetry) of the IOPs between the two eyes, and abnormal diurnal variation of the IOPs.[17]

CORRELATION BETWEEN INCREASED IOP AND THE INCIDENCE OF GLAUCOMA

Armaly did a study of subjects with normal eyes and visual acuity, who had no evidence of glaucomatous damage to the visual field and who could complete an entire battery of tests yearly. He used the development of visual field defects as the studies endpoint. The study found that almost 50% of the individuals who developed open-angle glaucoma had pressure readings of 20 mm Hg or less over a five year period before the onset of the visual field defect. Also shown was that 0.8% of the eyes with less than 16 mm Hg IOPs developed glaucomatous field defects while there was a tenfold increase to 8.4% in the incidence of glaucomatous field defects in the eyes with IOPs greater than or equal to 24 mm Hg.[4] While 8.4% is a small percentage, there is a significant correlation between increased IOP and the incidence of glaucoma.[4]

Pohjanpelto and Palva studied IOP as it relates to the incidence of optic nerve damage. The study was based on 307 patients who had a finding of optic nerve damage and/or ocular hypertension who were then either

admitted to the hospital or had their IOPs measured several times on an outpatient basis. They found that the incidence of glaucomatous nerve damage was only 7% with an IOP of 25-29 mm Hg, but rose to 70-80% with IOPs of greater than or equal to 45 mm Hg. The incidence of optic nerve damage rose slowly as the IOP rose until the pressure reading of 35 mm Hg, at which there was a steep climb in the incidence of POAG.[8]

David et. al. followed 61 subjects (117 eyes) with ocular hypertension in their study on the risk of developing glaucoma as it relates to the level of IOP from 1 to 11 years. Of the 75 eyes with pressures between 21-25 mm Hg only 2 (2.6%) developed glaucomatous visual field defects, of the 25 eyes with pressures between 26-30 mm Hg only 3 (12%) did, but 7 (41%) of the 17 eyes with pressures greater than or equal to 31 mm Hg developed glaucomatous visual field defects.'[0]

Schappert- Kimmijser studied 94 eyes with IOPs between 22-30 mm Hg in which the optic nerve and the visual field were normal. After 5 years, 12 eyes (13%) of the group had developed glaucomatous defects.[45]

Many epidemiologic studies have shown that while the pressure levels in patients with POAG are higher than their normal counterparts,[4,7,8] approximately a third of patients with glaucoma do not have statistically elevated pressures.[4,5,7,11] While it is clear that elevations of the IOP could cause the characteristic disturbances of the optic nervehead and the subsequent defects in the visual field, IOP is no longer recognized as a

reliable early sign of glaucoma, nor can the finding of normal IOP be relied on to exclude the development of glaucomatous damage in an individual eye.[4,5,7,11,12] However, IOP is recognized as an important risk factor in this disease. Intraocular pressures less than 21 mm Hg must be evaluated along with other patient data such as the case history, gonioscopy, visual fields and stereoscopic optic nerve assessment, just as those IOPs greater than or equal to 21 mm Hg must be. As the studies above reveal, the higher the IOP, the higher the risk of glaucomatous damage. Therefore, IOPs between 21-25 mm Hg are of some concern to the practicioner, while IOPs between 25-34 mm Hg are of much greater concern. Intraocular pressures greater than or equal to 35 mm Hg are of greatest concern to the practitioner, and prophylactic treatment must be considered in the absence of any other risk factor.

