Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

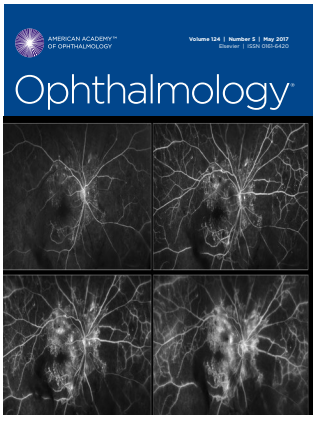
Selected by George B. Bartley, MD

Vancomycin-Associated Hemorrhagic Occlusive Retinal Vasculitis

May 2017

Witkin et al. sought to elucidate the presentation, diagnosis, and outcomes of hemorrhagic occlusive retinal vasculitis (HORV) that can occur after cataract surgery or intraocular injection. In this study, they found that all cases were associated with the use of intraocular vancomycin.

The American Society of Cataract and Refractive Surgery (ASCRS) and the American Society of Retina Specialists (ASRS) formed a joint task force and established an online registry to better understand the characteristics of this potentially devastating ocular condition. In addition, surveys were emailed to members and a literature search was performed to uncover more cases of suspected HORV. Drawing on these sources and using predetermined diagnostic criteria, the authors identified HORV in 36 eyes of 23 patients. All eyes in this group had received intraocular vancomycin through an intracameral bolus (33/36), an intravitreal injection (1/36), or the irrigation bottle (2/36).



The authors found that patients who developed HORV generally had an unremarkable undilated examination on postoperative day 1. Later characteristics included delayed-onset painless vision loss, mild anterior chamber and vitreous inflammation, sectoral retinal hemorrhages in areas of ischemia, and predilection for venules and peripheral involvement.

Patients presented for treatment 1 to 21 days after surgery or intravitreal injection. Various systemic and local treatments were tried in these patients, including photocoagulation, vitrectomy, anti-VEGF agents, antiplatelet drugs, and corticosteroids. Visual outcomes were poor in most cases: 22 of 36 eyes (61%) had visual acuity of 20/200 or worse, and 8 of 36 eyes (22%) had no light perception (NLP). Neovascular glaucoma developed in 20 of 36 eyes (56%). Seven eyes received additional intravitreal vancomycin after surgery; 5 of these 7 eyes had NLP visual acuity at the most recent examination. Three eyes that received intravitreal corticosteroids had final visual acuities of 20/40, 20/70, and hand movements.

The disease course and findings suggest that HORV is caused by a delayed hypersensitivity reaction to vancomycin. The researchers concluded that all of the patients in their case series had received intraocular vancomycin; however, because of the rarity of HORV, they are not yet recommending that surgeons discontinue its use. Rather, they developed a list of considerations for the use of vancomycin and provided recommendations for treatment if HORV is suspected, noting that early intervention with corticosteroids is likely to be beneficial. Subsequently, anti-VEGF injections and panretinal photocoagulation may be helpful in preventing neovascular glaucoma.

Adherence to Hydroxychloroquine Dosing Guidelines by Rheumatologists

May 2017

Braslow et al. examined rheumatologists' adherence to the hydroxychloroquine (HCQ) dosing guidelines published by the American Academy of Ophthalmology in 2011 and revised in 2016. They performed a review of records at a single integrated health care entity (NorthShore, Glenview, Ill.) and found that about half of the patients on HCQ were prescribed higher doses than those recommended in the guidelines.

The researchers used electronic medical records (EMR) to identify all patients in the system who had an order for HCQ between 2009 and 2016 and who had been evaluated by a NorthShore staff ophthalmologist during that time period (N = 554). Of these, 92 patients had been started on HCQ before publication of the 2011 guidelines, and 462 were started after. Recommended maximum starting

doses were calculated using 2 formulas based on either ideal body weight (per 2011 guidelines) or actual weight (per 2016 guidelines). The main outcome measure was the percentage of patients whose dose exceeded the recommended maximum.

