Pupillary Response to Chromatic Light Stimuli as a Biomarker at the Early Stage of Glaucoma

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Research Article

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Abstract

Glaucoma is a multifactorial neurodegenerative disease of the optic nerve currently considered a severe health problem because of its high prevalence, being the primary cause of irreversible blindness worldwide. The most common type corresponds to Primary Open-Angle Glaucoma (POAG). Glaucoma produces, among other alterations, a progressive loss of Retinal Ganglion Cells (RGC) and its axons, key to generate the action potential that reaches the visual cortex to create the visual image. It indicates a Visual Field (VF) loss whose main feature is to be painless, and this makes early detection difficult, causing a late diagnosis and delaying a timely treatment indication that slows down its progression. Intrinsically photosensitive Retinal Ganglion Cells (ipRGCs), which represent a subgroup of RGCs being sensitive to damage, are characterized by reacting to short-wave light stimulation close to 480 nm and among their non-visual function, the role in the generation of the pupillary reflex stands out. Currently, the sensitivity of clinical trials correlates to RGC damage, however the need for an early damage biomarker is still relevant. It is an urgent task to create new diagnostic approaches to detect an early stage of glaucoma in a prompt, quick, and economical manner. We suggest evaluating the pupillary response to chromatic light as a potential biomarker of disease, its diagnostic benefit, and its cost-effectiveness in clinical practice to reduce irreversible damage caused by glaucoma.

Introduction

Glaucoma is currently considered a global health problem due to its severity and prevalence [1]. Moreover, given the aging population, it is expected that the disease is increasingly more prevalent and socioeconomic relevant [2, 3]. Nowadays, it is the first cause of irreversible blindness worldwide [4–11], affecting 3.54% of the population between 40 and 80 years [12], estimating a total of 80 million people affected by 2020 [13].

This pathology defines as a heterogeneous group of optic neuropathies characterized by the progressive degeneration of Retinal Ganglion Cells (RGC) and their corresponding axons [8, 10, 14–17]. Glaucoma is classified into different types, first according to its pathophysiology as primary or secondary, or secondly, according to the morphology of the anterior chamber angle as open or closed [3, 11, 15, 16]. In this review, our focus will be mainly on Primary Open-Angle Glaucoma (POAG) due to is the most common type of glaucoma by covering about 70% of cases [7, 16, 18, 19] and usually occurs bilaterally and asymmetrically [20].

The Visual Field (VF) loss in this pathology is slow and painless [3, 8, 15] and irreparable damage that happens long before diagnosis [8]. Before the patients detect changes in their visual field, about 40% of retinal nerve fibers are destroyed [11, 21]. Glaucoma pathogenesis is not well-known with certainty. However, it is known Intraocular pressure (IOP) level at this moment is related to the RGC death [11, 20], with the decrease of the IOP being the most effective and used treatment, which can be pharmacological or surgical [3, 8, 22–24]. Nevertheless the vision loss and the RGC may continue in patients despite being controlled [25].

Among the RGCs sensitive to damage in glaucoma, there are a subgroup of cells called intrinsically photosensitive Retinal Ganglion Cells (ipRGCs) [26], which have been studied in different experimental models of mice, monkeys, and humans [27–33]. Precisely, studies in humans have reported that this cell group corresponds to less than 1% of the total number of RGCs [32, 34, 35]. But despite the percentage, it highlights among the non-visual functions of the ipRGCs its participation in pupillary light response (PLR) [36–41].

Since the first report on this cell type, much research has focused on studying pupillary dynamics as a biomarker of ipRGC activity in various diseases, including glaucoma [36]. A PLR and a modified pupillary response after illumination (PRFI) have been described as a result of evaluations at different stages of the disease [42–61]. Although there is evidence that ipRGCs are resistant to various forms of damage, such as ocular hypertension, optic nerve crush, and excitotoxicity from N-methyl-D-aspartic acid (NMDA) administration; partial susceptibility or sensitivity of the pupillary response has been described [62–69]. The knowledge of early dynamic alterations of the pupil in response to light stimulus in pathology has acquired great clinical relevance.

