
News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

Ocular Shingles Raises Stroke Risk

The disquieting reappearance of the varicella zoster virus (VZV), which manifests as shingles, not only causes patients painful skin lesions but has also been linked repeatedly to a higher risk of

stroke. A recent study conducted by Taiwanese researchers quantified this risk for the first time, finding that shingles raised the risk of stroke by 31 percent in adults 18 and older, regardless of which dermatome was involved.

Patients with herpes zoster ophthalmicus (HZO) were at even greater risk—more than four times as likely to have a stroke than those without shingles.¹ During a lifetime, each individual has about a 1 percent risk of developing HZO, which occurs when the virus presents in the ophthalmic division of the trigeminal,

or fifth, cranial nerve.²

Although the study was not designed to elucidate the reasons that shingles infection increases stroke risk, previous research indicates that vessel walls become damaged and inflamed following attack by VZV—the only human virus known to replicate in the cerebral arteries.¹

Reviewing data released by the Taiwan National Health Research Institute in 2006, the researchers studied 7,760 patients receiving shingles treatment at Taipei Medical University Hospital between 1997 and 2001. These patients were matched



AT RISK. A recent study found that herpes zoster ophthalmicus patients are at a fourfold increased risk for stroke.

by age and gender with 23,280 randomly selected adults without shingles. At one-year follow-up, about 1.7 percent of shingles patients and about 1.3 percent of controls had experienced strokes.

The study authors further analyzed the data by stroke type. Specific numbers were not provided for patients with HZO, but for the overall cohort of patients with herpes zoster, the risk of hemorrhagic stroke was roughly twice that of ischemic stroke. Consistent with previous findings, contralateral hemiplegia was the most common stroke-

related complication.

“Interestingly, survival analysis showed the occurrence of stroke to be roughly linear over the one-year time period,” said Emmett T. Cunningham Jr., MD, PhD, MPH, adjunct clinical professor of ophthalmology at Stanford University and director of the uveitis service at California Pacific Medical Center. He added that this may suggest mechanisms above and beyond acute VZV-related vasculopathy, such as secondary atherosclerosis or adverse emotional reactions from chronic pain.

Dr. Cunningham noted

that these indirect mechanisms are further supported by an increased risk of stroke observed following infection that involved dermatomes far removed from the face and scalp. "In these cases, direct trigeminal transport of the virus to the cerebral vasculature seems unlikely," he said. The specific pathophysiology of

stroke with nontrigeminal dermatome involvement remains unknown and was not a focus of this study.

Commenting on their findings, the study authors emphasized that the significantly increased risk of stroke is one that should not be overlooked, particularly given that the frequency of shingles could be as high as

1.3 to 1.6 per 1,000 people per year.

"Although the benefits of this study include its size and relatively homogeneous cohort of consecutively treated patients from a single university teaching hospital in Taiwan," said Dr. Cunningham, "the extent to which these findings can be generalized to non-Asian,

community-based patient populations remains to be determined."

—Annie Stuart

Dr. Cunningham reports no related financial interest.

1 Kang, J-H. et al. *Stroke* 2009;40;3443-3448.

2 Liesegang, T. J. *Ophthalmology* 2008;115(2);S3-S12.

Cornea Update

Flu Shot May Cause PK Transplant Rejection

Cornea surgeons are expressing concern that the widespread emphasis on influenza vaccinations this winter might increase the number of immunization-associated allograft rejection episodes in their penetrating keratoplasty patients.

Jorge L. Alió, MD, PhD, medical director of ophthalmology at Visum Corp. in Alicante, Spain, told colleagues anecdotally at the Academy's Joint Meeting in October that he had seen two such cases in 2009. And in November, David A. Goldman, MD, and Jonathan Etter, MD, associate professor of clinical ophthalmology and lecturer, respectively, at Bascom Palmer reported a rejection episode in a 25-year-old bilateral PK recipient. Her reaction occurred one day after she received the intranasal, live-attenuated H1N1 flu vaccine.¹

Topical corticosteroid drops promptly cleared the

inflammation in the woman's less affected eye, restoring visual acuity to 20/25. The other cornea had persistent, severe edema despite oral prednisone, sub-Tenon's triamcinolone injections and high-frequency topical steroid drops, Drs. Goldman and Etter reported. However, that eye slowly began clearing after several weeks, Dr. Goldman said. By early last month, it had improved to 20/70, with pinhole acuity of 20/25.

The literature contains only three reports of such rejection in PK allografts.²⁻⁴ In those cases, rejection signs were associated with flu, tetanus booster and hepatitis B immunizations and took one to eight weeks to develop. Drs. Goldman and Etter speculate that the method and site of the H1N1 immunization shortened the reaction time to one day in their patient.

"I think the risk of this is much greater with the live attenuated, intranasal vac-

cine because of its potential for inflammatory response as well as its inoculation site so close to the eyes," Dr. Goldman said.

With fear of H1N1 fueling public demand for flu shots, ophthalmologists should consider warning refractive surgery patients that immunization might trigger inflammatory complications for them, too, he added. "I think it's our duty to help spread the word so that patients undergoing eye surgery are aware the H1N1 live attenuated vaccine may affect outcomes of ocular surgery if taken around the time of their procedure—or further out, in cases such as our patient with the corneal transplants," he said.