The researchers found that approximately half of the patients had been placed on initial doses in excess of 2011 guideline recommendations, and there was no significant difference in percentages between those started before and after the guidelines were issued (54.3% and 49.4%, respectively; p = .381). Further, on the basis of the 2016 dosing guidelines, 56% of patients currently on HCQ continue to receive higher-than-recommended doses.

The researchers concluded that the published ophthalmology screening guidelines have had no appreciable impact on rheumatologists' prescribing patterns, as approximately half of all patients started on HCQ at NorthShore received doses above the recommended maximum, and more than half of all patients currently on treatment are receiving excessive doses. Such deficiencies in patient care pose substantial medicolegal risk. The researchers recommend instituting EMR-based alerts and dosing algorithms, which can be easily instituted and applied system-wide without creating added costs or requiring significant ophthalmology resources.

Peripapillary and Macular Vessel Density in Glaucoma Patients With Single-Hemifield Visual Field Defect

May 2017

Yarmohammadi et al. compared hemifield differences in the vessel density of the peripapillary and macular regions in open-angle glaucoma eyes with a visual field (VF) defect confined to 1 hemifield. Using optical coherence tomography angiography (OCT-A), they found that vessel density was higher in the intact hemiretina than in the affected hemiretina; however, both values were lower than in control patients.

This cross-sectional study included 58 eyes of 58 glaucoma patients with VF loss confined to a single hemifield and 28 healthy eyes. Retinal vasculature information was summarized as circumpapillary vessel density (cpVD) and perifoveal vessel density (pfVD). In addition, circumpapillary retinal nerve fiber layer (cpRNFL) and macular ganglion cell complex (mGCC) thicknesses were calculated with spectral-domain optical coherence tomography.

The researchers found that mean cpVD and pfVD in the intact hemiretinas of glaucoma eyes (59.0% and 51.1%, respectively) were higher than in the affected hemiretinas (54.7% and 48.3%, respectively) but were lower than in healthy eyes (62.4% and 53.8%, respectively). Similar differences in cpRNFL and mGCC thickness were found in affected versus intact hemiretinas within glaucoma patients and between patients and controls.

The strongest associations between mean sensitivity (MS) in the affected hemifields were found for cpVD, followed by pfVD, cpRNFL, and mGCC in the corresponding hemiretinas. Moreover, in the intact hemifields, correlations between MS and cpVD and pfVD were higher than those between MS and cpRNFL and mGCC thickness measurements.

The researchers concluded that among glaucomatous eyes with a single-hemifield VF defect, reduced peripapillary and macular vessel density was detectable in the perimetrically intact hemiretina as well as the affected hemiretina. Further, vessel density was associated with the extent of VF deficiency in the corresponding hemifields. They noted that OCT-A shows promise in identifying glaucomatous damage before focal VF defects are detectable.

—Summaries by Marianne Doran

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Comparison of Regional Versus General Anesthesia for Surgical Repair of Open-Globe Injuries

May/June 2017

McClellan et al. compared the clinical features and physician selection of either regional anesthesia (peribulbar or retrobulbar block) with monitored anesthesia care (RA-MAC) or general anesthesia (GA) for repair of open-globe injuries. They found that patients managed with RA-MAC had, among other factors, smaller, more anterior wounds and shorter operative time than those who received GA.

Participants in this nonrandomized comparative retrospective chart review were adults with open-globe injuries who received primary repair at a single university referral center between Jan. 1, 2004, and Dec. 31, 2014. Data collected from each patient included age, gender, injury type, location, length of wound, presenting visual acuity (VA), type of anesthesia used, duration of procedure, months of clinical follow-up, and final VA. Complete data were available for 448 patients.

