Can glaucoma affect sleep quality?

O glaucoma pode afetar a qualidade do sono?

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Glaucoma is an optic neuropathy characterized by the progressive loss of retinal ganglion cells (RGCs) and associated morphological changes to the optic nerve and retinal nerve fiber layer (RNFL)[1]. Although most RGCs are related with cortical image processing, a small proportion of RGCs, called intrinsically photosensitive RGCs (ipRGCs), are not involved in the thalamo-cortical pathway of image processing and mediate non-image-forming visual functions such as circadian photoentrainment and pupillary light reflex (PLR)[2,3].

In 2000, ipRGCs were described in mammalian inner retina as a new photoreceptor that expresses the photopigment melanopsin[3]. These cells account for approximately 3% of the entire RGC population in the human retina[3]. The ipRGC is most sensitive to short wavelength, i.e., blue light, and directly contributes to the post-illumination pupil response of sustained constriction (>6 s) after the offset of high luminance (250 cd/m^2)[4]. The loss of the ganglion cell population that happens in glaucomatous disease potentially leads to damaged function and/or a decreased number of ipRGCs[2].

The pupillary light reflex test is used as an indicator of the afferent input from the retina and optic nerve. Recently, studies using pupillography with different stimuli tested conditions to target specific retinal ganglion cell subtypes, such as ipRGCs. Evaluating this specific class of RGCs, our group demonstrated a significant correlation between structural damage, as measured based on RNFL thickness, and the sustained response to blue flashes with high luminance during the pupillary light reflex in glaucomatous patients[5]. In addition, we found a significant correlation between the severity of glaucoma, as measured by functional damage and the sustained pupillary response[5]. The main clinical finding in this study was the correlation between the RNFL thickness and pupillary response[5]. Probably, in the future, with further investigations clinical examination of the pupillary response could be used for monitoring glaucoma progression and assessing prognosis.

The true impact of ipRGC damage caused by glaucoma on sleep quality or circadian rhythm has only recently been elucidated. In the human brain, the primary circadian pacemaker is the suprachiasmatic nucleus (SCN), and light plays an important role in synchronizing the circadian system[6]. The light intensity seems to influence melatonin secretion, which in turn modulates sleep and the circadian rhythm. The responses driven by photic input from the eyes are transmitted through the retinohypothalamic tract to the SCN[7] and from there to the upper part of the thoracic spinal cord, the superior cervical ganglia, and the pineal gland[8]. The SCN receives photic input from ipRGCs. Their input synchronizes the SCN to the solar day, which keeps the human circadian rhythm close to a 24-hour cycle by driving the nocturnal synthesis of the pineal hormone melatonin and inducing the circadian phase and sleep[9]. Using polysomnography, we showed that compared with healthy subjects, glaucoma patients had worse sleep quality, and the polysomnographic parameters of sleep disorders were associated with a poorer sustained response to the pupillary reflex in glaucoma patients[10]. Therefore, the damage to the ipRGCs caused by glaucoma decreases their input synchronization, thereby leading to sleep disorders.

Moreover, some evidence has shown that the damage to ipRGCs caused by glaucoma is also correlated with increased daytime sleepiness as measured by a self-report questionnaire (Epworth sleepiness scale), and this symptom is also correlated with polysomnographic parameters and a decreased sustained pupillary response[11]. It is well known that excessive daytime sleepiness affects the quality of life, daytime function, and mortality. Therefore, these two major non-image-forming functions of ipRGCs should be considered in certain glaucoma evaluations.

In fact, certain specific drawbacks of this issue should be mentioned. Until recently, we investigated these non-image-forming visual functions in glaucomatous population using small sample sizes and cross-sectional designs that did not allow the longitudinal association of the pupillometry with the progression of glaucoma. There is a relatively weak association between the RNFL thickness and sustained pupillary response, and the strength of this association varies depending on the severity of the disease. Therefore, the pupillary reflex should be considered a good tool for progression detection but not for glaucoma diagnosis. Using this pupillary test as a surrogate measure for glaucoma instead of existing techniques is thus not recommended. However, a complete evaluation would also need to include a more thorough assessment of test-retest variability. Although we certainly believe that there is a relationship between glaucoma damage (measured by RNFL thinning) and

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ipRGC functions (i.e., polysomnography parameters), different issues could influence these complex systems, which comprise the circadian rhythm. Further studies with larger cohorts of patients should be performed to evaluate this hypothesis.

In conclusion, previous studies and our results provide ample evidence to suggest that glaucoma leads to RGC death, including ipRGC death. These cells are connected to several non-image-forming functions, including circadian photoentrainment and pupillary reflexes. Therefore, not only the image-forming but also non-image-forming visual systems are associated with glaucomatous disease. The circadian function has not been well investigated in clinical daily practice, but it can interfere with the quality of life of these patients. Concerns about sleep disturbances in glaucoma patients should be incorporated into clinical evaluations. In addition, abnormal PLR in glaucomatous patients is potentially associated with other consequences, such as sleep disorders.

REFERENCES

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901-11.
2. Li RS, Chen BY, Tay DK, Chan HH, Pu ML,So KF. Melanopsin-expressing retinal ganglion cells are more injury-resistant in a chronic ocular hypertension model. Invest Ophthalmol Vis Sci. 2006;47(7):2951-8.
3. Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD. A novel human opsin in the inner retina. J Neurosci. 2000;20(2):600-5.
4. Gamlin PD, McDougal DH, Pokorny J, Smith VC, Yau KW, Dacey DM. Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. Vision Res. 2007;47(7):946-54.
5. Gracitelli CP, Duque-Chica GL, Moura AL, Nagy BV, de Melo GR, Roizenblatt M, et al. A positive association between intrinsically photosensitive retinal ganglion cells and retinal nerve fiber layer thinning in glaucoma. Invest Ophthalmol Vis Sci. 2014;55(12):7997-8005.
6. Agorastos A, Huber CG. The role of melatonin in glaucoma: implications concerning pathophysiological relevance and therapeutic potential. J Pineal Res. 2011;50(1):1-7.
7. Ohi K, Takashima M, Nishikawa T, Takahashi K. N-methyl-D-aspartate receptor participates in neuronal transmission of photic information through the retinohypothalamic tract. Neuroendocrinology. 1991;53(4):344-8.
8. Moller M, Baeres FM. The anatomy and innervation of the mammalian pineal gland. Cell Tisseu Res. 2002;309(1):139-50.
9. Zele AJ, Feigl B, Smith SS, Markwell EL. The circadian response of intrinsically photosensitive retinal ganglion cells. PloS One. 2011;6(3):e17860.
10. Gracitelli CP, Duque-Chica GL, Roizenblatt M, Moura AL, Nagy BV, de Melo GR, et al. Intrinsically photosensitive retinal ganglion cell activity is associated with decreased sleep quality in glaucoma patients. Ophthalmology [Internet]. 2015 [cited 2015 Jan 21]. Available from: http://www.aaojournal.org/article/S0161-6420(15)00172-4/fulltext
11. Gracitelli CP, Duque-Chica GL, Moura AL, Roizenblatt M, Nagy BV, de Melo GR, et al. Relationship between sleep disorders and intrinsically photosensitive retinal ganglion cells in glaucomatous disease. Plos One. 2015. Submitted.