Even without objective data on this potential risk, it is prudent for physicians to inform PK patients about it, said Jayne S. Weiss, MD, professor of ophthalmology and pathology at Wayne State University in Detroit.

The ophthalmologist also must decide whether to recommend prophylaxis for patients who do choose immunization, she said. "The approach must be customized to the individual patient." It might be sufficient to remind low-risk PK patients to seek urgent



FLU SHOT CONCERNS. Recent case reports show that flu shots have caused corneal transplant rejections.

treatment at the first signs of rejection. For higher-risk patients, the approach might be to begin or increase topical corticosteroids before immunization and also for up to a month afterward, she said. "So, for example, a patient using Pred Forte (prednisolone acetate 1 percent) every day would increase this to three times a day for one month and then slowly taper back to the original dosage."

—Linda Roach

1 ophthalmologyweb.com/FeaturedArticle.aspx?spid=23&aid=594

2 Steinemann, T. L. et al. *Am J Ophthalmol* 1988;106(5):575-578.

3 Solomon, A. and J. Frucht-Pery. *Am J Ophthalmol* 1996;121(6):708-709.

4 Wertheim, M. S. et al. *Br J Ophthalmol* 06;90(7):925.

Retina Report

Eyedrops for Wet AMD Are Under Investigation

Imagine a therapy for neovascular AMD that can be administered as easily as glaucoma drops. While still years away from realizing a topical treatment, researchers report that results of an early phase 2 trial of pazopanib drops are promising enough to warrant a full-scale phase 2 investigation, which is slated to begin early this year.

At the Academy's Retina Subspecialty Day in October, Ronald P. Danis, MD, reported on a 28-day pazopanib study, involving 27

subjects with occult or minimally classic CNV. Patients in the high-dose arm of the study—5 mg/ml three times a day—showed an improvement of 4.3 letters at day 29, with the trend toward improvement beginning on day 8. Those on a lower dose and in the control group showed no improvement. Dr. Danis is professor of ophthalmology and visual sciences at the University of Wisconsin, Madison.

Pazopanib, developed by GlaxoSmithKline, is approved for systemic treat-

ment of advanced renal cell cancer in adults. Another potential advantage of pazopanib over the current crop of anti-VEGF drugs, said Dr. Danis, is that it affects multiple growth factors, which in animal models play a role in angiogenesis and are believed to play a role in new blood vessel growth in humans. "Unlike ranibizumab and bevacizumab, which inhibit neovascular growth by blocking VEGF-A, pazopanib targets the receptor tyrosine kinase so that it inhibits what happens after VEGF [and other growth factors] binds to its receptor," he said.

This small molecule accumulates in high concentrations in the posterior retina through a transcleral route, making it suitable for topical administration.

"Pazopanib does an end run around the front of the eye and goes to the back via the sclera," Dr. Danis said.

This study also found a dose effect favoring patients with a particular genotype, which, Dr. Danis said, advances the idea that pharmacogenetics may one day allow ophthalmologists to tailor a treatment to a patient's genotype, which already occurs in oncology.

"We're years away from FDA approval," Dr. Danis said. Nevertheless, he said, "pazopanib has the potential to limit the rather arduous reinjection schedule that patients currently have to go through to manage their wet AMD."

—Miriam Karmel

Dr. Danis is a consultant to GlaxoSmithKline.

Cataract News

AMD Patients Do Benefit From Cataract Surgery

Cataract surgery can improve visual acuity in patients with all stages of age-related macular degeneration, according to Age-Related Eye Disease Study researchers.¹ "Even those with advanced AMD can have improvement in vision," said AREDS investigator Emily Y. Chew, MD, of the National Eye Institute.

These results come in sharp contrast to several epidemiological studies, which found that cataract surgery may be harmful in patients with AMD and indicated

that incidence and progression were increased as much as threefold or more. "Earlier studies reported that it is a 'gamble' and dangerous to perform the surgery, but we found no clear evidence that cataract surgery is harmful for these patients," said Dr. Chew.

Several methodological factors differentiate AREDS from previous studies, and this may account for the opposing conclusions, said Dr. Chew. "Our study details the visual acuity outcomes from the largest cohort of

persons with AMD undergoing cataract surgery conducted to date. And we compared patients with AMD and cataract surgery with those who also had AMD but did not undergo cataract surgery. The population-based studies had fewer patients with AMD, and in general, most of the population did not have AMD. Further, in AREDS, patients were examined by retina surgeons rather than general ophthalmologists who may select patients in a more stringent manner, culling out some who may, indeed, be good candidates for surgery.

"If a cataract is the likely cause of vision loss in a patient, I would not hesitate to recommend the surgery," she said. "However, I strongly advise that surgeons who



PERFORM PHACO. According to a recent study, cataract surgery may not increase the incidence or progression of age-related macular degeneration.

proceed with AMD patients be vigilant with follow-ups and counsel patients about the potential natural history of increased risk of progression to advanced AMD.

—Leslie Burling-Phillips

1 Forooghian, F. et al. *Ophthalmology* 2009;116:2093–2100.