In this case series, repair was performed using RA-MAC in 78% of patients and GA in 22%. With regard to location of injury, the rates of RA-MAC versus GA, respectively, were as follows: Zone 1 (anterior to the limbus), 213/241 (88%) and 28/241 (12%); Zone 2 (<5 mm posterior to the limbus), 104/135 (77%) and 31/135 (23%); and Zone 3 (>5 mm posterior to the limbus), 34/72 (47%) and 38/72 (53%). Open-globe injuries repaired under RA-MAC had significantly shorter wound length, more anterior wound location, and shorter operative times, as well as a better presenting VA. However, neither class of anesthesia conferred a greater VA improvement, and use of GA did not lengthen the time between the injury and surgical repair.

The authors noted that the choice between RA-MAC and GA is debatable, as each type has particular risks and benefits in this setting. They concluded that RA-MAC is a reasonable alternative to GA for the repair of open-globe injuries in selected adult patients. Further, the study demonstrates that neither type of anesthesia, for any single zone of injury, provides a clear advantage in visual outcome and that the amount of improvement of VA is more likely related to the severity of injury than the type of anesthesia used.

—Summary by Peggy Denny

Selected by Richard K. Parrish II, MD

Myopic Surface Ablation in Patients With Asymmetric Topography

May 2017

Some individuals are not suitable candidates for refractive surgery because of their risk for iatrogenic corneal ectasia. **Brenner et al.** determined refractive results and theoretical elastic response of photorefractive keratectomy (PRK) among patients with asymmetric corneal topography and compared the findings with those of matched normal-topography controls. The authors found that in certain cases of asymmetric topography, myopic surface ablation could induce a premature and amplified corneal biomechanical elastic response rather than a long-term progressive pathologic process.

In this retrospective interventional study, patients with asymmetric topography (30 eyes; superior-inferior dioptric difference [SI index] >1.4 D) were observed for 1 year prior to PRK to monitor corneal stability. Patients in the control group (30 eyes) had normal anterior corneal surface and did not qualify for LASIK based on central corneal thickness. The study groups were matched for age, preoperative spherical equivalent (SE), mean keratometry, and percentage of tissue altered (PTA). All patients underwent myopic surface ablation for astigmatism.

The mean preoperative SI index was 2.06 ± 0.56 D for the group with asymmetric topography and 0.14 ± 0.73 D for the control group. From 3 to 12 months postoperatively, mean keratometric re-steepening was 0.51 ± 0.39 D in patients with asymmetry and 0.19 ± 0.40 D in the control group. The mean PTA of 14.42% generated theoretical elastic modulus reductions of 10.25% in patients with asymmetry and 2.45% in control participants. Three years postoperatively, 90% of all eyes were within ±0.50 D of SE, and the theoretical elastic modulus did not differ significantly between the groups.

Although refractive results were comparable between the study groups, the authors concluded that the asymmetric corneas had increased short-term stress relaxation, greater keratometric re-steepening, and reduced theoretical elastic modulus. In the long term, myopic surface ablation induced a premature and amplified, but not progressive, corneal biomechanical elastic response in some patients with asymmetric corneal topography.

Quality of Life, Mental Health, and Employment Among Young Adults With RP

May 2017

Chaumet-Riffaud et al. examined the impact of retinitis pigmentosa (RP) on young adults. In contrast to previous studies, the authors found that education levels and employment rates are comparable to those of the general population of young adults, which was represented by age-paired statistical data in this study.

The cross-sectional study included 148 patients (mean age, 38.2 years) with RP residing in France. Quality of life was assessed using the National Eye Institute Visual Function Questionnaire. Mental state was rated on the Hospital Anxiety and Depression Scale, and employment information was obtained with a tailored questionnaire.

Of the RP patients, 48% were legally blind, nearly 30% had low vision, and approximately 22% had mild visual impairment. Quality-of-life scores correlated with the radius of residual visual field ($p < .0001$). Mental health scores indicated that 36.5% experienced anxiety, and 15.5% were depressed. Rates were not higher for patients with more severe visual disability.

Although the proportion of subjects with higher education (at least 2 years of college) tended to decline with increasing disability, the differences were not statistically significant. Among blind patients, 56.3% achieved this level of education, compared with 42.3% of the sighted age-paired group.

