AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Intrinsically Photosensitive Retinal Ganglion Cell Activity Is Associated with Decreased Sleep Quality in Patients with Glaucoma

Carolina P.B. Gracitelli, MD,[1] *Gloria Liliana Duque-Chica, PhD,*[2] *Marina Roizenblatt, MD,*[1] *Ana Laura de Araújo Moura, MD, PhD,*[1,2] *Balazs V. Nagy, PhD,*[2] *Geraldine Ragot de Melo, MD,*[1] *Paula Delegrego Borba, MD,*[1] *Sérgio H. Teixeira, MD, PhD,*[1] *Sergio Tufik, MD, PhD,*[3] *Dora Fix Ventura, PhD,*[2] *Augusto Paranhos, Jr., MD, PhD*[1]

Purpose: To use the pupillary light reflex and polysomnography to evaluate the function of intrinsically photosensitive retinal ganglion cells (ipRGCs) and to correlate this function with structural damage in glaucoma.

Design: Cross-sectional study.

Participants: A study was conducted on both eyes of 45 participants (32 patients with glaucoma and 13 healthy subjects).

Methods: For the pupillary reflex evaluation, patients were tested in the dark using a Ganzfeld system (RETIport; Roland Consult, Brandenburg, Germany); pupil diameter was measured with an eye tracker system. To preferentially stimulate ipRGCs, we used a 1-second 470-nm flash with a luminance of 250 cd/m^2. To stimulate different retinal photoreceptors, we used a 1-second 640-nm flash with a luminance of 250 cd/m^2. All of the subjects underwent polysomnography. Subjects underwent standard automated perimetry and optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc, Dublin, CA).

Main Outcome Measures: Correlations between ipRGC activity, as measured by the pupillary light reflex, and polysomnography parameters, and correlations between retinal nerve fiber layer (RNFL) thickness and the pupillary light reflex and polysomnography parameters.

Results: The mean patient ages in the healthy and glaucoma groups were 56.8±7.8 years and 61.5±11.6 years, respectively ($P = 0.174$). Patients with glaucoma had significantly lower average total sleep time, sleep efficiency, and minimum oxyhemoglobin saturation compared with the healthy subjects ($P = 0.008$, $P = 0.002$, and $P = 0.028$, respectively). Patients with glaucoma had significantly higher arousal durations after falling asleep and more periodic limb movements ($P = 0.002$ and $P = 0.045$, respectively). There was an inverse correlation between the rapid eye movement latency and the peak of the pupillary response to the blue flash ($P = 0.004$). The total arousals were inversely correlated with the sustained blue flash response ($P = 0.029$). The RNFL thickness was associated with the peak and sustained responses to the blue flash ($P < 0.001$ for both comparisons); however, RNFL thickness was only associated with the mean oxygen desaturation index among the polysomnography parameters ($P = 0.023$).

Conclusions: This study demonstrated that decreased ipRGC function caused by glaucoma affected pupillary response and sleep quality. *Ophthalmology 2015;■:1–10 © 2015 by the American Academy of Ophthalmology.*

Sleep disturbances and abnormal circadian rhythms have been reported in patients with different types of blindness.[1,2] Blind patients, particularly those with no light perception, may not respond to light stimulus, which is considered to be one of the most important factors influencing circadian rhythms and leading to sleep disturbances.[3,4] Several studies have reported the association between circadian rhythms and different grades of visual impairment.[2,5] For example, Tabandeh et al[2] studied 403 blind subjects and observed a high frequency of sleep disturbance in these patients; however, these symptoms occur more frequently in patients with no light perception than in those with light perception or better visual acuity.

Of all the diseases that can lead to blindness, glaucoma is one of the most important diseases; it affects more than 70 million people worldwide, of whom approximately 10% are bilaterally blind.[6] Glaucoma is a group of optic neuropathies characterized by progressive degeneration of the retinal ganglion cells (RGCs) and their axons, resulting in a characteristic appearance of the optic disc and a concomitant pattern of visual field loss.[7,8] Loss of visual function in glaucoma is generally irreversible, and without adequate treatment, the disease can progress to disability and blindness.[7,8]

Ganglion cell damage in glaucoma might result in death in many different classes of neurons. Intrinsically photosensitive

http://dx.doi.org/10.1016/j.ophtha.2015.02.030
ISSN 0161-6420/15

retinal ganglion cells (ipRGCs) constitute a type of ganglion cell that express the photopigment melanopsin[9–12] and mediate "nonvisual" responses to light (e.g., regulating the photic synchronization of circadian rhythms[12–15] and the pupillary light reflex,[16] as well as modulating behavioral mood regulation and memory).[17,18]

The true impact of glaucoma on sleep quality, sleep disturbance, or circadian rhythm is controversial. Jakobs et al[19] reported that ipRGC degeneration was proportional to that of the entire ganglion cell population. However, Li et al[20] showed that there is a selective resistance to ipRGC death compared with the entire ganglion cell population. Nevertheless, a few preliminary studies in animal models of glaucoma have suggested that a loss of ipRGCs impairs circadian rhythm regulation.[21,22] A few human studies have described abnormal circadian rhythms for melatonin secretion and light-induced melatonin suppression in subjects with glaucoma.[23] However, no previous studies have investigated sleep quality or circadian rhythm abnormalities using polysomnography parameters and correlated them with the pupillary light reflex and structural damage parameters in patients with glaucoma.

