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Glaucomatous Optic Neuropathy Associated with Nocturnal Dip in Blood Pressure

Findings from the Maracaibo Aging Study

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Purpose: To determine which nocturnal blood pressure (BP) parameters (low levels or extreme dipper status) are associated with an increased risk of glaucomatous damage in Hispanics.

Design: Observational cross-sectional study.

Participants: A subset (n = 93) of the participants from the Maracaibo Aging Study (MAS) who met the study eligibility criteria were included. These participants, who were at least 40 years of age, had measurements for optical tomography coherence, visual field (VF) tests, 24-hour BP, office BP, and intraocular pressure <22 mmHg.

Methods: Univariate and multivariate logistic regression analyses under the generalized estimating equations (GEE) framework were used to examine the relationships between glaucomatous damage and BP parameters, with particular attention to decreases in nocturnal BP.

Main Outcome Measures: Glaucomatous optic neuropathy (GON) based on the presence of optic nerve damage and VF defects.

Results: The mean age was 61.9 years, and 87.1% were women. Of 185 eyes evaluated, 50 (27.0%) had signs of GON. Individuals with GON had significantly lower 24-hour and nighttime diastolic BP levels than those without. However, results of the multivariate GEE models indicated that the glaucomatous damage was not related to the average systolic or diastolic BP levels measured over 24 hours, daytime, or nighttime. In contrast, extreme decreases in nighttime systolic and diastolic BP (>20% compared with daytime BP) were significant risk factors for glaucomatous damage (odds ratio, 19.78 and 5.55, respectively).

Conclusions: In this population, the link between nocturnal BP and GON is determined by extreme dipping effects rather than low nocturnal BP levels alone. Further studies considering extreme decreases in nocturnal BP in individuals at high risk of glaucoma are warranted. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

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Glaucoma is an acquired and progressive optic neuropathy that is a leading cause of irreversible blindness worldwide.[1] Identifying and controlling risk factors in the early stages of glaucomatous damage are important to preventing blindness. To date, elevated intraocular pressure (IOP) is the only modifiable risk factor proven to be effective in preventing and controlling glaucoma progression.[1] However, glaucoma can develop and progress in eyes with IOP in the normal range.[2] Thus, the identification of new modifiable risk factors could open new therapeutic approaches to glaucoma prevention and therapy.[3]

The role of systemic blood pressure (BP) in glaucoma pathogenesis has been increasingly gaining attention. However, its role based on conventional snapshot BP measurements of glaucomatous damage is unclear given the diurnal variations of BP.[4–6] The 24-hour ambulatory BP monitoring (ABPM) provides information on changes in BP during the day and at night, as well as mean BP levels. Studies using ABPM have suggested that nocturnal hypotension is important to glaucoma progression[4,7]; however, it is unclear which nocturnal BP parameter (low average nighttime BP vs. extreme dipper status) is the most relevant risk factor. Furthermore, previous studies using ABPM included only patients with glaucoma[4,7–9]; thus, it appears important to study the relationships between ABPM components and glaucoma risk in the general population.

This study examined a subset of study participants from the Maracaibo Aging Study (MAS) to test the hypothesis that extreme dipper status (an exaggerated nighttime decrease in systolic or diastolic BP), and not simply low

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average nighttime BP levels, contributes to glaucomatous optic neuropathy (GON).

Methods

Sample Population

We studied 93 MAS participants who were evaluated for eye health and who met the selection criteria described next.[10] The MAS—a population-based epidemiologic study of age-related traits—currently includes approximately 3000 individuals, ≥40 years of age, living in the Santa Lucia neighborhood[10] or in the nearby community of Santa Rosa de Agua[11] in Maracaibo, Venezuela; all MAS participants received standardized assessments.[10] Randomly selected participants were invited to undergo an ophthalmological assessment. To be included in this study, individuals had to have completed OCT scans, visual field (VF) tests, ABPM, and office BP measurements. We decided to exclude 1 individual with an IOP ≥22 mmHg, which we believed would only add uncertainty to results. Ninety-three individuals met the criteria. Each participant signed an informed consent, which was approved by the Institutional Review Boards of the Cardiovascular Institute at University of Zulia and Columbia University.

Ophthalmological Assessment

Ophthalmologists conducted an ocular assessment of both eyes. This assessment included clinical ocular history; best-corrected visual acuity; a slit-lamp examination (gonioscopy); and a dilated evaluation of the lens, vitreous, and retina. The IOP was estimated with Goldmann tonometry. Standard automated perimetry was performed with the Heidelberg Edge Perimeter (Heidelberg Engineering, GmBH, Heidelberg, Germany). Spectralis spectral-domain (SD) OCT (software version 5.4.7.0; Heidelberg Engineering, GmBH) was used to measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). Peripapillary RNFL measurements were obtained in a circle scan centered on the optic disc. The RNFL analysis used an automated computer algorithm to identify the anterior and posterior margins of the RNFL, from which the RNFL thickness was calculated. In addition, if the visual acuity was 20/20 or better in each eye according to the Standard Early Treatment Diabetic Retinopathy Study protocol at 4 m, refraction was the lensometer reading of the individual's spectacle or plano. Otherwise, we performed a noncycloplegic autorefraction (Humphrey autorefractor model Hark 599, C. Zeiss, Meditec, Dublin). For individuals with visual acuity less than 20/20, subjective refraction was performed following standard protocols.

