

Journal Highlights

NEW FINDINGS FROM *OPHTHALMOLOGY*, *AJO*, AND *JAMA OPTHALMOLOGY*

Ophthalmology

Low Risk of Iris Nevus Growing Into Melanoma

Ophthalmology

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Shields et al. investigated the rate of and clinical risk factors for transformation of iris nevus to melanoma and found that the risk of this transformation was low. They also created a mnemonic “ABCDEF” guide for clinicians that serves as a checklist of risk factors: Age young (40 years and under at presentation), Blood (episodes of hyphema), Clock hour inferior (4 o’clock to 9 o’clock location of tumor), Diffuse tumor configuration (involving the entire iris surface), Ectropion uveae, and Feathery tumor margins. If a patient with iris nevus demonstrates any of these clinical features, the authors noted, he or she should be monitored regularly for tumor growth and appropriate management.

This retrospective, comparative case series included 1,611 consecutive patients with iris nevus referred to an ocular oncology center. The mean age at referral was 51 years. At presentation, the mean tumor basal diameter was 3 mm, and mean tumor thickness

was 0.8 mm. All patients were initially diagnosed with benign iris nevus. Growth of iris nevus to melanoma was confirmed in 2 percent of eyes over a mean follow-up of 68 months. This growth occurred in less than 1 percent at one year and rose to 8 percent at 20 years. Additional risk factors beyond the checklist included tumor seeding on the iris or in the anterior chamber angle, feeder vessels, and nodule formation.

The authors also noted that some traits of iris nevus overlap with iris melanoma, making it difficult at times to distinguish between the two conditions. For example, both can show brown color, small size, and inferior location. In these cases,

fine-needle aspiration biopsy can provide the clinician with key differentiating information.

Higher Mortality in PKP Patients With Rheumatoid Arthritis—Associated Corneal Ulceration

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Stylianides et al. investigated mortality and graft survival in patients undergoing penetrating keratoplasty (PKP) for rheumatoid arthritis—associated corneal ulceration (RACU), Fuchs endothelial dystrophy

(FED), and pseudophakic bullous keratopathy (PBK). They found that mortality and ocular morbidity were significantly increased in patients with RACU.

In this case-control study, the authors included 3,665 patients listed on the U.K. Transplant Registry who had undergone PKP for RACU ($n = 117$), FED ($n = 1,847$), or PBK ($n = 1,701$) between 1999 and 2006. The authors obtained comparative standardized mortality ratios and causes of death from the U.K. Office for National Statistics.

Five-year survival of patients with RACU was 42 percent, compared with 76 percent for FED and 55 percent for PBK. The standardized mortality ratios for female and male patients with RACU were 43.5 and 12.2, respectively, compared with 4.8 and 5 for patients with FED and 3.7 and 4 for patients with PBK. There were no significant differences in the causes of death among patients with RACU, FED, or PBK; infection was the most common cause. The five-year graft survival rate was 48 percent for RACU, 59 percent for PBK, and 84 percent for FED.

The authors concluded that accelerated immunosenescence should be considered in the differential diagnosis of patients presenting with RACU and that a multidisciplinary approach to management is recommended. They also suggested that patients with RACU, and especially those who need



a corneal transplant, be examined for the presence of vasculitis and a decline in their immune function.

Acute Anterior Uveitis Following Intravenous Zoledronate for Osteopenia

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Patel et al. investigated the incidence of significant adverse ocular side effects after intravenous zoledronate infusion for osteopenia. They found a 0.8 percent incidence of acute anterior uveitis in postmenopausal women with osteopenia receiving the medication. The severity of ocular inflammation ranged from mild to severe, with all patients requiring several weeks of treatment with intensive, potent topical corticosteroids.

This study involved 2,001 women with osteopenia randomized to either placebo or intravenous infusion of 5 mg zoledronate. Of the 1,001 women who received the study drug, eight (0.8 percent) developed painful redness in one or both eyes that was subsequently identified by an ophthalmologist as acute anterior uveitis. The mean time from infusion to onset of symptoms was three days. The mean duration of topical corticosteroid treatment was 45 ± 28 days.

According to the authors, this is the first study to assess the incidence of acute anterior uveitis after zoledronate infusion and the largest reported cohort of confirmed cases. They concluded that physicians and patients should be aware of the ocular inflammatory side effects associated with zoledronate infusion and the need for referral to an ophthalmologist if symptoms develop.

