Journal of Optometry (2017) 10, 71–78

Journal of Optometry

www.journalofoptometry.org

REVIEW

Glaucoma history and risk factors

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Received 4 December 2015; accepted 15 February 2016
Available online 23 March 2016

KEYWORDS
Glaucoma;
History;
Risk factors;
Diagnosis

Abstract Apart from the risk of developing glaucoma there is also the risk that it is not detected and irreversible loss of vision ensues. Some studies of methods of glaucoma diagnosis have examined the results of instrument-based examinations with great if not complete reliance on objective findings in arriving at a diagnosis. The very valuable advances in glaucoma detection instrument technologies, and apparent increasing dependence on them, may have led to reduced consideration of information available from a patient history in those studies. Dependence on objective evidence of glaucomatous pathology may reduce the possibility of detecting glaucoma suspects or patients at risk for becoming glaucoma suspects. A valid positive family history of glaucoma is very valuable information. However, negative family histories can often be unreliable due to large numbers of glaucoma cases being undiagnosed. No evidence of family history is appropriate rather than no family history. In addition the unreliability of a negative family history is increased when patients with glaucoma fail to inform their family members. A finding of no family history can only be stated as no known family history. In examining the potential diagnostic contribution from a patient history, this review considers, age, frailty, race, type and degree of refractive error, systemic hyper- and hypotension, vasospasm, migraine, pigmentary dispersion syndrome, pseudoexfoliation syndrome, obstructive sleep apnea syndrome, diabetes, medication interactions and side effects, the degree of exposure to intraocular and intracranial pressure elevations and fluctuations, smoking, and symptoms in addition to genetics and family history of the disease.

PALABRAS CLAVE
Glaucoma;
Historial;
Factores de riesgo;
Diagnóstico

Historial de glaucoma y factores de riesgo

Resumen Aparte del riesgo de desarrollar glaucoma, existe también el riesgo de no detectarlo, con la consiguiente pérdida de visión irreversible que entraña. Algunos estudios sobre los métodos para diagnosticar el glaucoma han examinado los resultados de los exámenes basados

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http://dx.doi.org/10.1016/j.optom.2016.02.003

en instrumentos, que dependen casi totalmente de los hallazgos objetivos para lograr un diagnóstico. Los muy valiosos avances en la tecnología instrumental para la detección del glaucoma, y el incremento aparente de la dependencia de dichos instrumentos, pueden haber llevado a reducir la consideración de la información disponible en la historia del paciente en dichos estudios. La dependencia de la evidencia objetiva de la patología glaucomatosa puede reducir la posibilidad de detectar los casos de sospecha de glaucoma, o los pacientes con riesgo de pasar a la categoría de sospecha, lo que puede mejorar los resultados de la supervisión de los candidatos a cirugía refractiva. Un historial familiar de glaucoma positivo y válido constituye una información muy valiosa. Sin embargo, los historiales familiares negativos pueden resultar poco fiables, debido al gran número de casos de glaucoma sin diagnosticar. La falta de evidencia de historial familiar es más apropiada que la ausencia de historial familiar. Además, la poca fiabilidad de los historiales familiares negativos se incrementa cuando los pacientes con glaucoma no informan a los miembros de su familia. Un hallazgo de ausencia de historial familiar puede establecerse únicamente como historial familiar desconocido. Al examinar la potencial contribución diagnóstica de la historia del paciente, esta revisión considera la edad, la fragilidad, la raza, el tipo y grado de error refractivo, la hipertensión e hipotensión sistémicas, el vasoespasmo, la migraña, el síndrome de dispersión pigmentaria, el síndrome de pseudo-exfoliación, el síndrome de apnea obstructiva del sueño, la diabetes, las interacciones medicamentosas y los efectos secundarios, el grado de exposición al aumento de la presión intraocular e intracraneal, el tabaquismo, y los síntomas, además de los factores genéticos y el historial familiar de la enfermedad.

Glaucoma involves a progressive loss of retinal ganglion cells (RGC) and characteristic changes in neuroretinal rim tissue in the optic nerve head (ONH) which are accompanied by visual field (VF) constriction.[1] There are several types of glaucoma constituting a group of eye diseases which are the leading cause of irreversible blindness worldwide.[2] Apart from the risk of developing glaucoma there is the risk that it is not detected and irreversible loss of vision ensues.[1] In a sample of 5000 urban Greek people over 59 years of age, 57.1% of glaucoma cases were found to be undiagnosed.[3] A study of 3654 predominantly white Australians (90.2% over 60 years of age and 24% over 80 years of age) found that the prevalence of POAG was 3.0% with 51% not having been previously diagnosed.[4] That so many cases of glaucoma can be undiagnosed means that studies based in hospitals or specialist clinics, for example, can be biased to particular classes of referred patients and so not representative of the Glaucoma cohort[5] which should ideally include all the undiagnosed cases. Identification of the risk factors for glaucoma development requires population-based studies.[5] The prevalence or incidence of glaucoma in a population study will depend on the thoroughness of the examination regime employed.

