

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Nocturnal BP Patterns That May Signal Glaucoma in Hispanics

June 2018

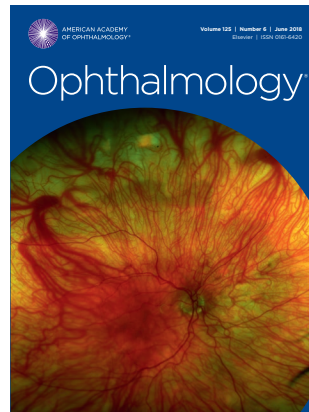
Melgarejo et al. observed nocturnal blood pressure (BP) readings from Hispanic patients to identify characteristics that may increase the risk of glaucomatous damage. They found that episodes of extreme reduction in blood pressure (“BP dipping”) are more worrisome than generally low BP itself during the night.

This observational study included 93 participants of the Maracaibo Aging Study who had normal intraocular pressure (IOP) and were at least 40 years old (mean, 62 years). They were required to have undergone optical coherence tomography scanning, visual field (VF) tests, and 24-hour and office BP monitoring. Approximately 14% of the study population had diabetes. Based on results of office and ambulatory BP monitoring, the prevalence of hypertension was 65% and 56%, respectively; and 47% of those with office-identified hypertension were taking antihypertensive medications.

The authors used univariate and multivariate logistic regression analyses to observe relationships between glaucomatous damage and BP parameters, with particular emphasis on nocturnal BP levels. The main outcome measure was glaucomatous optic neuropathy (GON), denoted by the presence of optic nerve damage and VF defects.

Of the 185 eyes evaluated, 49 had signs of GON. It was determined, via gonioscopy, that all GON cases in this study were open angle. Patients with GON had significantly lower nighttime and 24-hour diastolic BP than did those without this neuropathy ($p = .009$ and $.014$, respectively). However, the multivariate models with generalized estimating equations suggested that the glaucomatous damage was unrelated to average systolic or diastolic BP measured at daytime, at nighttime, or over 24 hours. Overall, extreme nocturnal drops ($>20\%$ compared with daytime BP) in systolic or diastolic BP were significant risk factors for glaucomatous damage (odds ratios: systolic, 19.78; diastolic, 5.55).

This research supports the use of ambulatory 24-hour BP monitoring to help identify individuals with extreme BP dips who require further ophthalmologic assessment. Additional studies of nocturnal BP decreases in people at risk of glaucoma are warranted to clarify the utility of “extreme dipper” status as a risk factor. Therapies that modify glaucoma risk are urgently needed, as are new approaches to avoid extreme dipping, which may include changing the time that antihypertensive drugs are administered.



Real-World Burden and Progression of Geographic Atrophy

June 2018

Chakravarthy et al. conducted research to better understand the progression of geographic atrophy (GA) to choroidal neovascularization (CNV) and the effect of GA on visual acuity (VA) in real-world settings. They found that the atrophy is

linked to substantial visual impairment that often renders those with GA ineligible to drive.

For this multicenter retrospective study, an anonymized dataset was constructed from the electronic health records (EHRs) from October 2000 to February 2016 at 10 clinical sites in the United Kingdom. An algorithm was used to identify cases with a GA diagnosis. From these records, the researchers isolated a study population of 1,901 patients (≥ 50 years of age) with bilateral GA and no history of CNV. A random sample of records from each center was used to validate the definitions of disease and progression.

Outcomes of interest were progression to blindness (VA < 20 Early Treatment Diabetic Retinopathy Study letters or Snellen 20/400 in the better eye), driving ineligibility (VA ≤ 70 letters or Snellen 20/40 in the better eye), progression to CNV, loss of ≥ 10 letters, and mean change in VA over time. Another goal was to identify risk factors associated with progression.

At the time of their first record of a GA diagnosis, 7.1% of patients had VA in the better eye that was at or below the threshold for legal blindness; 71.1% had VA that was too low for driving privileges. Over time, 16% patients became legally blind (median time to outcome, 6.2 years), and 67% became ineligible to drive (median time to outcome, 1.6 years). Among the participants with VA measurements at both baseline and 24 months, the mean decline in VA was 6.1 letters in the worse eye and 12.4 letters in the better eye. The rate of progression to CNV in either eye was 7.4% per patient-year. Older age and poorer VA at diagnosis were risk factors for a decline in VA to below the UK standard for driving.

Assessing Whiplash-Related Convergence Insufficiency

June 2018

Whiplash related to motor vehicle accidents may cause complaints of visual disturbance and ocular discomfort, including convergence insufficiency (CI). Stiebel-Kalish et al. compared CI findings between patients who experienced whiplash during an accident and age-matched controls. They found that although patients with whiplash had more visual symptoms, they did not have a higher incidence of CI by objective measures.