American Journal of Ophthalmology

Limbal Stem Cell Deficiency From Contact Lens Wear

March *AJO*

Chan and Holland described the characteristics of patients with severe limbal stem cell deficiency associated with contact lens wear. They

found that female biological sex, soft contact lens wear, and extended duration of wearing time were associated with this condition.

In a retrospective case series, the authors reviewed the charts of 12 patients (18 eyes). Outcome measures included patient demographics, contact lens type, duration of wear, indications for wear, symptoms, location and laterality of limbal stem cell deficiency, coexisting ocular disease, and treatment. The mean patient age at presentation was 42 years, and eight patients (67 percent) were women. Mean duration of contact lens wear was 14.1 years. Six patients (50 percent) had bilateral disease. And all 12 wore soft contact lenses for refractive error correction.

All patients had decreased vision at presentation (20/78, on average). Fifteen eyes (83 percent) had photophobia, pain, or both. Findings leading to the diagnosis of limbal stem cell deficiency included whorl-like epitheliopathy, corneal conjunctivalization, and late fluorescein staining of the involved epithelium for at least six clock-hours. On average, 10 clock-hours were involved, and 11 eyes (61 percent) had total ocular involvement.

Conservative treatments failed in all eyes. Fourteen eyes (78 percent) underwent limbal stem cell transplantation with systemic immunosuppression. After an average follow-up of 26.4 months, 12 of these eyes (86 percent) had complete resolution of symptoms, vision of 20/30 or better, and a stable ocular surface.

Photodynamic Therapy for Polypoidal Choroidal Vasculopathy

March *AJO*

Kang et al. evaluated the five-year efficacy of photodynamic therapy (PDT) in patients with polypoidal choroidal vasculopathy (PCV). They found that PDT was a good therapeutic approach and provided favorable long-term visual outcomes. At 60 months after initial PDT, about 88 percent of PCV patients showed stable or improved best-corrected visual acuity (BCVA), despite a high recurrence

rate of PCV.

In this retrospective study, the authors analyzed the records of 36 patients (42 eyes) with PCV. Patients were followed for at least 60 months after PDT. The main outcome measure was BCVA at baseline and at each follow-up visit. Eyes were classified into three groups: improved (improvement of 0.3 logMAR or more), decreased (deterioration of 0.3 logMAR or more), and stable.

During the mean follow-up of 73 months, the mean number of PDT treatments was 2.2. Recurrence was noted in 33 eyes (78 percent). The mean baseline BCVA was 0.78 logMAR (20/120 Snellen equivalent), and the final BCVA at 60 months was 0.67 logMAR (20/93 Snellen equivalent). On the final BCVA evaluation, the mean BCVA had improved in 14 eyes (33 percent), stabilized in 23 eyes (55 percent), and decreased in five eyes (12 percent).

Efficiency of Aspheric IOLs Based on Pupil Diameter

March *AJO*

Eom et al. looked at aspheric IOLs and pupil diameter to determine the minimum diameter required for the lenses to be effective. They found that when pupil diameter was smaller than 3.4 mm for a Tecnis ZCB00 (Abbott Medical Optics) and 3.7 mm for a Hoya AF-1 NY-60 (Hoya Surgical Optics), spherical aberration was not successfully corrected. Approximately 10 percent of study eyes had no benefit from the aspheric design because pupil sizes were smaller than the minimum effective diameter.

In this retrospective, cross-sectional study, the authors enrolled 86 patients (169 eyes) who were implanted with either a Hoya AF-1 NY-60 or a Tecnis ZCB00 one-piece IOL. Ocular, corneal, and internal spherical aberrations were measured during a one-month postoperative visit. Minimum pupil diameter was calculated using a regression equation.

The mean value of internal spherical aberration of the Tecnis group was

lower than that of the Hoya group. The negative spherical aberration of the Hoya group was $-0.18\ \mu\text{m}$ at a pupil diameter of 5.6 mm, which is the amount of negative spherical aberration presented by the manufacturer. For the Tecnis group, the negative spherical aberration was $-0.27\ \mu\text{m}$ at a pupil diameter of 6.1 mm.

JAMA Ophthalmology

Progression of Ocular Melanoma Metastasis to the Liver

February *JAMA Ophthalmology*

Grossniklaus examined sections of livers obtained postmortem from 10 patients who died of metastatic uveal melanoma to the liver. He found that uveal melanoma that spreads to the liver could be categorized as stage 1 metastases (50 μm or less in diameter), stage 2 (51 μm to 500 μm in diameter), or stage 3 (greater than 500 μm in diameter). The latter stage exhibited a lobular or portal pattern of growth. During progression, tumors became vascularized and mitotically active.

