A Selection of Hot Topics in Ophthalmology

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In a Hot Topics symposium, 9 speakers shared interesting current developments and trends in a variety of areas of ophthalmology.

Laura J. Balcer, MD, MSc, New York University Langone Medical Center, New York, New York, USA, discussed the use of the King-Devick (K-D) test to identify concussion in athletes. While a concussion is defined as a complex process that results from an impulsive blow to the head or body and involves any neurologic symptom or sign, Dr Balcer added that vision is affected in most cases. Consequently, a vision-based test is necessary in evaluating athletes for concussion, particularly because many underreport their symptoms to remain in the game.

The K-D test is an objective 3-card test that takes 1 to 2 minutes to complete [Galetta KM et al. *J Neurol Sci.* 2011]. The athlete reads a series of numbers from index cards or a tablet screen, and the total time to complete the test is recorded. This can be performed at the start of the season to produce a baseline assessment and then repeated on the sideline after injury. If test completion time after injury is longer than that at baseline, a concussion is diagnosed. The K-D test has proven to be a useful visual screening assessment for concussion in various collision sports, including boxing and mixed martial arts. Fatigue does not worsen the scores. Dr Balcer emphasized the value of the K-D test, sharing results from a recent study in which adding this simple vision assessment to sideline testing enhanced the identification of concussion, capturing 100% of affected athletes [Marinides Z et al. *Neurol Clin Pract.* 2014].

Elizabeth A. Bradley, MD, Mayo Clinic, Rochester, Minnesota, USA, provided an overview of immunoglobulin G4–related disease (IgG4-RD) of the orbit. IgG4-RD is an autoimmune disease of middle-aged people that has a male predominance and can affect multiple organ systems. In cases of orbital IgG4-RD, Dr Bradley stressed that ophthalmologic findings are periocular, not intraocular, and predominantly involve eyelid or periocular fullness, strabismus, or proptosis. Ten percent of cases are also associated with lymphoma.

She highlighted the importance of considering IgG4-RD in patients with the following:

- Multisystem orbital disease
- Bilateral orbital disease and a history of allergic or atopic disease
- Radiographic evidence of involvement of extraocular muscle, lacrimal gland, or infraorbital nerve

Although up to 70% of patients may also have elevated serum IgG4 levels, definitive diagnosis requires tissue biopsy to identify characteristic histopathologic features of lymphoplasmacytic inflammatory cell infiltrates with IgG4+ plasma cells and storiform fibrosis.

Dr Bradley noted that observation may suffice in patients without organ-threatening disease. However, most patients are treated with prednisone. Rituximab represents an appropriate second-line treatment. She also reported treatment success in some patients using intralesional injection of triamcinolone into the lacrimal gland.

According to Dan Z. Reinstein, MD, London Vision Clinic, London, UK, clinical outcomes in small-incision lenticule extraction (SMILE) laser surgery, a relatively new technique, are matched with those of the more established laser-assisted in situ keratomileusis (LASIK) technique in high and low myopia. He noted that SMILE is also an effective treatment for hyperopia.

Dr Reinstein added that SMILE offers inherent advantages over LASIK:

- An increase in corneal biomechanical strength—since SMILE does not involve an anterior side cut, the procedure reduces the biomechanical impact on the cornea, resulting in enhanced optical quality for patients [Reinstein DZ et al. *J Refract Surg.* 2013].

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- A decreased incidence of postoperative complications, such as postneurotrophic epitheliopathy
- A keyhole procedure, with no risk of flap dislocation, which is appealing to patients
- Avoidance of variables associated with excimer laser procedures, including difficult-to-control environmental factors in the operating room (eg, humidity)

In summary, SMILE is a relatively simple, painless, 3-minute keyhole procedure that is accurate and can correct approximately 98% of all refractive errors, concluded Dr Reinstein.

John Allan Vukich, MD, Dean Medical Center, Madison, Wisconsin, USA, discussed the use of small-aperture implants to achieve extended depth of focus. One such implant is the KAMRA inlay, a 3.8-mm diameter circular ring with a 1.6-mm central aperture. When implanted in the cornea, this device functions similar to a camera lens aperture, allowing manipulation of depth of field for near and far vision.

In a phase 3 clinical trial in individuals with presbyopia who received a KAMRA inlay, >80% of patients were able to see with 20/40 vision or better at 12-, 24-, and 36-month follow-up. There was an average 2.9-line gain in visual acuity (VA) at 12 months that was sustained to 36 months.

According to Dr Vukich, a retrospective analysis of KAMRA registry data worldwide has shown that uncorrected monocular and binocular visual acuities remain unchanged at 20/20 and 20/15, respectively, from preinlay VA and remain stable over time. He added that the rate of secondary procedures based on this technique compare with other presbyopia-correcting procedures, with primary reasons including enhancement of VA and device removal.

Scott R. Lambert, MD, Emory University, Atlanta, Georgia, USA, discussed the results of the Infant Aphakia Treatment Study [Lambert SR et al. *JAMA Ophthalmol.* 2014], demonstrating no benefit in VA at 4.5 years of age in children who underwent primary intraocular lens (IOL) implantation when compared with those who received a contact lens to correct aphakia.

