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Pathology of Primary Open-Angle Glaucoma: A Multifactorial Disorder. Review of the Literature

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Abstract

A glaucoma is a group of eye conditions that damage the optic nerve, which is vital to good vision and if not detected early eventually leads to irreversible blindness. Primary open-angle glaucoma the most common type of glaucoma which occurs due to an imbalance of the eye liquid drainage and production. Although, Primary open-angle glaucoma's optic neuropathic nature which features retinal ganglionic cell loss representing the most prevalent form of glaucoma, its exact a etiology and pathogenesis are unknown. Numerous studies have reported the genetic factor that contributes to the progression of POAG including molecular changes in the trabecular meshwork causing stiffness eventually leading to increased intraocular pressure. Therefore, studying the genetic factors and other causes of POAG could help lead to early diagnosis and eventually slow the progression of the disease. However, to this very day, several gene mutations have been described and established to be the causative factors of POAG with some genetic analyses including genome-wide association studies. In this review, we will be focusing on the factors that contribute to the pathology of POAG and the damages that occur to the visual cortex.

Keywords: Epidemilology; GWAS; Immunohistochemistry; Pathophysiology; POAG; Molecules; Progression of Visual Cortex

Introduction

The definition of glaucoma has changed drastically since its introduction during the time of Hippocrates (approximately 400 BC). The word glaucoma came from a Greek word "*glaucosis*" meaning clouded or blue-green hue. Over the years, past decades, comprehensive clarification of the perception and approach of glaucoma has been ongoing till this day. Glaucoma currently is described as a heterogeneous group of disorders with an inevitable result to blindness having various subtypes affecting individuals on a worldwide scale [1]. Primary open angle glaucoma [POAG] is the most common type and has a complex inheritance pattern which manifests by optic disc cupping defined by a distinctive arrangement of progressive retinal ganglion cell death [RGC], optic nerve head excavation and visual field loss. However, known risk factors for POAG include advanced age, IOP, family history of glaucoma, African ancestry and other genetic factors. Although, there are many theorized mechanisms of RGC damage, the exact aetiology of POAG is still not clear. POAG is a significant health problem worldwide and it's estimated to affect about 73.6 million people by 2020 [2] as it's usually associated with an IOP above the normal range 10-21mmhg. POAG is an intrinsically

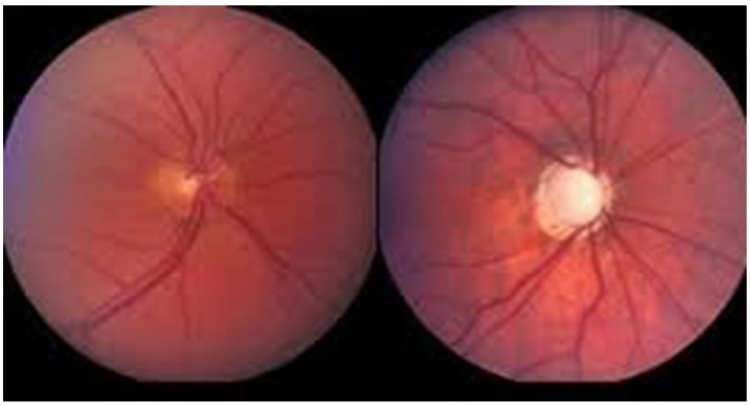

Figure 1: On right we have a healthy optic disc and left damage optic disc also known as glaucomatous disc

convoluted trait with a considerable fraction of it been heritable. Genetic linkage studies of large affected families have so far identified at least 20 chromosomal loci [GLC1A-P] that are linked to POAG. Genes capable of leading to or precipitating POAG with little impact or effect from other gene(s) or the surroundings and that have been constantly involved so far include myocilin [MYOC], optineurin [OPTN], WD repeat domain 36 [WDR36], and SOCS-box containing 10 [ASB10], Cytochrome P450 family 1, subtype B, polypeptide 1 [CYP1B1], and neurotrophin 4 [NTF4] [2]. Besides these genetic factors, microRNAs [miRNAs] also play important roles in the pathogenesis of POAG with these miRNAs encoded by MIR RNA genes. To further understand the role of miRNAs in POAG, it will be necessary to identify the genetic factors that regulate miRNAs expression in ocular tissues (Figure 1).