Using the liver samples, the author performed immunohistochemical staining and determined the mean vascular densities and mitotic indices for the metastases.

He identified stage 1 metastases in the sinusoidal spaces of nine of 10 patients. Stage 2 metastases and stage 3 metastases were found in all patients. Immunohistochemical stains were positive for S100 or HMB45 in all tumors. Overall, stage 1 metastases outnumbered stage 2 metastases, which, in turn, outnumbered stage 3 metastases. The mean vascular density and mitotic index increased from stage 2 to stage 3 metastases, with stage 1 tumors (micrometastases) exhibiting virtually no mitotic activity and no vascularization. The architecture of stage 2 metastases mimicked the surrounding hepatic parenchyma, whereas stage 3 metastases exhibited either lobular or portal growth patterns.

The author concluded that this study demonstrates, for the first time, the progression of small, apparently

dormant micrometastases to large, vascularized metastases in the livers of patient with metastatic uveal melanoma. These findings also support the concept that the establishment of melanoma cells in the liver is related to tumor burden and the mechanical properties of cells lodging in sinusoidal spaces.

Inflammatory Biomarkers and Risk of Diabetic Retinopathy

February *JAMA Ophthalmology*

Muni et al. investigated whether baseline levels of high-sensitivity C-reactive protein (CRP) and intercellular adhesion molecule (ICAM-1) predict the development and progression of diabetic retinopathy, clinically significant macular edema, retinal hard exudates, and proliferative diabetic retinopathy in the Diabetes Control and Complications Trial (DCCT) cohort. The authors found that increasing quintiles of baseline CRP may be associated with higher risk of clinically significant macular edema and macular hard exudates. Circulating levels of ICAM-1 may also be associated with the development of retinal hard exudates.

The DCCT was a large clinical trial of 1,441 patients, aged 13 to 39 years, with type 1 diabetes. The authors measured levels of CRP, ICAM-1, vascular adhesion molecule (VCAM-1), and tumor necrosis factor α (TNF- α) receptor 1 in stored baseline blood samples. They then assessed the association of these substances' levels with incident diabetic retinopathy endpoints, based on standardized seven-field stereoscopic retinal color photographs taken at baseline and every six months during follow-up.

After adjustment for randomized treatment assignment and other factors, the authors observed a statistically significant association between CRP and risk of clinically significant macular edema, with a relative risk for the top versus bottom quintile of 1.83. Similarly, in regard to the development of retinal hard exudates, the relative risk for the top versus bottom quintile

of CRP was 1.78, and for ICAM-1, the relative risk was 1.50. There were no statistically significant associations between baseline VCAM-1 or TNF- α receptor 1 and risk of any of the diabetic retinopathy endpoints.

Mass Drug Administration of Azithromycin in Communities With Trachoma

February *JAMA Ophthalmology*

The World Health Organization (WHO) recommends mass administration of azithromycin in areas where prevalence of follicular trachoma is greater than 10 percent of the population; WHO recommends that the drug be given annually for at least three years. **Yohannan et al.** conducted a randomized trial to determine whether fewer than three rounds would eliminate infection with *Chlamydia trachomatis* altogether. They found that none of the communities under investigation met the criteria to cease mass drug administrations.

In 16 Tanzanian communities with trachoma prevalence of 10 to 20 percent, the authors randomized 100 children aged 5 years or younger to either a usual care arm or a cessation arm. The usual care arm was scheduled to receive a round of mass drug administrations at baseline, 12 months, and 24 months. The communities in the cessation arm were also scheduled to receive three rounds; however, administration would cease if the arm reported no infection at six or 18 months.

None of the eight communities assigned to the cessation arm met the necessary criteria to stop administration after two rounds, and all went on to the third round. At 18 months, there was no significant difference in infection prevalence (2.9 percent versus 4.7 percent) between the usual care group and cessation group, respectively.

Ophthalmology summaries are written by Lori Baker Schena, EdD, and edited by John Kerrison, MD. American Journal of Ophthalmology summaries are edited by Thomas J. Liesegang, MD. JAMA Ophthalmology summaries are written by the lead authors.