Current nonclinical biomarkers of glaucoma focus mainly on molecular genetics [70–73] and metabolomics [74]. These procedures are hard to apply because they are unaffordable, sophisticated, and technically demanding. Furthermore, there are other complementary tests through blood tests. Nevertheless, their use has been reported only in advanced-stage patients of the pathology [75]. The above establishes an inability to diagnose glaucoma, even in relatively late disease processes [25]. In addition, since there is no single test for the diagnosis of glaucoma, a wide variety of periodic ophthalmologic evaluations are required. Demanding high availability of time and economic resources on the part of the patients [19].

Therefore, it is clear how helpful the PLR and PRFI could be as a simple, non-invasive, rapid-tested clinical instrument in patients with suspected glaucoma or initial glaucoma [36, 41]. Throughout the review, we present an overview of the glaucoma pathophysiology, current biomarkers, and the challenges and opportunities for pupillary response in ophthalmologic diagnosis (Fig. 1).

Primary Open-angle Glaucoma (Poag)

Correspond to a degenerative, chronic, progressive, irreversible, and complex optic neuropathy that produces a constant death of RGC, in addition to a cupping of the Optic Nerve Head (ONH) increase and a VF loss [7, 8, 10, 16, 17, 24, 76]. The main risk factors for the disease development are an IOP increase, an advanced age, an increase in the cut-to-disc ratio, thinner central corneas, belong to African Americans, family history of glaucoma, and high myopia [3, 8, 10, 15, 20, 77]. The most relevant risk factor is ocular hypertension (OH), defined as an elevated IOP above 21 mmHg. There is evidence of relative risk of 9.5% to develop GAP in the absence of treatment within 60 months [78].

The pathophysiology of this disorder is still unclear, but two theories are complementary to each other: the vascular (indirect) and mechanics (direct) theories. In both cases, the high IOP plays a significant role

[2, 7, 19]. In the first place, according to the vascular theory, glaucoma is considered as a consequence of insufficient irrigation supply, whether due to the IOP increase or other factors that decrease ocular blood flow [79]. In the second place, mechanics theory suggests the IOP increase causes stretching of laminar beams, producing mechanical stress and direct damage to RGC axons [79, 80].

Whatever the origin that causes glaucoma, every therapeutic model was designed to reduce the IOP, mainly using drugs and surgeries that generate an antihypertensive effect [3, 8, 22–24]. However, the IOP elevation grade does not necessarily correlate with the amount of optical damage [19]. Early diagnosis of pathology is therefore fundamental to achieving a good visual prognosis by starting treatment in time.

Intrinsically Photosensitive Retinal Ganglion Cells (ipRGCs)

The principal structural damage induced by glaucoma pathophysiology affects the RGC axons [16, 25, 81], which includes the small ipRGCs group, which were discovered less than two decades ago [26], and characterized by having the ability to respond to light through its endogenous melanopsin photopigment (also known as opsin-4 or OPN4), with or without synaptic input driven by classic retinal photoreceptor cells, rods, and cones [26–28, 33, 37, 43, 82, 85, 86]. This type of ganglion cell has both visual and non-visual functions, being the latter of interest in the study of glaucoma [33, 36, 37, 82]. These cells are characterized by projecting into different brain areas, mainly to non-visual centers, highlighting the projections towards the suprachiasmatic nucleus and olivary pretectal nucleus, region in the brain that run circadian rhythms and pupil reflex, respectively [28, 34, 82, 83].

Another notable characteristic of RGCs that facilitate their isolation for study are their photo-responsiveness. This process occurs after depolarization to light in a phenomenon similar to that occurring in invertebrates. It is the opposite of the process in rods and cones, which are noted for their hyperpolarization to light [27, 28, 84, 85, 87–89]. Also, the ipRGCs are much less sensitive to chromatic light than classic retinal photoreceptors and emit signals with a much slower kinetic [27], being their photoreception more sensitive to short-wavelength light with a maximum spectral sensitivity of ~ 482 nm, corresponding to the chromatic spectrum of blue [27, 34, 44, 46, 87, 90, 91]. The achromatic range spectrum of visible light for the human eye spreads from about 360 and 400 nm (violet color) at the lower limit to the upper limit between 760 and 830 nm (red color) [92, 93].