ASYMMETRY OF THE IOPs BETWEEN THE TWO EYES

Asymmetry of the IOPs between the two eyes could be an indication of glaucoma and there are studies that support this idea.[13,14] Davanger found that the difference in the IOP between the two eyes increased with increasing IOP, and that glaucomatous individuals had a greater difference in the IOP between the two eyes than individuals without glaucoma. This study found that 98% of the normal population have a difference of less than 4 mm Hg.[13] Carel et al. compared the IOPs in the two eyes of 13,000 non-glaucomatous subjects over 40 years of age and found the mean difference between the two eyes was 0.12 mm Hg. They found that 78%

had less than 3 mm Hg difference, 17% had a 3-4 mm Hg difference, and that 4.4% had a difference greater than or equal to 5 mm Hg. They also found that the difference in IOP between the two eyes increased with increasing IOP and increasing age.[14] These findings are consistent with the fact that glaucoma, though a bilateral disease, generally appears in one eyes before the other and may progress at different rates in the two eyes. Therefore, a difference in the IOP of greater than or equal to 3 mm Hg between the two eyes indicates the suspicion of glaucoma.

It is important for the practitioner to understand that in the time it takes to swing the tonometer from one eye to the other to measure the pressures, it is possible for the measurement of the IOP to change by 3 mm Hg.[12] Leydhecker stresses that the IOP in healthy eyes is not fixed but variable for the following reasons: The heartbeat will produce one oscillation per second in the eyes causing a variation of 1 mm Hg to 7 mm Hg in the IOP. Periods of only 3 or 4 seconds related to the breathing cycle will produce similar oscillations in IOP. In addition to these normal variations, 2.5 mm Hg must be accepted as the possible clinical error of clinical results using applanation tonometry. Clinical error is not due to the construction of the instrument but to user variation in reading the instrument.'[5] Leydhecker also stresses that it would be an unfortunate misunderstanding of this discussion of the difficulties of measuring IOP to think that tonometry is not important. It is more reproducible than perimetry and there are less inter-observer variations than in the estimation of the cup to disc ratio. While a single reading of the

tonometer is open to doubt, repeated tonometry at different times of the day was found to be the safest method for early diagnosis of POAG.[15]

DIURNAL VARIATION IN THE IOP

The amount of diurnal variation in the lOPs could indicate the early onset of glaucoma. Drance studied 220 normal subjects (404 eyes). The first IOP was recorded at 6 a.m. followed by additional readings taken at 9 and 11:30 a.m. and 5 and 10 p.m. The mean diurnal pressure variation was 3.7 mm Hg, with 84% of the eyes with IOP fluctuations less than or equal to 5 mm Hg, and only 16% of the eyes had diurnal fluctuation of greater than or equal to 6 mm Hg. In this study the proven cases of glaucoma were excluded, however, it is possible that over a period of time the individuals with greater fluctuation in IOP may show evidence of glaucomatous damage. lnspite of this drawback, Drance states that statistical analysis suggests that diurnal variation of IOP of greater than or equal to 7 mm Hg indicates abnormality.[16]

Kitasawa and Horie studied the diurnal variation of IOP by measuring it every hour for 24 hours. They categorized their subjects into three groups by using the results of IOP measurement and Goldmann visual field tests. Normal subjects by their definition had lOPs less than 20 mm Hg and no visual field defects. Ocular hypertensives had lOPs greater than or equal to 21 mm Hg but had no visual field defects. Subjects with glaucoma had lOPs greater than or equal to 21 mm Hg and visual field defects. In the

normal subjects, the average IOP peak was 18 mm Hg with a mean diurnal variation of 6.5 mm Hg. In the ocular hypertensive subjects the average IOP peak was 24 mm Hg with a mean diurnal variation of 8 mm Hg. In the subjects with glaucoma, the average peak in IOP was 38 mm Hg with a mean diurnal variation of 16 mm Hg.[18]

The practitioner should take IOPs throughout the day if glaucoma is suspected or if there is ocular hypertension since the IOP can peak at any time of the day.[12,13,16,17,18,19,20] The literature varies as to a specific diurnal amplitude that is considered pathologic, but investigators generally consider a daily fluctuation of greater than 7 mm Hg to be indicative of glaucoma.[12,16,17,18,19,20] Eskridge's strong opinion is that a diurnal variation greater than 7 mm Hg is the first clinical evidence of POAG.[17]

RISK FACTORS THAT INFLUENCE IOP AND THE INCIDENCE OF POAG

Much effort has gone into finding risk factors associated with POAG. After initial enthusiasm, investigators have shown that the prognostic value of the known risk factors is limited.[12,21,22,23,24] However, such factors as genetics, age, sex, race, refractive error, diabetes mellitus, and others can influence IOP and the incidence of POAG. These risk factors can be useful in identifying those segments of the population which require closer observation.