Comprehensive history findings may make an important contribution to the valuable identification of glaucoma suspects prior to any evidence of glaucomatous changes. Apart from diagnostic potential, decisions about treatment and follow-up schedules may be improved by reference to history findings indicating risk for and likely speed of glaucoma progression for example. The findings of a thorough history may aid decisions about the range of objective testing required during a clinical examination. The potential for history to contribute to diagnosis and patient management may be critically more evident when objective testing indicates borderline or conflicting diagnostic findings. Screening of higher-risk groups may be the most cost-effective method of reducing the volume of undiagnosed glaucoma[6] and patient history appears to be a practical means of screening to identify the higher risk target population.

Various combinations of patient history and objective methods for the evaluation of the ONH, retinal nerve fibre layer (RNFL), VFs, tonometry, corneal thickness, tonography and provocative testing, for example, can be used to classify subjects as healthy, glaucoma suspects or having glaucomatous pathology. A patient's family history may improve the accuracy of glaucoma patient diagnostic classification in population studies as well as diagnosis in a clinical setting.[7] In a general medical outpatient setting, a correct diagnosis was found to be determined in 82.5% of cases based on the information provided by a medical history.[8] There is a wide range of supplementary information in a patient history which may improve glaucoma diagnosis and treatment decisions. However, except for patient age in some cases, the findings of a patient history may not be included in glaucoma studies.[9–13] Some studies may include the use of only family history rather than a full patient history.[14–16] Other studies may be limited to objective findings from instrument-based examinations with reliance on objective findings to determine diagnostic classifications without reference to history or other clinical findings. For example, accuracy of diagnosis of early glaucoma was found to be greatest (although not always

significantly so) for ocular coherence tomography (OCT) RNFL thickness parameters, followed by Frequency-Doubling Technology VF anomalies, Scanning Laser Polarimetry RNFL anomalies, and lastly Short-Wavelength Automated Perimetric VF anomalies.[9] However, dependence on significant evidence of glaucomatous pathology reduces the capacity to detect glaucoma suspects. The emphasis on the very valuable advances in the technology of glaucoma detection instruments, and associated increasing applications for them, could lead to reduced attention being given to information available from a patient history. In a study by Miki and coauthors glaucoma suspects were defined as those having glaucomatous optic neuropathy, or suspicious-appearing optic discs based on stereophotograph review by two experienced graders, or ocular hypertension (intraocular pressure (IOP) >21 mmHg at baseline without evidence of repeatable glaucomatous visual field defect (VFD) at baseline.[17] That study found that the rate of RNFL loss over time may be a useful tool to help identify patients who are at risk for developing VF loss.[17] Such results may be interpreted as indicating that OCT alone is a suitable method of examination. However, notwithstanding the usefulness of these findings, the question remains as to whether a comprehensive patient history could have identified more subjects at risk for having reduced RNFL thickness and VF loss. Case detection can be improved by combining RNFL thickness analysis with visual function tests.[18] However this review re-evaluates the potential for patient history to also contribute to the diagnosis of glaucoma and glaucoma suspects. The detection of glaucoma suspects depends on patient history when there is no detectable objective evidence of glaucoma.

Increased monitoring of glaucoma patients reduces the risk of undetected progression.[19] Use of dynamic and personalised testing schedules can enhance the efficiency of detecting open-angle glaucoma (OAG) progression and reduce diagnostic delay compared with fixed yearly monitoring intervals.[19] Ideally, monitoring schedules could be determined according to individual risk of developing or progressing glaucoma. The performance of a forecasting model might be improved by consideration of any significant factors revealed by patient history. This review examines history details which may help determine diagnostic classifications as well as help determine individual treatment and follow-up schedules according to the risk and anticipated rate of subsequent progression. PubMed searches for 'glaucoma suspects' and 'glaucoma examination' as well as for 'glaucoma suspects' and 'glaucoma diagnosis' yielded 119 and 500 references respectively. The most relevant of these to this review have been cited.