Recent and still under study evidence has shown that the ipRGCs are resistant to various forms of damage [62–65]. Among them, we can mention more resistance to chronic ocular hypertension compared to RGC that do not express melanopsin [62, 66], more endurance to the squashed optic nerve [67], and excitotoxicity through NMDA administration, where some studies suggest they are relatively resistant [64], and highly tolerant [68, 69]. It is thought that the latter may be a key point since NMDA-induced excitotoxicity is the basis for the pathogenesis of the retina's ischemic damage characterized by the ipRGC death in glaucoma [64].

Pupillary Response

The pupillary dynamic given by the constriction (miosis) and dilation (mydriasis) of the pupil, is determined by the interaction of the parasympathetic and sympathetic nervous systems. The first leads to myosis to reaction to light and visual stimuli from a close distance, with its main center in the dorsal midbrain, while the second act directly upon dilator muscle peripherally or centrally by inhibiting the Edinger-Westphal nucleus, producing pupillary mydriasis in response to a variety of excitation factors, both physiological such as wakefulness, and pathological such as pain [94, 97].

Evaluation of pupil morphology, size, and reactivity is one of the most commonly used ophthalmologic and neurologic examinations in clinical practice [98, 99]. Currently, ipRGCs are known to be involved in pupillary size regulation [36–41]. On the one hand, this involvement is observed in the relative control of PLR since this response could be activated intrinsically through melanopsin and extrinsically given the stimulation they receive from rods and cones located on the external retina zone [49, 55, 96, 100]. While in the case of PRFI, changes in their magnitude from the beginning of light stimulation are considered a unique function of ipRGC, which is independent of rods and cones functions [38, 100, 101]. Anomalies of physiological functions produce alterations in size, form, and the pupillary response to stimuli [38]. It is associated with a high rate of complications such as Leber's hereditary optic neuropathy, nonarteritic ischemic optic neuropathy, among other optic nerve neuropathies including glaucoma; therefore, on this basis is that the way to apply the pupillary response as a biomarker in this disease has begun to develop [48, 101]. In particular, in the advanced stages of this disease, a Relative Afferent Pupillary Defect (RAPD) has been described, which is often a sign of unilateral or asymmetrical deterioration of afferent structures of the visual pathway [53, 61, 102–104].

Recent research has evaluated the functions of ipRGC through PLR and PRFI in patients with different stages of glaucoma evolution using chromatic pupillometry, where it has been concluded that the response is altered [42–50, 52, 55–60]. Most of these studies are based on the analysis of differences in pupillary dynamics upon the presentation of chromatic stimuli. Concluding that the variations found depend on the methodology of each study. Some rely on the measurement of pupillary constriction amplitudes, diameter, or pupillary area [42, 46–50, 52, 55–60]. Others focus on measuring and comparing speeds and times of constriction-dilation [43–45, 58, 60]. But generally, regardless of the method used, it is possible to deduce that the measurement of pupillary dynamic is a helpful test to detect glaucoma in the early stages, and further studies are required to help distinguish the most relevant characteristics of this response, to generate indicators of progress to help prevent vision loss.

Current Biomarkers Of Glaucoma

A biomarker is a factor that can be objectively measured as an indicator of normal or pathological processes or a response to a therapeutic intervention [70]. In glaucoma, we have a series of genetic and molecular biomarkers related to particular genes in the pathogenesis of the disease, microRNA dysregulation, with molecular variations of the tear film, markers of oxidative stress, metabolomic study, proteomic, imbalance in the immune system, among other laboratory studies [70–75, 105–114]. Despite having various biomarkers, glaucoma continues to cause irreversible visual damage worldwide, as they

are not appropriately implemented in routine clinical procedures and therefore fail to achieve their purpose of generating an early diagnosis.