The employment rate decreased with declining visual function, but not significantly. At baseline, the employment rate was 67.6% for the blind patients, 79.5% for those with low vision, and 80.2% for the sighted group. All patients had worked at least 12 consecutive months in the preceding 5 years, except for 3 blind patients who had never worked. The employment rate was significantly higher for patients with more education and lower for patients with depression.

In conclusion, the authors' findings differ from those showing relatively low levels of education and employment for young adults with RP. Studies with matched sighted controls and larger populations are needed to better understand the relationship between RP and mental health, education, and employment, as well as the impact of employment aids and workplace conditions on young adults with RP.

Lymphoma of the Eyelid: An International Multicenter Retrospective Study

May 2017

Svendsen et al. conducted a multicenter observational study to examine subtype-specific clinical features of eyelid lymphoma and determine their effect on survival outcomes. The authors identified 5 main subtypes and found prognosis to be significantly better for 3 of them: extranodal marginal-zone lymphoma (EMZL), follicular lymphoma (FL), and mycosis fungoides (MF). Survival rates were poorer for diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

Data for 86 patients with primary or secondary lymphoma of the eyelid were collected from 7 international eye cancer centers. A primary outcome measure was 5-year disease-specific survival (DSS) rates.

Non-Hodgkin B-cell lymphoma was present in 72 patients; T-cell lymphoma occurred in 15 patients. The most common subtypes were EMZL (n = 32), FL (n = 20), DLCBL (n = 9), MCL (n = 7), and MF (n = 8). EMZL had a female predilection, whereas MCL and MF were more common among males. MCL, DLBCL, and MF often were secondary lymphomas. The median duration of symptoms prior to diagnosis

was longer for low-grade EMZL and FL (8 and 5 months, respectively) than for high-grade DLBCL (1 month). Orbital spread occurred more frequently in B-cell lymphomas, a finding noted previously.

Localized EMZL and FL generally were treated with external beam radiation therapy. Chemotherapy was commonly used for DLBCL, MCL, and high Ann Arbor stage EMZL and FL. Prognosis was poor for DLBCL and MCL (5-year DSS: 21% and 50%, respectively) but favorable for EMZL, FL, and MF (5-year DSS: 88%, 88%, and 86%, respectively). Patients with primary lymphoma had a significantly better 5-year DSS rate than those with secondary lymphoma (85% vs. 64%).

The authors concluded that histologic subtype was the predominant predictor of prognosis, which was significantly better for patients with subtypes EMZL, FL, and MF. It may be helpful to incorporate this information into cancer staging systems.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Effectiveness of SD-OCT in Detecting Elevated Intracranial Pressure in Children

April 2017

Conventional techniques to detect elevated intracranial pressure (ICP) in children are invasive and often unreliable. **Swanson et al.** assessed whether retinal measurements obtained by a noninvasive method, spectral-domain optical coherence tomography (SD-OCT), would be effective for this purpose. The measurements were found to have high specificity and sensitivity for detecting elevated ICP.

This cross-sectional prospective study enrolled 79 patients treated at Children's Hospital of Philadelphia. Of these, 40 patients had craniosynostosis, 5 had hydrocephalus and suspected elevated ICP (positive controls), and 34 were patients undergoing a minor procedure who otherwise were healthy (negative controls). All 79 participants underwent SD-OCT preoperatively. Children with cranial pathology (but not the negative controls) also underwent direct intraoperative measurement of ICP. The primary outcome measure was the association between peripapillary retinal OCT parameters and directly measured elevated ICP.

ICP correlated positively with maximal thickness of the retinal nerve fiber layer ($r = 0.60$, $p \leq .001$), maximal retinal thickness ($r = 0.53$, $p \leq .001$), and maximal anterior retinal projection ($r = 0.53$, $p = .003$). Using cut points derived from the negative controls, the sensitivity of OCT parameters for detecting elevated ICP was 89%, and their specificity was 62%. The OCT measures had high intereye agreement (intraclass correlation, 0.83-0.93) and high intragrader-intergrader agreement (intraclass correlation ≥ 0.94). Conversely, the sensitivity of conventional clinical signs for detecting elevated ICP was low (11%-42%).

