International Journal of Science and Technology Research Archive

ISSN: 0799-6632 (Online)

Journal homepage: https://sciresjournals.com/ijstra/

(REVIEW ARTICLE)

The importance of family history in the risk of open-angle glaucoma

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International Journal of Science and Technology Research Archive, 2022, 03(02), 253–257

Publication history: Received on 01 November 2022; revised on 19 December 2022; accepted on 21 December 2022

Article DOI: https://doi.org/10.53771/ijstra.2022.3.2.0157

Abstract

Objective: We aim to carry out a topic review on the available literature about the relationship between family history of glaucoma and the development of primary open-angle glaucoma in such a way that we can provide ophthalmologists, non-ophthalmologists, optometrists, and all those involved in visual health care a general understanding of this relationship.

Methods: A bibliographic search of manuscripts published in English and Spanish was carried out using PubMed and Scopus databases. For the search, the following terms were used: glaucoma, open-angle, family history, and risk factors. From the retrieved articles, those relevant to this review's topic were selected.

Findings and conclusions: A family history of glaucoma is an essential risk factor for suffering from this disease, as demonstrated by both population-based epidemiological and clinical studies. This association is more robust in first-degree blood relatives, especially when those affected are siblings of the index case. The preceding justifies screening these patients due to the increased risk of suffering from an illness that can lead to visual disability.

Keywords: Open-angle Glaucoma; Family history of Glaucoma; Risk factors; Colombia

1 Introduction

Glaucoma is a heterogeneous group of diseases whose common characteristic is damage to the optic nerve caused by the death of retinal ganglion cells and excavation of the optical disc with the consequent loss of vision. It is a serious pathology, which, if not intervened in time, can lead to blindness. It is usually classified depending on the open or closed state of the chamber angle in open and closed-angle glaucoma, respectively [1]. In turn, these can be subdivided into primary or secondary depending on the absence or presence of an identifiable cause that explains glaucoma [1].

Glaucoma is the second leading cause of blindness worldwide, disproportionately affecting women and Asians [2]. It is estimated that 76 million people worldwide have some glaucoma, of which 57.5 million are affected by primary open-angle glaucoma (POAG) [3], with a global prevalence in the population over 40 years of age of 2.4% [4]. The frequency with which this disease occurs and its consequences have increased. In 1990 the global percentage of blindness caused by glaucoma was 4.4%, and by 2010 (the year in which 2.1 million blind people were calculated), it was 6.6%. Therefore, one in 15 blind people was blind due to glaucoma, and in that same year, it was responsible for 2.2% of all moderate to severe visual impairments [2,5]. Mathematical models estimated an increase in bilateral blindness due to open-angle glaucoma from 4.5 million people in 2010 to 5.9 million in 2020 [5]. Similarly, the number of people between 40 and 80 years of age affected by glaucoma worldwide is expected to increase by 74% to 111.8 million in 2040, mainly attributed to Asian and African cases [3].

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The pathophysiology of glaucoma is still the subject of numerous investigations; what is clear is that it is a multifactorial process. Although an altered ocular blood flow, decreases in intracranial pressure, or abnormal individual susceptibility of the cribriform plate are frequently implicated, the increased intraocular pressure has received most attention [1]. Thus, the latter is considered one of the most critical risk factors for developing the disease and, to date, is the therapeutic target of the surgical and non-surgical treatment options currently available.

Additionally, other risk factors have been described for the development of one or another type of glaucoma, among which are but are not limited to advanced age, race, sex, refractive defects, genetics, and family history [6].

In this review, we show the available literature on the relationship between family history of glaucoma and the development of primary open-angle glaucoma, including those large-scale classic population studies. There is a strong relationship between a Family history of Glaucoma and the presence of the disease. Screening strategies should seek family members of patients with glaucoma to detect the disease's presence in the early stages.

2 Methods

A bibliographic search of manuscripts published in English and Spanish was carried out using PubMed and Scopus databases. For the search, the following terms were used: glaucoma, open-angle, family history, and risk factors. The search sought to include large-scale classic population studies also references as recent as possible were included. From the retrieved articles, those relevant to this review's topic were selected.