In clinical terms, current markers used in diagnosis and tracking are focused on different types of damage that are characteristic in glaucoma: structural and functional injury, which are established in that order [24]. So, the diagnosis requires markers to carefully detect structural damage of the optic nerve and functional biomarkers of the visual field deterioration [80]. Due to this, the tests that form the current screening protocol are as follows (Fig. 2):

1. Applanation tonometry: As elevated IOP is the principal risk factor for POAG, this clinical test is essential in glaucoma patients to monitor treatment efficacy and look for suspicious cases. IOP changes throughout the day, so more than one measurement should be performed at different times. In addition, it is complemented by pachymetry, which is the measurement of corneal thickness. Depending on whether it is higher or lower than the dimensions considered normal (10–21 mmHg), the IOP adjustment should be made [24, 115].
2. Ocular fundus: Visible structural damage of the optic nerve is evaluated by observing the optic disc located in the retina by an ophthalmoscope. In a normal eye, the neuroretinal edge meets the ISNT rule, which means thicknesses follow that order (bottom > upper > nasal > temporal) in glaucoma, this rule is altered [15, 116]. Moreover, the size of the cupping of the ONH is evaluated by ophthalmoscopy. Normal is less than 0.3 ratio, suspect between 0.4–0.6 and glaucomatous over 0.6 ratios.
3. Computerized visual field: The automated tool evaluates functional damage, characterizing and monitoring vision loss in glaucoma [24, 117]. In this disease, we have pathognomonic defects of the visual field, such as the Bjerrum scotoma and nasal step [118, 119].
4. Optical Coherence Tomography (OCT): It evaluates the structural damage of the nerve; this is a non-invasive technique and allows to obtain cross-sectional images of the head of the optic nerve and the retina in vivo [24, 120]. The distinctive feature of this equipment is that it can detect structural damage in fibers, being useful for early diagnosis since it presents a normative basis for normal for each age. However, the problem is that it is expensive equipment and therefore not accessible to the entire population [120].

Challenges And Future Considerations

While these clinical trials focus mainly on detecting the already established damage [15, 24, 115–120], on the other hand, we have the case of genetic and molecular biomarkers whose purpose is to find the disease at the initial stage [70–75, 105–114], but given its high complexities of implementation, they have not been used yet, and we are probably still a long way from that. All these techniques are now being found far from conventional medicine and clinical tests. The study of chromatic pupillary response appears as an actual alternative to filling the need for a method that focuses on the early detection of glaucoma through dysfunction in pupillary dynamics. As a complementary method to procedures such as CVC and OCT, currently widely used in clinical practice.

Discussion

Glaucoma is a worldwide impact disease of great relevance because of its irreversible consequences on the patient's vision and increased prevalence given the aging population [12, 13, 121]. Despite the clinical and therapeutic advances, the pathological diagnosis is usually late, and biomarkers developments play a crucial role in improving these results. For an early diagnosis, many non-invasive techniques are necessary, which are very expensive and difficult to access for patients [24, 117, 120]. Therefore, searching for a new diagnostic approach is required.

Based on current research, the idea of studying chromatic pupillary response as a feasible option to recognize in time changes generated by glaucoma through a simple, fast-application method, affordable and easily transportable, allows an expanded diagnostic evaluation of different risk groups [122]. In addition, it is a non-invasive method and does not depend on the high cooperation of the patient or their health condition, achieving more reliable results and overcoming both the barriers generated by the physical and psychological state.

Recent evidence has shown possible alterations of the PRFI and PLR in the early stage of glaucoma [43, 48, 49, 52]. Nevertheless, the resistance of some ipRGCs to different types of glaucoma damage was reported [62–69]. Though some of these cells could be more resistant to injury than RGC without melanopsin, it does not imply that the pupillary function does not alter early in the pathology. Particularly in humans, three ipRGC subtypes (M1, M2, and M4) have been defined [29]. M1 ipRGCs located in the external IPL are divided into two subtypes, gigantic and displaced M1 RGCs (GM1 and DM1 cells, respectively). Both RGCs have inputs from bipolar cells and projections to the dorsal lateral geniculate nucleus (dLGN).

In particular, M2 ipRGCs correspond to the inner part of the inner plexiform layer (IPL), closer to the ganglion cell layer. M2 ipRGCs have a larger soma and more branched dendrites than M1 ipRGCs. They are also known to receive inputs from bipolar S-On cells and contribute to the blue cone pathway. In addition, M2 ipRGCs project to the pretectal olivary nucleus (OPN) in the thalamus, which is responsible for regulating the pupillary response to light. Despite current evidence providing a possible crucial role of ipRGCs in glaucoma pathology, their role in the early stages of pathology remains to be elucidated. Accurate determination of the level of susceptibility to damage in the early stages of glaucoma of the M2 subgroup of ipRGCs is key to the usefulness of this biomarker as a complementary test in the early diagnosis of the pathology [123].