For this prospective study, adults with whiplash-associated disorder (WAD) following a motor vehicle accident ($n = 57$; mean age, 37 years) were recruited from an orthopedic emergency department between July 2014 and March 2017. Control participants ($n = 39$; mean age, 39 years) were hospital personnel and relatives of the patients with WAD. All participants completed the Convergence Insufficiency Symptom Survey (CISS), which is a validated questionnaire, and underwent a detailed visual exam. Assessments included near and distance best-corrected visual acuity and near and distance cover tests, as well as Randot stereopsis and Maddox distance and Maddox-Thorington near heterophoria tests. The CISS score and binocular measure findings of CI were document-

ed and analyzed with the Student t test, chi-squared test, and multiple logistic regression; and adjustments were made for age and gender.

The analyses showed that 26 (45.6%) of the 57 patients with WAD had a pathologic CISS score of at least 16, compared with only 6 (15.4%) of the 39 controls ($p = .002$). The absolute CISS score was higher for the WAD group (15.3 ± 10.0 vs. 7.7 ± 7.7 ; $p < .001$). However, objective findings consistent with CI were similar for the WAD and control groups (7.0% and 7.7%, respectively).

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Baseline Predictors and Vision in Comparison of AMD Treatments Trials Study

June 2018

In a secondary analysis of data from the Comparison of AMD Treatments Trials (CATT) study, Ying et al. set out to determine baseline predictors of 5-year visual acuity (VA) outcomes in patients who were treated with either bevacizumab or ranibizumab for wet age-related macular degeneration (AMD).

For this study, the researchers evaluated 647 patients who had participated in CATT and completed a 5-year follow-up visit. At the 5-year mark, the mean VA in the study eye was approximately 20/63, and the mean loss from baseline was 3.3 Early Treatment Diabetic Retinopathy Study letters. Of these patients, 114 (17.6%) had gained ≥ 3 letters, and 129 (19.9%) had a VA of 20/200 or worse.

In keeping with their earlier analyses of the CATT patient population, the researchers found that the presence at baseline of worse VA, larger choroidal neovascularization (CNV) lesion area, and any retinal pigment epithelium (RPE) elevation remained independently associated with worse VA at the 5-year mark. The researchers also evaluated 5-year VA outcomes according to genotype; in another confirmation of earlier findings, no association emerged between VA outcomes at 5

years and any of the 21 SNPs (single nucleotide polymorphisms) evaluated. Finally, they found that male sex, cigarette smoking, absence of subretinal fluid, and treatment with ranibizumab during the first 2 years of CATT were independently associated with worse visual outcomes at 5 years.

The association with current smoking had not emerged in the earlier analyses; in this study, current smokers were 2.6 times more likely than nonsmokers to have a VA of 20/200 or worse at 5 years.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Large Intereye Asymmetry in Vessel Density May Signal Glaucomatous Damage

June 2018

Hou et al. measured intereye retinal vessel density of glaucomatous and healthy eyes to assess whether asymmetry may indicate early glaucomatous damage, which often is asymptomatic. They found that intereye asymmetry of vessel density is much greater in glaucoma suspects than in people with healthy eyes.

This cross-sectional study included 55 individuals with healthy eyes, 32 glaucoma suspects, and 66 patients with mild or moderate glaucoma. Age, sex, and racial distributions were comparable for the 3 cohorts. Retinal vessel density was measured using optical coherence tomography angiography (OCTA) of the macula and optic nerve head. Thickness of the peripapillary retinal nerve fiber layer and the macular ganglion cell complex was measured with spectral-domain OCT. Intereye asymmetry was calculated as the difference in vessel density and thickness between each subject's eyes. Univariate and multivariate analyses were performed to compare findings.

Results showed substantial differences between the study groups. Univariate and multivariate analyses demonstrated that intereye asymmetry in both peripapillary and macular vessel density was significantly greater for glaucoma

suspects than for individuals with healthy eyes, but intereye asymmetry in thickness was similar for these groups. For all thickness-related parameters, there were significant differences between glaucoma suspects and glaucoma patients, both with and without adjustment for confounders; median values for glaucoma patients were roughly double those for suspects.

Examining intereye asymmetry of retinal vessel density may be a helpful adjunct to glaucoma screening programs; a better understanding of events that precede the onset of glaucoma would facilitate early diagnosis. Longitudinal studies are needed to further characterize the relationship between intereye variation in vessel density and the development and progression of glaucoma.