Inclusion criteria included the presence of a unilateral, visually significant cataract at the time of surgery. The study enrolled 114 children who were equally randomized to either treatment group. At 4.5 years of age, there was no significant difference in VA between the 2 treatment groups ($P=.54$). However, children who underwent IOL implantation had more complications than those who received a contact lens, such as lens proliferation into the visual axis (40% vs 4%), pupillary membrane development (28% vs 4%), and corectopia (28% vs 2%). Children in the IOL group needed more additional intraocular surgeries ($P<.001$), including surgery to clear visual axis opacity (68% vs 14%) and glaucoma surgery (9% vs 4%). Ocular alignment outcomes were similar in both groups with respect to requirement for strabismus surgery ($P=.57$) and to the numbers of children with distance ($P=.16$) or near ($P=.99$) orthophoria.

Dr Lambert concluded that, when operating on a child aged <7 months with a unilateral cataract, one is better off leaving the eye aphakic and focusing it with a contact lens. IOL implantation should be reserved for cases where parents might find it too difficult to manage and afford contact lens wear.

Graham E. Quinn, MD, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, discussed the use of telemedicine screening for retinopathy of prematurity (ROP). He presented primary outcome data of a study [Quinn GE et al. *JAMA Ophthalmol.* 2014] from the eROP Cooperative Group, demonstrating the validity of telemedicine screening for ROP to identify eyes of at-risk children who require a diagnostic evaluation by an ophthalmologist experienced in ROP.

In the study, 1257 infants with a birth weight of <1251 g (mean gestational age, 27 weeks) were examined. Of these, 63.7% had ROP, and 19.4% had referral-warranted (RW) ROP. Children underwent a diagnostic examination by a certified ophthalmologist and retinal imaging by nonphysician–certified retinal imagers. The images selected for grading were composed of all images from infants with RW ROP (n=242) and all those from a random sample of infants without RW ROP (n=613), for a total of 5520 image sets from 855 infants. These were independently graded by 2 trained nonphysician readers, with discrepancies adjudicated by a reading supervisor. The sensitivity for detecting RW ROP at a single session in either eye of an infant was 90.0%; specificity was 87.0%; and negative predictive value was 97.3%. Based on all imaging sessions, sensitivity increased to 97.1%, and among infants treated by ophthalmologists, sensitivity increased to 98.2%.

With respect to image quality, sensitivity was 84.7% and specificity was 90.6% in image sets in which all 5 images were gradable. However, when any image was not gradable, sensitivity decreased to 68.0% and specificity to 88.6%. Interestingly, image evaluation was also shown to detect RW ROP approximately 2 weeks earlier in approximately 45% of affected eyes, concluded Dr Quinn.

Neil M. Bressler, MD, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, discussed the use of aflibercept, dexamethasone intravitreal implant, and fluocinolone acetonide implants that are approved for use in diabetic macular edema (DME).

When one is deciding which treatment to use in DME, Dr Bressler emphasized the need to consider all available evidence, including data from systematic reviews and meta-analyses—not just those from randomized clinical trials. He noted that of the 3 approved medications, the strongest evidence exists for intravitreal aflibercept injections in DME. In the VIVID-DME [NCT01331681] and VISTA-DME [NCT01363440] trials, Dr Bressler explained that, on average, patients in the aflibercept groups gained 10 more letters when compared with the laser treatment group ($P < .0001$). The treatment schedule involved a total of 21 treatments over 3 years [Korobelnik JF et al. *Ophthalmology*. 2014].

In comparison, the Diabetic Retinopathy Clinical Research Network (DRCR.net) provided evidence for anti–vascular endothelial growth factor (anti-VEGF) therapy using ranibizumab on an as-needed basis. With this regimen, although 8 or 9 injections were required in the first year, the number decreased to 2 or 3 by the second year and 0 or 1 by the third, fourth, and fifth years, with sustained VA improvement whether prompt or deferred laser was used. Data also showed that in pseudophakic eyes, intravitreal triamcinolone with laser therapy was somewhat effective, though not superior to ranibizumab [Elman MJ et al. *Ophthalmology*. 2012; Elman MJ et al. *Ophthalmology*. 2011]. Consequently, anti-VEGF agents should probably be considered as a first-line treatment in DME, while corticosteroid therapy should be reserved for cases that do not respond to anti-VEGF treatment, concluded Dr Bressler.

Baruch D. Kuppermann, MD, PhD, University of California at Irvine, California, USA, discussed emerging experimental treatments for dry age-related macular degeneration (AMD).

Although data from the AREDS trial [Age-Related Eye Disease Study Research Group. *Arch Ophthalmol.* 2001] showed that antioxidant and zinc supplementation decreased the risk of progression to neovascular AMD, it did not prevent progression of DME. However, in the AREDS2 trial [Age-Related Eye Disease Study 2 Research Group. *JAMA*. 2013], supplementation with lutein and zeaxanthin resulted in a 10% decrease in the risk of progression to advanced AMD, although no such benefit was found with supplementation of omega-3 fatty acids. Additionally, elimination of beta-carotene and reduction of the zinc dose did not affect progression to advanced AMD.

Numerous complement inhibitors have also been investigated as potential therapeutic agents for dry AMD, according to Dr Kuppermann, and lampalizumab, an inhibitor of complement factor D, has shown promising results in the phase 2 MAHALO trial. Although it reduced the risk of disease progression by 20%, data from a biomarker-defined subset were even more interesting, showing a 44% reduction of disease progression.

According to Dr Kuppermann, since amyloid-β deposits have been demonstrated in the drusen in patients with AMD, phase 2 studies are now underway to evaluate the efficacy of an amyloid-β inhibitor. He also discussed 2 oral agents that modulate the visual cycle: fenretinide and ACU-4429. Although reduced dark adaptation is an adverse effect of ACU-4429 treatment, the hope is that phase 2 studies will investigate this further, concluded Dr Kuppermann.