We propose that alterations in pupillary dynamics, particularly in the short-wavelength chromatic spectrum, represent a selective response of a small group of ipRGCs that are more sensitive to the early changes generated by glaucoma. In this way, some studies suggest exceptions such as those observed in mitochondrial optic neuropathies, where ipRGC are protected from the effects of ganglion cell degeneration. On the contrary, evidence is clear in suggesting that in glaucoma and other non-mitochondrial diseases, the RGC is frequently damaged [34, 124]. Therefore, it is not possible to be sure

that this resistance is total or relative, given the diversity found in several studies. The only clear thing is that RGC degeneration is a feature of glaucoma pathogenesis [64].

In summary, the chromatic pupillary response based on published evidence seems to have potential as a biomarker for early glaucoma. It could acquire a crucial role as a new clinical trial, and it would facilitate the detection and monitoring of glaucoma by specialists in daily practice. Slower vision loss, with timely treatment, would significantly improve the quality of life of these patients. Highlighting the impact that early diagnosis would have on glaucoma and the need for permanent treatment [125]. Additionally, it would contribute to the decrease in economic expenditure that involves dealing with visual disability for each country [126–129]. However, it is still necessary to establish more clinical evidence to support it as a reference technique for early diagnosis and thus introduce its use in clinical practice.

Conclusions

At present, there is a need to create new diagnostic techniques to detect early-stage glaucoma. This review proposes the clinical evaluation of pupillary response to chromatic light, which has been considered in recent years as a possible and sensitive biomarker of the disease, as its role is precisely diminished by the damage of a subgroup of ganglion cells. New diagnostic techniques, such as analysis of chromatic pupillary response, arise to take early actions to reduce the progression and complications that lead to pathologies such as glaucoma, improving the visual prognosis of patients.

Abbreviations

RGC

Retinal Ganglion Cells

ipRGC

intrinsically photosensitive Retinal Ganglion Cells

POAG

Primary Open-Angle Glaucoma

PCAG

Primary Closed-Angle Glaucoma

VF

Visual Field

IOP

Intraocular Pressure

ONH

Optic Nerve Head

dLGN

Dorsal Lateral Geniculate Nucleus

IPL

Inner Plexiform Layer

OPN

Pretectal Olivary Nucleus

PLR

Pupillary Light Response

PRFI

Pupillary Response following Illumination

RAPD

Relative Afferent Pupillary Defect

OCT

Optical Coherence Tomography

NMDA

N-Methyl-D-aspartic acid

Declarations

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Authors' contributions

IPR and CAL: designed the study, wrote, and published the manuscript. SM: supplemented and reviewed the manuscript. IPR, CAL: prepared the manuscript for publication. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Figure 1

An altered pupillary mechanism as a possible biomarker of early glaucoma. On one side, the retinal structure of a normal eye, without RGC alterations, and the ipRGCs correctly perform their function in

pupillary dynamics. On the other hand, we observe the frequent retinal changes in an eye with glaucoma, highlighting the diminished RGC and the damage of the ipRGCs, altering the normal pupillary dynamics.

Figure 2

A schematic drawing of the most representative changes in clinical tests of glaucoma. On the left, a healthy eye, and on the right is an eye with glaucoma. Both cases show the expected results in the battery of tests for the detection and follow-up of glaucoma. (A) Aplanatic tonometry: measured by exerting pressure to flatten the cornea. The measurement of IOP is reached when the half rings (green/yellow) touch. However, if the rings are separated (for example, the glaucomatous eye), this is an indicator that there is still a lack of pressure to equalize the internal pressure. (B) Ocular fundus: Normal excavation vs. increased excavation. (C) Computerized visual field: Normal blind spot versus typical defects such as enlarged blind spot, paracentral scotomas, nasal step. (D) Optical Coherence Tomography: Normal fiber thickness (green) in all quadrants (N: nasal, NS: superonasal, NI: inferonasal, T: temporal, TS: superotemporal, TI: inferotemporal) versus altered thickness (red) in some quadrants in the glaucomatous eye.