3 Family history of glaucoma and primary open-angle glaucoma

Through genome-wide association studies (GWAS), more than 80 loci associated with the development of primary open-angle glaucoma have been identified, although among the best-established genes are CAV1, TMCO1, CDKN2B-AS1, SIX6, ABCA1, GMDS, AFAP1, GAS7, TGFBR3, TXNRD2, ATXN2 y FOXC1 [7].

GWAS shows a promising future for the genetic diagnosis of this entity. However, the family history of glaucoma currently summarizes with clinical importance the presence of these genetic alterations related to the development of open-angle glaucoma in the absence of a clinically available genetic test to confirm them. Even so, due to the lack of knowledge regarding whether any of their family members have been diagnosed with glaucoma and what type by patients, the identification of family history during the anamnesis as a risk factor for developing this disease could leave more than half of glaucoma cases undiagnosed, thus affecting the reliability of this antecedent [6].

In contrast to early-onset glaucomas inherited with autosomal dominant and recessive inheritance patterns, both normal-tension glaucoma and adult-onset primary open-angle glaucoma have a much more complex way of inheritance not following the guidelines described by the Austrian Gregor Mendel [8]. It is well known that when there is no Mendelian inheritance pattern, the presence of isolated mutations does not necessarily have a causal relationship; on the contrary, it is the sum of several mutations with environmental factors that increases the host's susceptibility to the disease. Adult-onset glaucomas usually affect several members of the family, which is known as familial aggregation [8], thus describing a family history of glaucoma with a relative risk of 2.1 with a 95% confidence interval (95%CI 1.03-4.2) [9], clarifying that its importance will vary with the degree of consanguinity between the patient and the affected family member [6].

Using information from a population-based prevalence survey (The Baltimore Eye Survey) that found 161 cases of primary open-angle glaucoma among 5,308 residents of eastern Baltimore, Maryland. This study included Caucasians and black with 40 years or more years of age; Tielsch and colleagues set out to examine the strength of the association between a positive family history of glaucoma and having the disease. The interview determined family history and included all first-degree relatives (parents, siblings, and children). 16.1% of cases reported a family history of glaucoma among first-degree blood relatives compared to 7.2% reported by controls. In general, it was possible to establish a relationship between the explanatory variable (positive family history) and the response variable (primary open-angle glaucoma) with an odds ratio [OR] adjusted for age and race of 2.85. However, the strength of the association varied with the type of family members affected, being most vital with siblings (OR adjusted for age and race = 3.69), followed by parents (OR 2.17), and weakest with children (OR 1.12) [10].

Subsequently, Wolfs et al. conducted a population-based family aggregation study to determine relative and absolute risks for first-degree blood relatives. Forty-eight first-degree relatives of glaucoma patients and 155 control subjects from the Rotterdam population-based study were evaluated. The prevalence of glaucoma was 10.4% in siblings of

glaucoma patients and 1.1% in their offspring, compared to 0.7% and 0% in controls, respectively. There was an increased risk of elevated intraocular pressure of 42.5% in cases versus 6.7% in controls, and a risk of glaucoma of 22% in cases compared to controls where the risk was nearly 10-fold lowest (2.3%). The relative risk for glaucoma was 9.2 (95% CI 1.2-73.9) [11].

Leske and coauthors conducted a cohort study on people of African descent to assess risk factors for open-angle glaucoma, the Barbados Eye Study. 3,222 people between the ages of 40 and 84 who, at the beginning of the study, had no diagnosis of open-angle glaucoma and followed them for nine years were evaluated. At the end of this period, 125 subjects had developed the outcome for an incidence of open-angle glaucoma of 4.4%; (95% CI, 3.7–5.2), finding that, among others, family history of glaucoma behaves as a risk factor for this entity (RR 2.4; 95% CI, 1.3–4.6) [12]. With the population of said study, Nemesure *et al.* concluded that the inheritance of open-angle glaucoma could follow a Mendelian codominant inheritance model [13].