Pathogenesis of Primary Open Angle Glaucoma, Elevated Intraocular Pressure, Genetic Effects

Glaucoma occurs when there is an imbalance between production and the AH drainage. In glaucoma, visual field worsening practically begins tangentially and advances in the direction of the fovea at the end stage. The occipital pole area corresponds to the central retina [3] with the ample majority of the AH leaving through the trabecular meshwork [TM]. Figure 2 the reason for hyper tonicity could be as a result of changes in the thickness of the TM while in most of cases, the various molecular modifications that resolves or regulates POAG are indistinct. However, factors such as intraocular pressure [IOP], family history, myopia, race and individuals above 40 years old have been described as major key factors. Increased IOP is the most studied of these risk factors because as it is the main clinically and identifiable treatable risk factor for glaucoma. Although, raised IOP is an important risk factor for POAG but only a quota of individuals with elevated IOP tend to develop POAG with most patients of European ancestry having normal IOP levels otherwise known as normal-tension glaucoma [NTG]. This has, however, lead to the notion that other risk factors can cause optic nerve degeneration with a growing evidence of mitochondrial dysfunction in optic nerve susceptibility to glaucoma [4]. Notwithstanding, POAG accounts for about 74% of all glaucoma cases globally with this number expected to skew up to about over three million in 2020 as a result of the advanced aged population. A recent epidemiological studies suggested that in 2013, almost 64.3 million people between the aged of 40 and 80 years old are affected by glaucoma globally and its likely expected to increase to about 76.0 million and 111.8 million by 2020 and 2040 respectively [5] with yet another recent metaanalysis estimating a worldwide increase of POAG cases in 2015 at 50 million which is expected to rise to 65.5 million by 2020 with 47% of these expected to be of Asian descent, 24% European descent with men more likely to have POAG than their opposite counterparts while the prevalence of POAG in individuals40 years old and above for African Americans is 398,000 and 1.57 million for Caucasian. Glaucoma and its subtypes differ among various race and countries [6] with a recent meta-analysis carried out by the Eye Disease Prevalence Research Group which showed that in the United States, African Americans have a much increased POAG ratio as compared to Caucasians and found to be highest among Hispanics over the past 10 years with low incident rates in East and Southern Asia. In all the age groups on out-patients clinic visits, individuals of African descent there was an elevated increase on prevalence of glaucoma as compared to their European counterparts [7]. Similarly, findings from another meta-analysis from the Eye Diseases Prevalence Research Group shows that increase in the occurrence of glaucoma were similar in all ethnicities [Europeans, Blacks, and Hispanics] [8] as age in POAG patients doubles the change of developing ocular hypertension as evident in two large population-based studies [9]. Furthermore, family history and Myopia are also another important risk factor as any slight positive family history of POAG greatly increases the probability of developing POAG [7]. Myopia, on the other hand, leads to increasing the susceptibility of myopic nerves glaucomatous damage [10] with myopic nerve damages is set to increase two to three-fold in the US, Australia [11] and Chinese populations [12]. Diabetes, as well as hypertension, is also under scrutiny as one of the leading silent leading cause for POAG development over the last past five years. Although, there are still conflicting reports cornering the risk of POAG in diabetic patients [13], a current meta-analytic study and systematic review which included six population-based cohorts have shown an increased risk of POAG in individuals with diabetes and hypertension with a relative risk of 1.4 and 1.49 respectively [14] with numerous epidemiological studies reporting the role of hypertension as a risk factor for POAG [15]. The mechanism(s) by which hypertension induces optic nerve damage is still unclear as treatments of hypertensive patients with beta blockers only result to nocturnal hypotension which is a potential risk factor for neuropathic optic glaucoma [16]. The characteristic loss of visual field however seen in glaucoma is as a result of the injury to the head of the optic nerve located at the site of the RGC. The myelinated and unmyelinated RGC axons play key roles in reception with the unmyelinated axonal segment representing the longest node of Ranvier in the body which sustains the action potential as it is endowed with an ample supply of mitochondria required to generate sufficient amount of ATP to maintain action potential propagation in the absence of myelin. RGC loss is a multifactorial diseases caused by DNA mitochondrial mutations, Leber's hereditary with optic nerve region particularly susceptible to mitochondrial dysfunction as a result of the high energy requirement [17,18]. A study conducted by Khawaja AP, Cooke Bailey JN, Kang JH, *et al.* showed a link interaction between the six main pathways of Mitochondrial Gene-Sets and POAG [19]. Also in a large case-control study conducted by the group showed the significant associations between POAG and groups of nuclear genes necessary for specific aspects of mitochondrial function namely; carbohydrate metabolism (butanoate metabolism) and lipid metabolism (fatty acid elongation, synthesis and degradation of ketone bodies). These associations were particularly apparent as they have important pathogenetic role in the development of POAG. However, these miRNAs are been encoded by miR RNA genes, for instance, miR-183 targets integrin-b1 and affects TM physiology [20]. Regulated tissue growth factor [TGF-b2], miR-29b modulates the expression of extracellular matrix genes which plays a role in the AH outflow pathway. Induced miR-24 expression in the TM by cyclic mechanic stress also regulates FURIN and TGF-b1 of which higher expression levels leads to elevated IOP [21]. An increase IOP is perceived as the most frequent, modifiable and vary risk factor in the advancement and progression of POAG, several large population-based studies in the past have confirmed that the reduction of IOP reduces the progression of glaucoma in patients with or without