Age and frailty

Glaucoma risk increases with age.[20–22] As a consequence, glaucoma can be expected to be associated with other age-related diseases such as macular degeneration,[20] vascular diseases,[23] and obstructive sleep apnea[24] for example. However this is not a direct link for most age-related diseases. The concept of frailty is a non-specific state of vulnerability which results in a higher risk for accelerated physical and cognitive decline, disability and death.[25] Assessment of frailty depends on the accumulation of health deficits[26] such as hypertension, hypotension, diabetes, migraine, obstructive sleep apnea syndrome, cataracts, glaucoma and the need for medications.[27] As is the case for glaucoma, the prevalence of many other health problems tends to increase with frailty and may be an important reason for their concurrence in some patients. A frail patient at a younger age may have greater risk for developing glaucoma.

Gender

In the Ocular Hypertension Treatment (OHT) study, male gender was found by univariate analysis to be a useful predictor for the onset of primary open angle glaucoma (POAG).[28] A Bayesian meta-analysis found that men were more likely to have OAG with the reservation that gender influence depends on the definition of glaucoma.[29] For example, a review of the literature concluded that women are at higher risk for angle-closure glaucoma (ACG) but that there is no clear gender predilection for OAG.[30] These findings may only be relevant to the groups studied. That women usually live longer than men increases their risk for glaucoma and glaucoma blindness.[29]

Genetics and family history

Evidence of the significance of Myocilin mutations in advanced primary open angle glaucoma (POAG)[31] and copy number variations of TBK1 in normal tension glaucoma (NTG)[32] illustrate the diagnostic potential for genetic testing. However, the contribution of genetics in glaucoma risk prediction has usually been limited to knowledge of family history[33] although, too often, patients are unaware of family members who have been diagnosed with glaucoma.[34] That more than 50% of glaucoma cases can be undiagnosed[3] adds to the unreliability of family history. A family history of glaucoma was found to carry a relative risk of 2.1 times for being associated with at least possible OAG[20] However, the relative importance of family history may vary according to the closeness of relationship of a patient to an affected family member (first. second or even third degree).[35] Around half of all primary OAG patients have a positive family history, and their first degree relatives (parents, siblings or children) have an approximately 9-fold increased risk of developing glaucoma.[32] Wolfs and co-authors found that the first degree relatives of glaucoma patients were found to have a 22% lifetime risk of glaucoma themselves in comparison to 2.3% in relatives of normal controls.[36] The prevalence of glaucoma was 10.4% in the siblings of glaucoma patients compared to 0.7% in the siblings of normal controls.[36] In addition, the risk of inheriting glaucoma may increase with the number of relatives diagnosed with the disease. Approximately 60% of a glaucoma patient sample was found to belong to families in which other members have the disease.[7]

Race

A review of the findings from 11 population-based studies found a wide range in the prevalence of POAG among populations of the ''same race''.[37] Variable prevalence reported in different studies may have been due to different methods of examination as well as being a consequence of

differences in exposure to geographic, social, behavioural and environmental factors.[37] For certain age groups Racette and co-authors estimated the prevalence of POAG in a black American population, to be six times higher compared to whites.[38] Although black populations have the highest prevalence of OAG, white populations showed the steepest increase in OAG prevalence with age.[29] A higher glaucoma prevalence has been found in Asian populations including a higher incidence of primary angle-closure glaucoma (ACG) compared to white patients.[39]

Myopia

Myopia has been found to be a significant risk factor for glaucoma.[21,39–44] That myopia is a risk factor for glaucoma and that it is also more prevalent among Asian patients may help explain increased prevalence.[39] In addition, that high myopia[42] and increased axial length in certain age groups have both been identified as risk factors[43,44] suggests that the risk of glaucoma development and progression increases with the degree of myopia.[44]

The type of glaucoma may vary with refractive error

The significance of history items may vary with the type of glaucoma. For example, risk factors for acute ACG include hyperopia[45] and myopia is a significant history item for progression of ocular hypertension (OHT) and POAG.[40]