The Los Angeles Latino eye study recruited Latinos 40 years or older for epidemiological purposes [14]. Kim and Varma reviewed their findings regarding the prevalence of glaucoma in Latinos and identified factors associated with the development of glaucoma in this population. Of the 6172 participants, 291 were diagnosed with open-angle glaucoma [4.74% (95% CI 4.22–5.30%]), with a higher prevalence among individuals older than 80. They found that a history of glaucoma among siblings [OR 3.47 (95% CI 1.91–6.30)] is a more substantial risk factor than a similar history among parents [OR 1.56, (95% CI %) 0.88 –2.74] and children [OR 1.02 (95% CI 0.11–9.41). Additionally, they found a "dose-response relationship" with the number of affected siblings: one brother with glaucoma (OR 5.64, 95% CI 1.63–19.48) vs. two affected brothers (OR 3.08, 95% CI 1 .57-6.04) [15].

Ekström studied the effect of potential risk factors on the development of open-angle glaucoma (OAG) in a population in which pseudoexfoliation is a common finding and found that positive family history of open-angle glaucoma was associated with the development of the same in the said population (age-standardized rate ratio 2.04 95% CI [1.04–4.00]) [16].

Table 1 Population-based studies

First author (year)	Total study population	Race	Familial glaucoma (percentage)	OR/RR [95% CI]	Age (years)	Pseudoexfoliacion (percentage)
Tielsch JM (1994) [10,21]	5308	White and black Americans	16.1	2.85 [1.82-4.46]	40-≥80	NA
Wolf RC (1998) [11,22]	203	Europeans *(Netherlands)	11.5	[a]9.2 [1.2-73.9]	55-≥75	NA
Le A (2003) [9,20]	3271	Australian residents *(Australia, UK, Italy, Greece, Other Asians/Europeans)	18.2	[a]2.1 [1.03-4.2]	40-≥80	6.4
Leske MC (2008) [12]	3222	African descent	6.7	[a]2.4 [1.3-4.6]	40-84	NA
Kim E (2010) [15]	6142	Latinos of Mexican ancestry	NA	3.47 [1.91-6.30]	40-≥80	NA
Ekström C (2010) [16]	679	Europeans *(Sweden)	NA	2.04 [1.04-4.00]	65-74	NA
O'Brien JM (2018) [17]	2365	African American, African descent and African Caribbean	58.8	3.4 [2.8-4.1]	50-≥80	NA

*Birthplace, [a]RR: relative risk, OR: odds ratio, UK: United Kingdom, NA: non-available

One study evaluated 2365 subjects from the Primary Open-Angle African American Glaucoma Genetics (POAAGG) cohort. In them, positive family history was associated with an increased risk of primary open-angle glaucoma (age-adjusted odds ratio and 95% confidence interval). 3.4[2.8, 4.1]). Likewise, it was associated with an earlier age of

presentation, higher intraocular pressures, and a higher rate of glaucoma surgeries in the past [17]; all population-based studies given are summarized in table 1.

All of the above brings with it the question of performing screening on those people with a positive family history of glaucoma. Although screening is usually discouraged in the general population as it is not cost-effective, it could be helpful in high-risk groups. A patient with glaucoma is more likely to find relatives with the disease [18]. Different tools have been evaluated for screening individually or together, including but not limited to intraocular pressure measurement, central corneal thickness, evaluation of the optic nerve and the nerve fiber layer retinal by optical coherence tomography, assessment of visual fields, and clinical assessment of cup-disc ratio; none of them used in isolation is helpful for the detection of glaucoma while a combination of them is likely to generate better performance [19]. The performance of all these tests as screening tools exceeds the objective of this review.

4 Conclusion

A family history of glaucoma is an essential risk factor for suffering from this disease, as demonstrated by both population-based epidemiological and clinical studies. This association is more robust in first-degree blood relatives, especially when those affected are siblings of the index case. It could even have a dose-response relationship with the number of siblings affected by the disease. The preceding justifies screening these patients due to the increased risk of suffering from an illness that can lead to blindness and for which there are currently medical and surgical treatments capable of avoiding said outcome.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare no conflict of interest.

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