The authors concluded that OCT parameters show promise as a surrogate noninvasive method for assessing ICP. SD-OCT may be transformational for at-risk patients who have factors suspicious for elevated ICP but without objective findings from currently used methods, allowing many young patients to avoid invasive procedures. *(Also see related commentary by Michael C. Brodsky, MD, et al. in the same issue.)*

Association of Smoking During Pregnancy and Birth Weight With RNFL Thickness in Preadolescence

April 2017

Smoking during pregnancy and low birth weight have been implicated in impaired development of the retina. **Ashina et al.** examined the specific relationship between these risk factors and the thickness of the retinal nerve fiber layer (RNFL) later in childhood. Both factors were found to be independently associated with a thinner RNFL in preadolescence.

At 11 or 12 years of age, participants of the Copenhagen Child Cohort 2000 Eye Study underwent examination of their right eye. RNFL thickness was measured using optical coherence tomography (OCT). Maternal smoking status was determined from interviews with the children's parents. Birth weight and other relevant details were obtained from the Danish Medical Birth Registry. The main outcome was peripapillary RNFL thickness measured by OCT at the 11- or 12-year examination.

Among the 1,323 patients included in the analysis, mean RNFL thickness was 104 µm. The RNFL of children whose mothers had smoked while pregnant with them (n = 227) was 5.7 µm thinner than that of children whose mothers had not smoked, after adjustment of variables including age, gender, birth weight, current height/weight, axial length, and spherical equivalent refractive error, as well as self-reported Tanner stage. The RNFL in children with low birth weight (<2,500 g) was 3.5 µm thinner than that in children of normal birth weight, after adjustment of all variables. Other characteristics associated with a thinner RNFL were female sex, longer axial length, higher myopia, and shorter current stature.

These observations from a large cohort support others indicating that perinatal factors can have long-lasting effects on the retina and optic nerve. In conclusion, the authors' findings augment the large body of evidence supporting the avoidance of smoking during pregnancy and the promotion of maternal and fetal health. *(Also see related commentary by Christopher Kai-Shun Leung, MD, in the same issue.)*

Incidence and Risk Factors Associated With Idiopathic Macular Hole

April 2017

To help clarify the pathophysiology of idiopathic macular hole (MH) and identify potential new methods to treat and prevent it, **Ali et al.** determined the incidence and risk factors associated with this condition in a large-scale longitudinal study. Female gender and older age were the most obvious risk factors, as noted in previous research.

Study enrollees were at least 40 years old and had participated continuously in a nationwide managed care plan for

at least 3 years. Of the 659,357 individuals, an MH requiring vitrectomy occurred in 144 (0.02%), 105 (72.9%) of whom were female. After adjusting for confounding factors, the risk was found to be 64% higher for women (adjusted hazard ratio [aHR], 1.64; p = .01 vs. men), and the effect of gender varied by age. The cumulative overall incidence of MH was 41.1 cases per 100,000 person-years (men, 34.1; women, 55.9). Cases per 100,000 person-years in the different age groups were as follows: 40-49 years, 6.0 cases; 50-59 years, 30.3 cases; 60-69 years, 98.2 cases; 69 years and older, 77.1 cases.

The risk of MH in Asian Americans was 177% higher than in whites (aHR, 2.77; p = .01). In the study, 109 affected individuals were white, 16 were black, 7 were Asian, and 4 were Latino (8 were of other races or were missing race/ethnicity data).

Cataract was associated with an 86% greater risk of MH (aHR, 1.86; p = .001 vs. those without cataract). The risk of MH among individuals with hypertension, myocardial infarction, cerebrovascular accident, hyperlipidemia, or congestive heart failure did not differ significantly from that of individuals without these conditions.

The authors' work confirmed that the greatest risk factors for MH are older age and female gender. If future studies affirm that menopausal changes in estrogen levels contribute to the higher risk of MH among older women, such information may guide the development of treatments targeting the vitreoretinal interface that may prevent or reduce the risk of this vision-impairing condition.