Glaucomatous optic neuropathy diagnosis based on clinical examination and confirmation with SD OCT abnormalities had to include at least 2 peripapillary sectors flagged as "borderline" ($P < 0.05$) or 1 sector "outside normal limits" ($P < 0.01$). All patients underwent clinical examination with indirect ophthalmoscopy with a 78/90 diopter lens. In addition, reflectance images of the optic disc were evaluated, looking for signs of cupping and RNFL thinning. Finally, the attending clinician and OCT/VF reader followed the recommendations of the American Academy of Ophthalmology Preferred Practice Patterns.[12] The OCT RNFL b-scans had to be free of segmentation errors and blinking/eye movement artifacts. The VF abnormalities required at least 3 neighboring points that were 5%, 5%, and 1% probability, or 5%, 2%, and 2% probability or poorer within a hemifield on pattern deviation plots, with only 1 point allowed on the edge of the VF. The VF results had false-negative, false-positive, and fixation-loss rates less than 30%. Glaucoma was diagnosed during the clinical optic disc evaluation and confirmed with SD OCT peripapillary RNFL thickness measurements, based on the presence of GON and VF abnormalities. Suspected glaucoma was diagnosed if the patient met the criteria for GON, but not for VF abnormality. The ophthalmologist determined, via gonioscopy, that all cases of GON identified in our population were open-angle. An abnormal optic disc was defined as diffuse or focal narrowing, or notching, of the optic disc rim, or optic disc neural rim asymmetry of the 2 eyes consistent with loss of neural tissue. An abnormal VF, when present, was defined as (1) VF damage consistent with RNFL damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites) based on the presence of abnormal clusters; or (2) VF defects consistent with glaucomatous optic nerve damage.

The diagnosis of glaucoma or suspected glaucoma was performed by one of the investigators (CGDM) from the Optic Nerve and Visual Field Reading Center at Columbia University Medical Center in New York. Because of the small number of individuals with glaucoma in the study, we combined the 2 diagnostic groups (i.e., glaucoma and suspected glaucoma) as the main outcome measure of GON.

Blood Pressure Measurements

The office systolic BP and diastolic BP were obtained for each participant by trained nurses at the Cardiovascular Institute of the University of Zulia, using a validated automated device (Dynamap, XL). After participants had rested in a sitting position for 5 to 10 minutes, 5 consecutive (1 per minute) BP measurements were taken in a sitting position and averaged. The ABPM devices (validated oscillometric 90202 or 90207 SpaceLabs monitors, Redmond, WA) were programmed to obtain readings every 15 minutes during daytime hours (06:00-22:59) and every 30 minutes during nighttime hours (23:00-05:59).

The hypertension diagnosis followed the guidelines of the European Societies of Cardiology and Hypertension, 2013. Office hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive drugs. The 24-hour BP, daytime BP, and nighttime BP measurements were the average BP recordings during the appropriate intervals. Ambulatory hypertension was defined as 24 hours of systolic BP ≥130, diastolic BP ≥80 mmHg, or the use of antihypertensive drugs.

Dipper statuses were defined as follows: (i) extreme dipper: an abnormal decrease in the nocturnal BP levels more than 20% in relation to diurnal BP levels; (ii) dipper: a normal decrease in the nocturnal BP levels between 20% and 10% in relation to diurnal BP levels; (iii) nondipper: a minor or no decrease in nocturnal BP levels, ranging from 10% to 0%; and (iv) reverse dipper: an abnormal increase in nocturnal BP levels in relation to daytime BP levels. To identify the decrease or increase in nocturnal BP levels in relation to daytime BP levels, we used the ABPM to calculate the night/day BP ratio, as suggested by Fagard et al.[13] Night/day BP ratios ≤0.8 indicated an extreme dipper, >0.8 to 0.9 indicated a dipper, >0.9 to 1.0 indicated a nondipper, and >1.0 indicated a reverse dipper. Dipper status was determined separately for systolic BP and diastolic BP. We combined reverse dippers with nondippers for analysis because of the small number of participants who were reverse dippers and the fact that nondipper and reverse dipper status did not add any significant risk for GON (Table S1, available at www.aaojournal.org).

Other Information

Participants provided their medical history, including age, sex, level of education, smoking history, alcohol intake, and