Does Cataract Surgery Improve Vision in Patients With Neovascular AMD?

June 2018

The question of whether cataract surgery improves vision in patients with certain types of age-related macular degeneration (AMD) continues to be the subject of some debate. **Daien et al.** looked at visual acuity (VA) data for patients with neovascular AMD who did and did not receive cataract surgery. They found that, although cataract surgery appeared to modestly increase the activity of choroidal neovascular (CNV) lesions, visual outcomes were good.

For this retrospective case-control study, the researchers gathered information from the Fight Retinal Blindness! observational database. Records for eyes that underwent cataract surgery and were monitored since the start of neovascular AMD treatment ($n = 124$) were compared with records for unoperated phakic eyes that also were being treated for neovascular AMD (control group; $n = 372$). Cases were matched for age, baseline VA, and duration of treatment and follow-up.

By 12 months postoperatively, cataract surgery resulted in a mean gain of 10.6 letters, and the mean VA was better for operated eyes (65.8 vs. 61.3

letters; $p = .018$). The mean number of anti-VEGF intravitreal injections and the proportion of visits in which CNV lesions were active did not change substantially after cataract surgery. However, both numbers declined in the control group, suggesting that the surgery increased lesion activity. Patients whose surgery occurred in the first 6 months of receiving intravitreal injections were more likely to lose rather than gain vision. Factors that had no discernible influence on VA outcomes included age, type of CNV lesion, and intravitreal injection at least 2 weeks before surgery.

These findings suggest that, when possible, cataract surgery should be avoided in the first 6 months of treatment for neovascular AMD. The authors emphasized that observation is a sensible design for studying the efficacy of cataract surgery because it does not pose the ethical concern of assigning patients who require surgery to a nonsurgical control group.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Small Uveal Melanoma: Yield Rates and Other Traits of FNAB May 2018

Assessing the adequacy of biopsy samples intraoperatively may help to ensure appropriate cell yield, which can be challenging for small lesions. In a retrospective study, **Kim et al.** documented yield rates for transscleral and transvitreal fine-needle aspiration biopsies (FNAB) of small uveal melanomas (apical height <3.6 mm); they found that intraoperative evaluation was associated with high yield and a favorable safety profile.

This observational study of consecutive cases included 44 patients (mean age, 63.3 years) with uveal melanoma of the ciliary body or choroid. In all cases, FNAB and intraoperative histopathologic analysis were performed before administration of iodine-125 (^{125}I) brachytherapy. Tumor locations and dimensions were determined from

B-scan ultrasonography and histopathologic analysis. Transscleral biopsy was performed for tumors anterior to the equator, and transvitreal biopsy was used for posterior lesions. The adequacy of each biopsy specimen was checked intraoperatively. Specimens underwent hematoxylin-eosin staining, double immunostaining with human melanoma black 45 and Ki67, and gene expression profiling.

The median tumor height was 2.7 mm (interquartile range, 2.3–2.9 mm). Of the 44 biopsy samples, 40 (90.9%) contained ample cells for gene expression analysis. Yield rates were 100% (11 of 11) for transscleral specimens and 87.9% (29 of 33) for transvitreal specimens.

Localized vitreous hemorrhages occurred in 24 eyes, and most resolved within 3 months. A moderate association was observed between localized vitreous hemorrhage and the transvitreal biopsy method (phi value, -0.526 ; $p < .001$).

As the role of genetic testing for uveal melanoma continues to expand, greater emphasis is being placed on obtaining specimens of adequate size. The authors' findings suggest that intraoperative assessment helps ensure that samples contain a sufficient number of cells for analysis. Their research also affirms the safety and efficacy of FNAB as a diagnostic tool for uveal melanoma. Large prospective multicenter trials of various biopsy techniques are needed to determine the ones best suited for achieving high yield rates. The authors are participating in such an effort and plan to report their findings. (*Also see related commentary by Carol L. Shields, MD, Arman Mashayekhi, MD, and Jerry A. Shields, MD, in the same issue.*)

Preferred Practice Pattern Guidelines and the Process of Attaining Reliable Evidence

May 2018

Golozar et al. described their experience in identifying reliable evidence supporting the topics addressed in the 2016 update of the Academy's 2011 *Preferred Practice Pattern (PPP)* guidelines for treating cataract in adults. They

found that the partnership between the Academy and Cochrane Eyes and Vision US Satellite (CEV@US) facilitated the process of locating robust data relevant to the update.