elevated IOP [22] with another large prospective study clearly showing how POAG with early Para central visual field loss displays distinct as well common risk factor profiles compared to those with peripheral vision loss [23]. Central corneal thickness [CCT] is also reported to be associated with POAG particularly in ocular hypertensive patients [24]. Although the precise mechanism(s) are still unclear as this may be in part due to the effect of CCT on IOP measurement and increased susceptibility to optic nerve damage 40. The IOP which is generated and maintained by the AH circulatory system and exists the eye through the iridocorneal angle and Schlemm's canal [SC]. A vast majority of the AH leaves the eye through the TM across the SC and finally entering the general circulation, its passage through the TM outflow pathways draining into the episcleral venous system [25] is critical as it provides resistance to AH outflow. As the decisive factor leading to hypertonicity is as a result of an alteration in the thickness of the TM. Therefore, an increase a thickened TM may alter the drainage of AH due to the presence of higher resistance [26]. As elevated IOP is the primary risk factor for neuropathic optic glaucomatous patients, progressive vision loss and molecular change hinders the outflow in all POAG patients. Although as this particular mechanism is yet to be properly clarified, one hypothesis based observations that the exposure of trabecular cells to mechanical stress causes an increases expression of TGF-β1 and TM pathways. The over expression of TGF-β1 results in proliferation which determines the remodeling of the extracellular matrix [ECM], trabecular obstruction an elevated IOP [27]. The increase of TGF-β1 is due to the loss of the blood eye barrier thus the concentration of plasma-derived TGF-β1 increases in the plasma contributing to high-pressure levels in the eye. By comparison, TGF-b1 immunoreactivity is noted in the epithelial cells of the cornea, within corneal epithelial cells, ciliary body, AH, and limbal epithelial cells [28]. In the cornea, healing and scar formation is mediated by TGF-b2 [29] which is largely through TGF-b2 mediated enhancement of ECM synthesis and deposition as well as induction of fibroblast mitosis [30]. In TM cells, the mechanisms that promote up-regulation of TGF-b2 mRNA/protein expression include endogenous activation of the Rho GTPase pathway [30]. In other cell types, it is known that TGFb1 or all Trans' retinoic acid promotes TGFb2expression through RhoA/ROCK signaling [31]. Although, POAG is a multifactorial disease where a substantial 5% of POAG is linked with a genetic basis where interactions from genetic to environmental factors play vital roles. To date, up to five genes have been revealed to be a probable causative gene of POAG namely; myocilin [MYOC] for GLC1A [32], optineurin [OPTN] for GLC1E [33], WD repeat domain [34] [WDR 36] for GLC1G 36, neurotrophin 4 [NTF4] for GLC1O 64 and Tank-binding kinase 1 [TBK1] for GLC1P [35], MYOC [cytogenetic location-1q24.3; OMIM-601652] is the most studied glaucoma causing gene worldwide having an autosomal dominant mode of inheritance in juvenile glaucoma forms consisting of mainly three axons with most of the glaucoma-causing mutations found in the third exon [36]. OPTN is second gene causing glaucoma which was identified through large NTG investigation pedigrees. OPTN [cytogenetic location-10p13; OMIM-602432] contains three non-coding and 13 coding exons. Park *et al.* [37] observed up-regulation of endogenous MYOC in human TM cells linked directly to OPTN over expression. Subsequently, OPTN mutations were known to cause up to 1.5% of NTG cases [38] with the well documented Glu50Lys mutation in OPTN found to cause oxidative stress to the cells [39]. Mutations in WDR36 gene (cytogenetic location-5q33-q35; OMIM-609887) and its implication in adult-onset POAG was established in 2005 [40] where WDR36 gene comprises of 23 exons which encodes a member of the WD protein family. However, associated links [41] with the WDR36 mutation is rare in glaucoma [42]. Nonetheless few studies have identified rare WDR36 variants that are associated with POAG in some populations in Neurotrophin-4 (NTF4) gene (cytogenetic location-19q13.33; OMIM-162662) which have 7 exons to be related to glaucoma. This interaction of a known gene NTG (optineurin) further supports the role for TBK1 in glaucoma pathogenesis. In addition, TM cells have contractile features; hence, an increase in TM tone changes the resistance to outflow pathways [43].