Systemic hypotension and hypertension

Systemic hypertension, vasospasm, and acute hypotension have been proposed as potential risk factors for glaucoma in clinic-based studies.[46–48] Several studies have reported associations between low diastolic pressure, lower ocular perfusion pressure (OPP) and higher prevalence and/or incidence of glaucoma.[46–49] Low systemic blood pressure (BP), especially when combined with an elevated IOP, will lower OPP and risk a reduction in the volume of blood flow to the ONH in eyes with an impaired auto-regulatory system,[50] leading to ischaemic and reperfusion oxidative stress damage to the axons and associated atrophy of the RGCs. A history of antihypertensive treatment and associated lower BP could increase the risk of glaucoma by this mechanism.[51] The Blue Mountains population study found that mean IOP increased linearly from 14.3 mmHg for systolic BP <110 mmHg to 17.7 mmHg for systolic BP >200 mmHg.[52] A study of 4297 subjects over 40 years of age in a defined predominantly white population found a positive correlation between systemic BP and IOP and an association between POAG and systemic hypertension.[47] However, a cross-sectional population study concluded that the association between hypertension and POAG was most likely due to the correlation between age and hypertension.[21]

Vasospasm

Vasospasm represents vascular dysregulation associated with inappropriate constriction or insufficient dilatation in the microcirculation.[53] The eye is frequently involved in a vasospastic syndrome with vasospasm associated with anterior ischaemic optic neuropathy and glaucoma.[53] Vasospasm is often falsely equated with Raynaud's phenomenon.[53] Vasospasm patients often present with cold hand symptoms but they usually do not have the pale fingers which are characteristic of Raynaud's disease.[53] Vasospasm patients frequently have low BP[53] which, as discussed, may also be associated with reduced OPP and glaucoma risk.

Migraine

An association between NTG and migraine has been suggested, with a potential common vascular aetiology for both diseases.[54] However, an association between OAG and migraine was found to only be significant for subjects aged 70–79 years.[55]

Pigmentary dispersion syndrome

Pigmentary glaucoma characteristically develops in young myopic patients with pigmentary dispersion syndrome.[56] Male gender, black race, severe myopia, and Krukenberg spindles were identified as possible risk factors for the development and severity of glaucoma in the pigment dispersion syndrome.[57]

Pseudoexfoliation syndrome

Pseudoexfoliation syndrome is a common age-related generalised fibrotic matrix process[58] with significance because it increases the risk of developing glaucoma.[20,22]

Obstructive sleep apnea syndrome

Compared to normal patients, obstructive sleep apnea syndrome patients were found to have 1.67 times greater likelihood of developing glaucoma over a 5 year follow-up period.[24]

Diabetes

A meta-analysis by Zhou and co-authors found that six case-control studies indicated diabetes as a risk factor for POAG with a mean odds ratio greater than one, while a seventh study found an odds ratio of 0.61.[59] Of six population-based cohort studies five indicated a significant association between diabetes mellitus and POAG.[52] It appears that diabetes may increase the risk of POAG, especially as hyperglycaemia results in heightened sensitivity to IOP and risk of neuronal injury.[53] When 80 NTG and 4015 control patients were compared in a Korean population, a higher proportion of fasting capillary glucose $\geq$200 mg/dL was identified as a risk factor for OAG in both univariate and multivariate analyses.[35] Nevertheless, the association between diabetes and glaucoma remains controversial.[60]

Medication-related IOP elevation

The concomitant use of glaucoma and systemic medications for co-existing systemic disorders creates the potential for drug interactions, as well as side effects from both groups of drugs.[61] For example, ACG due to pupillary block, can be caused by local or systemic administration of adrenergic agents, as well as by sulfa-based drugs[62] Corticosteroid-induced glaucoma and OHT is a response to increased resistance to aqueous outflow.[63] Treatment for systemic hypertension or Raynaud's disease could increase the risk of glaucoma.[51] For example, a five year follow-up of 3271 subjects found the risk factors associated with the incidence of POAG development included having ever taken calcium-channel or alpha-blocker medication.[20] However, whether alpha-blocking medications have any haemodynamic influence on the ONH remains to be elucidated.[20]

Smoking

Studies of the association between glaucoma and smoking have been contradictory.[60] It has been hypothesised that, in the presence of genetic risk factors, exposure to environmental stresses such as smoking, corticosteroid medication and diabetes, results in an earlier age of onset of glaucoma.[60] The risk of glaucoma in smokers may be higher in men.[60]