ROUNDUP OF OTHER JOURNALS

Shared Inflammatory Pathways in Behçet Disease, Ankylosing Spondylitis, and Psoriasis

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Individuals with Behçet disease suffer from uveitis, skin inflammation, arthritis, enterocolitis, and inflammation in other organs. The disease is relatively common in Turkey and Japan and is a significant cause of vision loss in these countries. In an attempt to discover new susceptibility loci for the disease, Kirino et al. conducted a genome-wide association study and found new associations at *CCR1*, *STAT4*, and *KLRC4*. In addition, two single-nucleotide polymorphisms in *ERAP1*, encoding *ERAP1* p.Asp575Asn and p.Arg725Gln alterations, recessively conferred disease risk.

This study involved the analysis of 779,465 single-nucleotide polymorphisms with imputed genotypes in 1,209 Turkish patients with Behçet disease and 1,278 controls. All findings were replicated in 1,468 independent Turkish samples and 1,352 Japanese samples.

In addition to the results above, the authors found evidence for common pathogenic mechanisms among Behçet disease and two spondyloarthritis: ankylosing spondylitis and psoriasis. All three diseases possess significant major histocompatibility (MHC) class I associations, specifically HLA-B*51 in Behçet disease, HLA-B*27 in ankylosing spondylitis, and HLA-C*06 in psoriasis. In addition, the authors added *ERAP1* as a shared genetic factor, as each of these three diseases demonstrated interactions between the MHC class I region and *ERAP1*.

The authors concluded that the possibility of shared inflammatory pathways in Behçet disease, ankylosing spondylitis, and psoriasis may result in the development of common therapeutic approaches to treat these inflammatory disorders.

Genetic Association Between Central Corneal Thickness and Both Keratoconus and Glaucoma

Nature Genetics

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Ocular biometric parameters comprise a set of highly heritable and often correlated quantitative traits. One notable example is central corneal thickness (CCT), which has an estimated heritability of up to 95 percent. Lu et al. investigated whether CCT is genetically associated with keratoconus and glaucoma. They identified 16 new loci associated with CCT and demonstrated that two of the loci associated with CCT—*FOXO1* and *FNDC3B*—conferred relatively large risks for keratoconus. *FNDC3B* was also associated with primary open-angle glaucoma.

The authors collected 13 genome-wide association studies totaling more than 20,000 patients. Because of differences in the sample attributes, they performed meta-analyses of CCT within each subset, including 13,057 individuals with European ancestry who were unaffected by eye disease, 6,963 individuals with Asian ancestry who were unaffected by eye disease, 1,936 primary open-angle glaucoma patients with European ancestry, and 198 normal-tension glaucoma patients with Asian ancestry. All samples were genotyped on commercially available genotyping arrays. The majority of studies in the first two sets were imputed according to the phased haplotypes of HapMap reference samples, whereas few studies in the other two sets had imputation data available by the time of the study.

In addition to the findings above, the authors demonstrated that loci associated with CCT converge on the collagen and extracellular matrix pathways and that similar pathways regulate corneal thickness in both European and Asian populations. According to the authors, this points to

the possibility that collagen genes may be important for CCT.

Latanoprost May Reverse Bimatoprost-Related Deepening of Upper Eyelid Sulcus

Japanese Journal of Ophthalmology

Published online Dec. 13, 2012

Although useful for reducing intraocular pressure (IOP), bimatoprost can cause deepening of the upper eyelid sulcus (DUES), one of the symptoms of prostaglandin-associated periorbitopathy. Sakata et al. found that switching to latanoprost may reverse this condition.

In this prospective, observer-masked, open-label study, the authors enrolled 25 Japanese patients with primary open-angle glaucoma who were treated with latanoprost in both eyes for longer than six months and required further IOP reduction.

During the first six months after the switch to bimatoprost, 15 of the 25 patients (60 percent) developed DUES. Among these patients, 13 were switched back to latanoprost and re-examined for DUES at two-month intervals for an additional six months. Two months after the switch back to latanoprost, 11 of the 13 patients (85 percent) experienced a decrease in or total disappearance of DUES symptoms. These results remained steady through the end of the six-month observation period. Two of the younger patients involved in the study, ages 37 and 45, continued to experience DUES symptoms. No significant change in IOP was reported after the patients switched back to latanoprost.

The researchers recommended that clinicians consider switching bimatoprost patients who experience DUES symptoms to latanoprost and closely observe changes in DUES and IOP.

Roundup of Other Journals is written by Lori Baker Schena, EdD, and edited by Deepak P. Edward, MD.