Therefore, on the basis of the hypothesis that ipRGC loss is involved in the natural history of glaucoma damage and that the loss of these cells can affect sleep quality and the pupillary light reflex, this study aimed to use polysomnography and the pupillary light reflex to evaluate ipRGC function in patients with glaucoma and to correlate these functions with structural damage parameters in these patients.

Methods

This cross-sectional study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board at Federal University of São Paulo (CEP 262.470). Written informed consent was obtained from all participants.

Study Sample

A total of 45 participants were recruited from the Federal University of São Paulo. Thirty-two of these patients had primary open-angle glaucoma, and 13 patients served as the healthy control group. Methodological details involving the inclusion and exclusion criteria, as well as the ophthalmological assessment, are described in detail next and were also previously used by our research group.[24] All of the subjects underwent complete ophthalmological examinations, including a medical history review, best-corrected visual acuity measurement, slit-lamp biomicroscopy, gonioscopy, intraocular pressure measurement, dilated funduscopic examination using a 78-diopter (D) lens, refraction, and standard automated perimetry using the Swedish interactive threshold algorithm (SITA Standard 24-2; Carl Zeiss Meditec, Inc, Dublin, CA). Subjects (i.e., healthy controls and glaucoma patients) were excluded if they were aged younger than 40 years or older than 80 years; had a best-corrected visual acuity of <0.2 logarithm of the minimum angle of resolution; had a history of ophthalmic surgery; had any corneal, retinal, or orbital diseases; presented with an absolute spherical refractive error >5 D or an absolute cylindrical error >3 D; or were using alpha-adrenergic agonist eye drop medications or any systemic medication that could affect the pupillary response. Patients with glaucoma were using at least 1 of the following classes of medication: prostaglandin analogs (i.e., bimatoprost 0.03%), beta-adrenergic antagonists (i.e., timolol maleate 0.05%), or carbonic anhydrase inhibitors (i.e., c. dorzolamide 2%). Only patients with an open angle on gonioscopy were included in our study.

Patients were diagnosed with glaucoma if they had at least 3 repeatable, consecutive, abnormal visual field test results, defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside of the normal limits and matching the appearance of the optic disc. Patients were also considered to have glaucoma if they had signs of glaucomatous optic neuropathy, based on clinical examination by a glaucoma expert and confirmed by stereophotographs. Glaucomatous damage to the optic disc nerve was considered if the patient had retinal nerve fiber layer (RNFL) defects or localized or diffuse neuroretinal rim loss.

Patients were considered to be healthy if they had normal ophthalmological examination results, with an intraocular pressure of <21 mmHg, normal visual field testing, and the absence of glaucomatous optic neuropathy on funduscopic and stereoscopic optic disc photography evaluations.

Pupillary Light Reflex Test

Measurement of the pupillary stimulus response was based on the method developed by Park et al,[25] which has been used in previous studies.[24,26] To stimulate the ipRGCs preferentially, we used a 470-nm (blue) flash with a luminance of 250 cd/m^2 and a 1-second duration. Alternatively, to stimulate different retinal photoreceptors, such as the cones and rods, without direct stimulation of the ipRGCs, we used a 640-nm (red) flash with a 1-second duration and luminance of 250 cd/m^2. For each stimulus, a red flash was presented first, followed by a blue flash 60 seconds after the offset of the red flash. The intervals between stimuli allowed the pupil size to return to baseline before the presentation of the subsequent stimulus. Both eyes were tested monocularly, and the testing order of each eye was randomly chosen. The patients were dark-adapted for 10 minutes; then, alternating 1-second red and blue flashes with a luminance of 250 cd/m^2 were presented.

Stimuli were generated by corresponding light-emitting diodes in a Ganzfeld system (RETIport; Roland Consult, Brandenburg, Germany), and responses were recorded using an eye-tracking camera system with an infrared light-emitting diode (Arrington Research, Scottsdale, AZ).[25,27,28] Peak amplitude was calculated as the maximum pupil constriction and was expressed relative to the baseline value (peak amplitude = max constriction diameter/baseline diameter). The sustained response was expressed as the pupil diameter at 6 seconds after the flash offset relative to baseline.[25]

Polysomnography

To obtain the sleep parameter information, all polysomnographic recordings were performed over a full night in a temperature-controlled and sound-attenuated room (EMBLA_S7000, Embla Systems Inc, Broomfield, CO). By using standard techniques, surface electrodes were used to record the following issues: electromyogram, electrocardiogram, electrooculogram, and pneumographic impedance (for recording thoracic-abdominal movements). Patients were also equipped with thermal sensors (to allow the recording of nasal and oral airflow), body position sensors, and an infrared sensor for the pulse oximeter, which was connected to the distal phalanx (to record oxyhemoglobin saturation). A snoring sensor also was used.[29]

The following parameters were included in the polysomnography assessment: sleep latency (i.e., the amount of time before starting the effective sleep time), sleep latency rapid eye