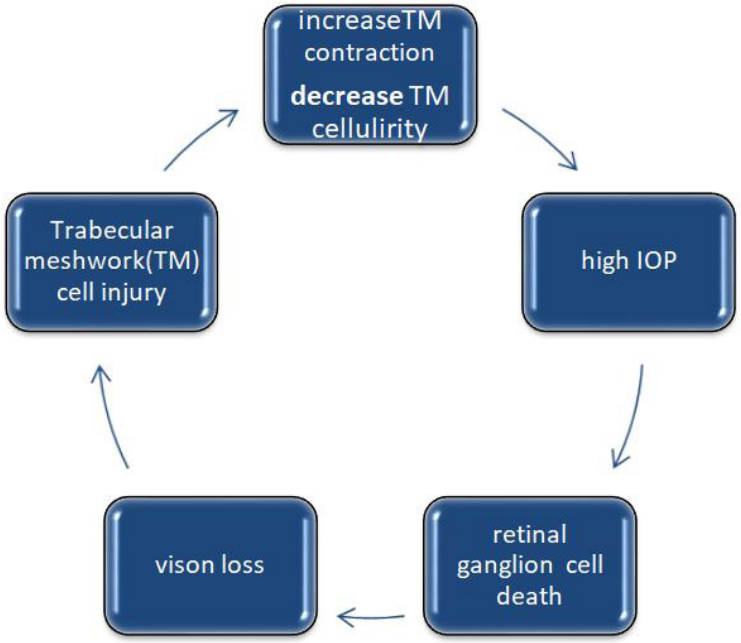

Figure 2: Development of Primary Open Angle Glaucoma

Visual Cortex Progression, Lamina Cribrosa, Cerebrospinal Fluid

POAG is a progressive optic neuropathy that affects the central nervous system as well as the eye and is characterized by irreversible RGCs and optic nerve fibers [44] resulting in psychological and physical abnormalities such as visual field loss. Although, in the retina, glaucoma affects RGCs layers selectively with glaucomatous damage which extends from the RGCs to the lateral geniculate nucleus and even to the primary visual cortex [V1, V2 strait] 82. Several voxel-based morphometry studies have demonstrated a significant decrease in grey matter in the V1 and V2 areas corresponding to the visual field defects caused by POAG [45]. However, the majority of POAG cases presents with little to no difference in V1 and V2 cortex atrophy in its various stages of POAG which is important to consider for clarity in understanding the dynamic changes seen in the visual cortex [46]. High-resolution functional magnetic resonance imaging (fMRI), which is based on the blood oxygen level–dependent (BOLD) contrast technique, provides an ideal choice because it possesses the advantages of high spatial resolution, noninvasiveness, and the ability to reflect task related neuronal activity 50 Consistent with previous studies, it suggests that even in the visual field defined as the normal central area, there may be a functional decrease in POAG patients. In addition, eyes with LC defects are seen to progress faster than eyes without LC defects in a way that the structural characteristics of the LC in patients with glaucoma could occur in both generalized and localized patterns. The LC depth and thickness which is one of the generalized characteristics of the LC is associated with age and IOP while focal LC defects which is one of the focal characteristics of the LC is associated with localized retinal nerve fiber layer, normal-tension glaucoma, and myopic refractive errors. However, cerebrospinal fluid pressure (CSFP) is the counter-pressure against the IOP across the LC and is part of gradient between trans-lamina cribrosa pressure differences (TLCPD) as IOP – CSFP. Notwithstanding, higher CSFP, higher body mass index and a higher diastolic blood pressure. TLCPD is the difference between the pressures in the intraocular compartment and the CSFP compartment. Developmental glaucoma like primary congenital glaucoma (PCG) and juvenile-onset open angle glaucoma (JOAG) manifest as goniodysgenesis and are the cause of glaucoma at an early period in life.

Structures effected	functional effect
Retina and optic nerve	deficits in visual temporal processing
Subcortical structures	visual field impairment
Visual cortex	disturbance of visuo -motor coordination

Figure 3: Primary Open Angle Glaucoma Effects Structures of Visual Tract and also Causes Functional Defect

Discussion