Genetics. There is a positive correlation between family history and the incidence of ocular hypertension and/or glaucoma.[11,21] In fact, the IOP with in the general population appears to be under hereditary influence, with relatives of POAG patients having higher IOPs and greater incidence of POAG than in the general population.[25,26,27,30,40,41] One study revealed that a family history of glaucoma was found in 50% of patients with POAG and 43% of patients with ocular hypertension.[40] Although the exact hereditary mode is unknown, it is possibly through a multifactorial or polygenic mode consisting of autosomal dominant, autosomal recessive, and x-linked chromosome inheritance.[20,25,26,28] A positive family history is generally considered to be a significant prognostic indicator.

Age. The IOP distribution in the general population is Gaussian between 20 and 40 years of age, thereafter the curve begins to shift towards the right to the higher pressures.[24] However, there are conflicting statements in the literature regarding the association of IOP and age. Some investigators have found a positive correlation between IOP and age, while other investigators argue that other factors such as blood pressure and obesity, which are largely age dependent, may be responsible for the apparent rise in IOP with increasing age.[20,31] Some investigators suggest the if there is a true positive correlation between IOP and age, it is probably related to reduced aqueous formation and outflow facility with age.[20,32,33]

In contrast to the conflicting literature on the relationship between IOP

and age, all studies agree that the incidence of POAG increases with increasing age.[20,42,43] While it is unusual for this progressive disease to reach the clinical stage before the age of 40, POAG is by no means limited to those 40 years of age and older.[40] In most cases, however, POAG is clinically present after 65 years of age. Therefore, age becomes an increasingly significant risk factor after 40 years of age, and this risk increases with each decade that passes.[20, 40, 42,43]

Sex. One study showed that IOP is equal between the sexes from 20 to 40 years of age, thereafter the apparent increase in the mean IOP with age is greater in females and coincides with the onset of menopause.[24] Another study showed that women had higher applanation pressures than men except for the 40 to 45 year age group. Although the difference was approximately 1 mm Hg, it is statistically significant and was present in both the right and left eyes.[7] Another study found that there was a normal (Gaussian) distribution curve for IOPs between 10-22 mm Hg, with a male median of 16.5-17.1 mm Hg and a female median of16.5-18.3 mm Hg. However, above 22 mm Hg an excess of high values were found which exceeded the frequency expected in the normal distribution curve, and that this excess increased in both males and females as the age group became higher.[45] This study also found that the IOP of females tends to be about 1 mm Hg higher than for males (which is statistically significant) throughout the life cycle.

The literature varies in regard to the relationship between sex and the

prevalence of POAG. Some studies suggest that POAG is higher among men.[20,46] For example, investigators who used the Framington Eye Study data to examine the effect of alternative definitions of POAG found that when visual field defects irrespective of blind spot enlargement is used as a standard of comparison, more men than women have glaucomatous field defects.[46] Another study found that there was no difference in the prevalence of glaucoma between the sexes except for women 90 years of age or older who had a higher rate.[43]

Race. Blacks have been found to have higher pressures than whites. One study found that black patients had significantly higher mean IOPs, and that blacks become ocular hypertensives at an earlier age than whites. This same study also found that 18% of the black ocular hypertensives developed glaucoma while only 5% of the white ocular hypertensives did.[48] In fact, blacks are much more at risk for developing POAG with its associated visual field loss and eventual blindness.[34,48,49] several studies have shown that the prevalence of POAG is significantly increased in the black population , and that it develops at an earlier age and is more more severe than in the white population.[34,47,48,49]