Exposure to IOP elevation and fluctuation

IOP is the only known modifiable factor in OAG.[12] One of the factors associated with progression of glaucoma is fluctuation in IOP either over the 24 h diurnal period or across visits.[64–67] For example, in NTG patient's progression of VF losses was found to be associated with a higher 24 h peak IOP and greater IOP fluctuation over 24 h.[68] Exposure to IOP elevations and fluctuations which occur during a variety of regular or occasional activities may increase the risk for the development or progression of glaucoma.[69–71] For example activities involving sleep-related postures,[71] lid squeezing/squinting, eye wiping, massaging or rubbing, inverted body positions (such as in the practice of Yoga), wearing swimming goggles, muscular effort, increased expiratory effort such as during physical exercise or when playing high wind resistant musical instruments, and wearing a shirt or tie which are tight around the neck are all known to elevate IOP,[67] sometimes in conjunction with intracranial pressure elevation.[72] Reducing participation in activities which elevate either or both IOP and intracranial pressure will decrease exposure to higher levels of lamina cribrosa displacement and/or lamina cribrosa compression with the associated possibility of risk of damage to RNFL axons passing through the lamina cribrosa.[72] Although a single short-term fluctuation is likely to be of negligible significance, the cumulative effect of constant or frequent fluctuation could be significant in contributing to glaucoma pathogenesis.[73] Any risk associated with a single short-term fluctuation may increase with the degree of elevation involved. IOP measured with the patient sitting with neck in a neutral position (no flexion or extension) is probably the lowest of any body position.[74] Estimation of the degree of exposure to IOP elevation and fluctuation episodes, sometimes to levels many times the sitting-position level, can be aided by questionnaire responses.[67] (Copies of the questionnaire can be obtained from c.mcmonnies@unsw.edu.au.)

Symptoms

Glaucoma progression carries a burden of both nonvisual and visual symptoms which are a considerable concern to patients in more advanced cases.[75] However, at the time of diagnosis, most patients are relatively free of glaucoma-induced impairments.[76] The absence of symptoms which are specific to early glaucoma appears likely to contribute to the high number of undiagnosed subjects found in population studies.[75,76] The Glaucoma Symptom Scale provides a valid and reliable estimate of symptoms associated with glaucoma and its treatments.[75] However, for the early stages of glaucoma, sensitivity may be high and specificity correspondingly low with this instrument because many of the Glaucoma Scale symptoms such as burning, smarting, stinging, tearing, dryness, itching, soreness and tiredness[75] can occur in many diseases such as any of the dry eye syndromes, and even in otherwise healthy eyes during exposure to adverse environmental conditions. However, these types of symptoms may occur as a consequence of glaucoma treatment. In both clinical and research settings this scale should prove to be a valuable patient-centred tool for the assessment and comparison of symptoms experienced by patients with glaucoma especially perhaps for those who present with new symptoms while undergoing treatment.[75]

Discussion

Comprehensive history findings may make an important contribution to the identification of glaucoma suspects prior to any evidence of glaucomatous changes. The findings of a thorough history may aid decisions about the range of objective testing required during a clinical examination. The potential value for a comprehensive history in decision making may be greater when objective testing indicates borderline or conflicting diagnostic findings. For example, OCT using guided progression analysis software, perimetry and stereophotography examinations were repeated during follow-up to examine for glaucomatous progression in 246 eyes.[13] Notwithstanding some agreement between the three methods, most cases with detectable changes were identified by only one of these methods of examination. These findings suggest that reference to history information may assist decision making when glaucoma monitoring examination findings obtained with different instruments are not in agreement or are at a borderline level in regard to recommended diagnostic cut-offs for particular instruments. It is important to stress that a predictive instrument such as a comprehensive history[15] as well as an instrument-based objective predictive risk model should always be supplemented by clinical judgement.[12] The need for clinical judgement may be reduced if it was possible to appropriately weight the significance of individual history items in relation to glaucoma diagnosis in order that the combined predictive performance of a history could be maximised. Combining multiple-screening strategies together with

family history can be a very powerful diagnostic method for glaucoma.[15] No evidence of a family history can be an appropriate finding whereas a finding of no family history cannot be made confidently. However, given its potential for unreliability, rather than considering only the presence of a family history of glaucoma, the combination of a comprehensive history and clinical assessment[20] may be more successful, especially in marginal/suspect diagnoses. Genetic variations related to OAG may provide additional indication of risk.[77] Apart from diagnostic potential, treatment and the appropriateness of follow-up schedules may be improved by reference to history findings. For example, a patient's history may also contribute to difficult management decisions in cases of ocular hypertension. Screening of higher-risk groups may be the most cost-effective method of reducing the volume of undiagnosed glaucoma[78] and patient history appears to be a practical means of helping to identify patients with higher risk for developing glaucoma. As a possible consequence of the importance placed on objective findings in recent literature, the potential usefulness of history findings may sometimes be ignored or underemphasised.

Funding

There are no funding, proprietary or financial interests to declare in relation to this paper.

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