Initially, searches of systematic reviews on the management of cataract, published in English or Chinese, were conducted. Reliable systematic reviews were required to include the following: eligibility criteria, a comprehensive search/review of the literature, assessment of methodologic quality of studies included, use of appropriate meta-analysis methods, and conclusions derived from the studies reviewed. Each relevant review was mapped to at least 1 of the 24 management categories listed in the table of contents of the 2011 Academy PPP guidelines. Data were extracted from each review to determine its reliability, and the reviews deemed reliable were cross-checked against the guidelines. The authors studied whether any reliable reviews published before February 2010 (the cutoff search date for the 2011 guidelines) had been cited in the 2011 version. (CEV@US did not supply systematic reviews for the 2011 guidelines.)

The search returned 99 systematic reviews on cataract management, 46 of which were classified as reliable. The most common reason for exclusion was no mention of a comprehensive literature search. All 46 reliable reviews have been cited in the Academy's 2016 PPP guidelines. In the 2011 guidelines, which were published before the Academy/CEV@US partnership began, only 8 of 15 reliable systemic reviews were referenced.

The authors believe that the partnership was successful for producing robust evidence to enrich the practice guidelines and, in turn, improve the care of adults with cataract.

Vitamin A Supplements and Retinitis Pigmentosa in Children May 2018

Supplementation with vitamin A may slow the loss of retinal function in adults with retinitis pigmentosa (RP), but little is known about its effect in children with the disease. Berson et

al. compared the disease course of RP between children using oral vitamin A palmitate and a control group. Although definitive conclusions could not be drawn from their small retrospective study, the findings suggest that vitamin A therapy may slow the loss of cone function in children with common forms of RP.

For this nonrandomized retrospective study, the researchers evaluated 80 children with RP; 55 of whom received $\leq 15,000$ IU of vitamin A palmitate per day. The remaining 25 children served as a control group. Both cohorts were followed for several years by the Electroretinography Service of the Massachusetts Eye and Ear Infirmary (dates for patient evaluations ranged from 1976 to 2016, and data were analyzed in 2016). Sex distribution and mean age appeared similar for the study cohorts. The primary outcome was the mean exponential rate of change of full-field cone electroretinogram (ERG) amplitude to 30-Hz flashes, estimated by repeated-measures longitudinal regression, with and without adjustment for potential confounders.

According to the unadjusted model, the estimated mean rate of change was $-0.0713 \log_e$ unit/year for the vitamin cohort and $-0.1419 \log_e$ unit/year for the control cohort (difference, $0.0706 \log_e$ unit/year; $p = .01$). The adjusted model showed that the mean rate of decline was slower for the vitamin cohort (difference, $0.0771 \log_e$ unit/year; $p = .009$). Ocular safety and the mean exponential change rates in visual acuity and visual field area appeared similar for the study groups.

The authors acknowledged that their study has several limitations, but the findings appear to support consideration of age-appropriate vitamin A therapy in children with common forms of RP and normal liver function. They suggest that vitamin A supplementation may be particularly beneficial for children with long cone ERG implicit time, who have a high risk for aggressive disease. (Also see related commentary by Caroline C.W. Klaver, MD, PhD, and Alberta A.H.J. Thiadens, MD, PhD, in the same issue.)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

IV or Oral Corticosteroids for Acute Optic Neuritis

JAMA Neurology

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Morrow et al. compared visual recovery after treatment of acute optic neuritis (ON) with either a high-dose intravenous (IV) corticosteroid or a bioequivalent oral corticosteroid. They found no significant difference in outcomes.

This randomized trial was conducted over several years at a tertiary care center in Canada and included a 6-month follow-up period. Assessors were masked with respect to treatment assignment. Eligible patients were adults aged 18 to 64 years who presented within 14 days of onset of unilateral demyelinating ON, had no prior history of ON in the affected eye, and had no evidence of recovery by the time of randomization. Other criteria were best-corrected visual acuity (BCVA) of 20/40 or worse and a documented need for corticosteroid treatment.

Of the 89 candidates screened, 55 were enrolled and received IV methylprednisolone sodium succinate (1,000 mg) or oral prednisone (1,250 mg) daily for 3 days. Visual evoked potentials were measured, and the primary outcome was recovery of the VEP P100 latency at 6 months. Secondary outcomes were P100 latency at month 1 and BCVA at months 1 and 6.

Forty-five patients completed the analyses (23 in the IV group, 22 in the oral group). By 6 months, P100 latency had improved to 62.9 ms (from 181.9 ms) in the IV group and 66.7 ms (from 200.5 ms) in the oral group ($p = .07$). There were no significant differences in P100 latency recovery at 1 month or BCVA recovery at 1 or 6 months, including low-contrast BCVA. In addition, there was no significant difference in adverse events between the groups.

—Summaries by Lynda Seminara



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