POAG is a multifactorial condition by which an increase in IOP becomes the therapeutical target (Figure 3). Glaucoma is, however, a bilateral ocular disease where the fellow eye exhibits visual damage years after that of the first eye was affected. As a result of its silent progression and binocular compensation, patients usually visit their physicians with both eyes affected. Pathophysiological changes take place in different anatomic locations and stages of the disease right from the TM to the optic disc prelaminar region. POAG patients may have a functional decrease in the apparently normal central visual field. Since the advent of GWAS studies, more and more genes and SNPs have been discovered in the association of POAG. As for the development of new therapeutic agents, it might take several years before effective therapeutic modalities for POAG are available including the whole process from discovering new genetic markers (SNPs) or genes. Furthermore, with the use of genetic linkage and/or association studies, several genetic regions have been revealed where some have been strongly involved in specific phenotypes such as elevated IOP while others are associated with POAG irrespective of IOP and in normal phenotypic variations. It is, however, pivotal to identify true causative variants or genes for possible link pathways of glaucoma pathogenesis only after clarifying its genetic region. Likewise, early detection of POAG is only more variable at paying more attention to the clinical progressive thinning in the visual cortex as the dorsal pathways may be damaged more as compared to the usual ventral visual pathway in central visual system where the cortical degeneration in V1and V2 are discrepant when the disease deteriorates from mild to severe stage. Thus, more attention should be paid to this aspect so as to prevent of cortical degeneration in the early stages of the eye disease as these would improve the clinical outcomes for patients with POAG. More future studies need to be done to issues such as identification of molecular factors, associated genes and pathways involved in TM stiffness regulation as this would only but help improve the therapeutic options for patients with POAG and further improve the current understanding of glaucoma with the already established knowledge on genetics, NTG, AH, increased IOP, mechanical properties of TM [stiffness] and its pathways which are times affected by some pharmacological agents used for its early or late treatments as well as intrinsic alterations in TM and SC cells.

Conclusion

In this review we conclude many factors that cause POAG (TM stiffness, high IOP, corneal thickness, high myopic and probable causative gene of POAG namely; myocilin [MYOC], optineurin [OPTN], WD repeat domain 36 [WDR 36], neurotrophin4 [NTF4] and Tank-binding kinase 1 [TBK1], MYOC [cytogenetic location-1q24.3; OMIM-601652) to prevent the development of the disease and find way to approach the treatment because this disease it's the most common cause of irreversible visual damage.

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Conflict of Interest

Authors declare no conflict of interest.

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