—Summaries by Lynda Seminara

OTHER JOURNALS

Visualization of Dietary Patterns and Their Associations With AMD

Investigative Ophthalmology & Visual Science
2017;58(3):1404-1410

Chiu et al. set out to visualize the relationship among predominant dietary patterns and their associations with age-related macular degeneration (AMD) through a qualitative analysis process encompassing logistic regression, Boolean algebra, and Venn diagrams. They first identified 2 major and 8 minor dietary patterns and evaluated which were healthy, unhealthy, or neutral in relation to AMD.

A total of 8,103 eyes from 4,088 participants from the Age-Related Eye Disease Study (AREDS) were classified into 3 groups: control (n = 2,739), early AMD (n = 4,599), and advanced AMD (n=765). Using principal component analysis, the researchers characterized 2 major (Oriental and Western) and 8 minor dietary patterns. In general, the 8 minor patterns were subsets or extensions of the 2 major dietary patterns but consisted of fewer characteristic foods. Unlike the 2 major patterns, which were more strongly associated (positively or negatively) with both early and advanced AMD, none of the 8 minor patterns were associated with early AMD, and only 4 minor patterns, including the Steak pattern (odds ratio [OR] comparing the highest to lowest quintile of the pattern score, 1.73), the Breakfast pattern (OR, 0.60), and the Caribbean pattern (OR, 0.64) showed significant association with advanced AMD. The research also suggested several potentially beneficial foods for AMD, including peanuts, pizza, coffee, and tea.

The researchers concluded that a diet of various healthful foods may be optimal for reducing AMD risk. They recommended further study on the effects of certain specific foods in the context of overall diet.

Ocular Toxicity of Mitogen-Activated Protein Kinase Inhibitors

JAMA Oncology
2017;3(2):275-277

A research letter written by **Purbrick et al.** reported on the ocular toxic effects of 3 different mitogen-activated protein kinase inhibitors (MEKIs) in clinical development for oncology indications. The researchers found that, overall, 18% of patients receiving one of these drugs had ocular adverse effects.

The Oxford Eye Hospital and the Oxford Experimental Cancer Centre, which collaborate in monitoring patients in a number of early-phase clinical trials, reviewed the clinical records of 40 patients enrolled in trials of 3 different MEKIs (including 11, 19, and 10 patients in MEKI trials A, B, and C, respectively) from March 16, 2011, to April 25, 2013. Data included baseline visual acuity and ophthalmic imaging data, relevant ophthalmic and general medical history, and evidence of ocular toxic effects in addition to the clinical course.

Altogether, 7 of 40 patients in these trials developed ocular adverse effects. In the MEKI A group, 3 of 11 patients (27%) developed bilateral central serous chorioretinopathy (CSC), which was multifocal in 1 case; in all 3 cases, CSC was self-limited and resolved after cessation of the drug. In the MEKI B group, 2 of 19 patients (11%) developed ocular adverse effects: 1 patient had a central retinal vein occlusion, and 1 had bilateral, multifocal CSC-like changes. In the MEKI C group, 2 of 10 patients (20%) developed ocular adverse effects: 1 had bilateral, multifocal CSC-like changes, and 1 had a severe increase in intraocular pressure.

Because the ocular complications of MEKIs have not yet been fully assessed, it is important to monitor for them prospectively, with appropriate validated techniques. The investigators recommend a baseline ophthalmic examination before treatment, including visual acuity and intraocular pressure measurements, dilated fundus examination, macular optical coherence tomography, and fundus photography.

The researchers concluded that these cases highlight the wide spectrum of ocular adverse effects associated with the introduction of these drugs in clinical practice. Moreover, this study confirms a previous observation that some complications, particularly CSC, can resolve spontaneously after drug cessation. Further studies may help determine which patients may be at particular risk of ocular toxic effects.

—Summaries by Marianne Doran

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