Full-blooded indians in a New Mexico tribe were found to have significantly lower IOPs than a control population, adjusting for age and sex differences. The IOPs of this indian tribe were also found to not increase with increasing age. No individuals had glaucoma or a family history of glaucoma.[35]

Refractive error. A positive correlation between IOP and increasing degrees of myopia has been reported.[37,39] There is also a statistically significant relationship between applanation tension and axial length of the eyeball. The greater the axial length the higher the ocular tension.[38] Results of another study suggests that myopic eyes are more susceptible to the effects of a raised IOP than are nonmyopic eyes, and that myopes with ocular hypertension have a particularly high risk of developing glaucomatous visual field defects.[36] Therefore, there is an increased prevalence of POAG among myopes.[20,36,37,39]

Diabetes mellitus. According to many surveys the prevalence of POAG in individuals with diabetes mellitus is several times higher than for individuals in the normal population.[50-52] One study found that POAG was 3 times more prevalent in the diabetic subjects than in the control subjects and about 2 times that reported in most studies of the general population.[50] In turn, positive glucose tolerance tests are more likely to be found in POAG patients than in the general population.[51] Clearly, the diabetic population needs to be watched closely for POAG and many other ocular pathologies.

Short-term risk factors that influence an elevation in IOP include physical exertion, lid and eye movements, tobacco, and caffeine. Risk factors that influence a depression in IOP include physical exertion, general anesthesia, alcohol, heroin, and marijuana.[20]

Other risk factors that increase the prevalence of POAG have to do with endocrine disorders which may influence IOP.[20] Another association is between optic nerve damage and a sudden loss in blood pressure, such as when a patient begins therapy for systemic hypertension or has their medication adjusted. There is evidence that glaucomatous patients are more at risk of optic nerve damage after a sudden drop in blood pressure than the normal population.[20] However the association between POAG and systemic blood pressure is unclear, with some investigators finding a correlation with low diastolic blood pressure, some finding a correlation with increased systemic pressure, and yet other investigators finding no correlation to systemic blood pressure at all.[20]

CONCLUSION

Primary open-angle glaucoma is the most common form of glaucoma and early diagnosis is essential in order to prevent permanent visual impairment. Increased intraocular pressure is a factor that is correlated with the incidence of POAG though glaucoma can occur in individuals with IOPs less than or equal to 21 mm Hg. Ocular hypertensives are termed "glaucoma suspects" because they are at greater risk for developing glaucoma, while normal findings cannot be relied on to exclude the development of glaucomatous damage in an individual eye. However, as the studies above reveal, the higher the IOP, the higher the risk of glaucomatous damage. Therefore, IOPs greater than 21 mm Hg are of concern to the practitioner, and every patient who is found to be an ocular

hypertensive should have tonometry repeated on them at various times of the day. Repeated pressure readings increase the reliability of the IOP as an indicator of POAG and knowledge of the peak diurnal IOP is an important consideration in evaluating the patient and the need for medical treatment.

The amount of diurnal variation in the IOPs can indicate the early onset of glaucoma, and investigators generally consider a daily fluctuation of greater than 7 mm Hg to be indicative of glaucoma.

Asymmetry of the IOP between the two eyes can also indicate the early onset of glaucoma since the disease generally appears in one eye before the other and may progress at different rates in the two eyes. A difference in the IOP of greater than or equal to 3 mm Hg between the two eyes indicates the suspicion of pathology.

All risk factors that influence IOP and the incidence of POAG have not been discussed, but an attempt has been made to cover the primary risk factors. Risk factors that influence IOP and the incidence of POAG include genetics, age, sex, race, refractive error, and diabetes mellitus. Age in particular is becoming ever more important as a risk factor since by the year 2000 over 13% of the population will be at least 65 years of age or older. A thourough case history may reveal these and other risk factors.

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