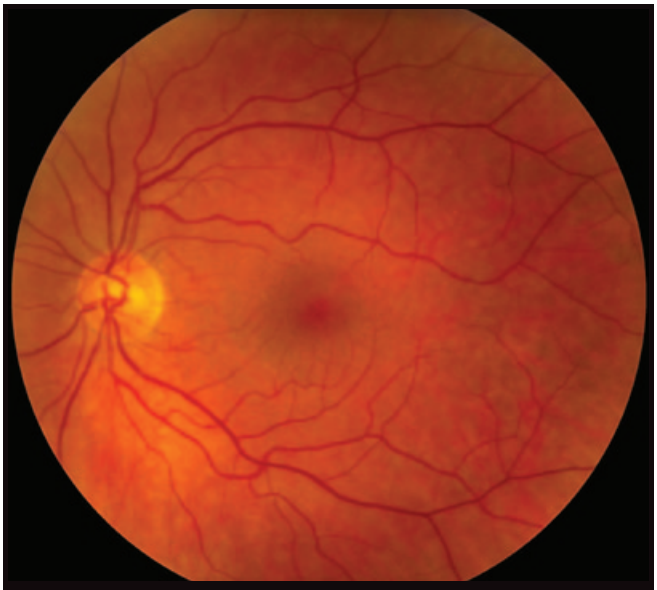
Kidney Function and TB-Drug Vision Loss

Physicians have known since the early 1970s that the same drug that was curing patients' tuberculosis was causing severe vision loss in a few of them. Now, 40 years later, ethambutol-induced optic neuropathy (EON) is still taking its blinding toll on an estimated 100,000 people worldwide every year.[1] But why do a few people—around 2 percent of them—suffer irreversible vision loss, while others are spared?

Taiwanese ophthalmologists reported on three answers that point to a common toxic pathway: kidney function, or lack of it. After examining 12 years of national health system records on ethambutol-treated adults, they found that increased age, hypertension, and renal diseases (with or without end-stage cases included) were risk factors for this type of optic neuropathy. A total of 231 EON cases (3.63 percent) among 6,369 ethambutol-treated cases and 924 controls were included.[2]

The lead author, Hsin-Yi Chen, MD, a glaucoma specialist and associate professor of ophthalmology at China Medical University Hospital in Taichung, Taiwan, noted that the analysis confirmed the results of earlier studies linking higher risks of ethambutol damage with factors that correlate with impaired kidney function: increased age (adjusted odds ratio = 1.93 for age older than 65) and coexisting renal disease (adjusted OR = 2.11 without end-stage disease; 3.73 with it).



ADVERSE EFFECT. Optic neuropathy from ethambutol.

A third patient factor, hypertension, was a slight surprise because it has seldom been reported as a risk factor for this complication of TB treatment (adjusted OR = 1.62), said Dr. Chen.

Alfredo A. Sadun, MD, PhD, an expert on ethambutol ocular toxicity, said, "Our contention is that pretty much all of this blindness is preventable. Ethambutol toxicity is a dose-dependent problem, and the dose depends not only on how many pills you take but also on urinary excretion. It's the blood dose that counts," said Dr. Sadun, professor of ophthalmology and neurological surgery at the University of Southern California's Doheny Eye Institute.

Ethambutol is widely used by millions of people who contract TB each year

NEI

(9 million in 2011, according to the CDC) and is mainly recommended for use during the initial two-month phase of multidrug therapy.[3] More than half of the TB patients in the United States receive it, Dr. Sadun said.

He said that he sees five to 10 new cases a year of blindness induced by ethambutol. Patients who have taken the drug for six months or less can regain nearly all of their lost vision; after eight or nine months, they regain less; however, after a year of daily dosing with ethambutol, the loss is largely irreversible, Dr. Sadun said.

He advises pulmonary specialists to individualize their dosing regimens based on creatinine testing and to switch patients who develop vision loss to another drug. "Once the patient starts to lose vision, you really have to act fast," he said.

—Linda Roach

1 Sadun AA, Wang MY. J *Neuroophthalmol.* 2008;28(4):265-268.
2 Chen HY et al. *Br J Ophthalmol.* 2012;96(11):1368-1371.
3 MMWR Recomm Rep. 2003;52(RR11):1-77. Find it at www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

***Drs. Chen** and **Sadun** report no related financial interests.*

Retina Report

Anti-VEGF Drugs for Pregnant or Nursing Moms

German researchers authored a case study suggesting that ranibizumab (Lucentis) may be the drug of choice for pregnant or nursing patients who need treatment for choroidal neovascularization. Their report shows that ranibizumab has less effect on VEGF levels in serum and breast milk than does bevacizumab (Avastin).[1]

Christoph Ehlken, MD, and associates saw a 32-year-old patient with recurring scar-associated choroidal neovascularization who had just given birth. "We had to decide whether it was safe to use VEGF inhibitors in a nursing mother," said Dr. Ehlken, at the University Eye Hospital in Freiburg, Germany. "We did the study because of the lack of information on safety of VEGF inhibitors in this group."

After extensive discussion with the patient (who was a pharmacist), therapy was started with intravitreal bevacizumab. The patient was advised to stop breastfeeding. She underwent regular blood tests and provided breast milk for analysis, continuing the tests after switching to ranibizumab.

After the bevacizumab injection, serum VEGF dropped such that levels were not detectable, rising slowly until the patient needed retreatment. Ranibizumab was then injected; the patient's serum VEGF levels dropped by 10 percent before rising.

As for VEGF levels in breast milk, the authors reported a 35 percent decrease at two weeks after bevacizumab injection. After ranibizumab, they noted that VEGF levels remained relatively stable. "There has been growing evidence that systemic VEGF levels are reduced after intravitreal injection of bevacizumab and, to a lower degree, after ranibizumab. This, to our knowledge, is the first description of reduced VEGF levels in breast milk after intravitreal injection of bevacizumab. It appears that even the low concentration of intravitreal bevacizumab—compared with the concentrations used for systemic therapy—can cause a significant decrease of VEGF in other tissues," said Dr. Ehlken.

CASE STUDY. Concentrations of VEGF in breast milk decreased from 13.3 ng/mL to 8.6 ng/mL in the two weeks after bevacizumab injection.

This difference between the two drugs could have to do with the molecular structure of the proteins. Bevacizumab consists of a humanized IgG antibody with a fragment crystallizable (Fc) region, which allows transport through the blood-retina barrier mediated by an Fc-binding receptor (neonatal Fc receptor). Ranibizumab consists of only the fragment antigen-binding (Fab) region and thus lacks the binding site for the transport system, said Dr. Ehlken.

He cautions that as VEGF inhibitors are increasingly used in younger patients (e.g., for diabetic macular edema or uveitis), "we have to expect a higher number of pregnant or nursing patients who need anti-VEGF treatment. These constellations are not—and will not be—covered in randomized clinical trials. Safety issues have to be considered carefully and individually with every patient."

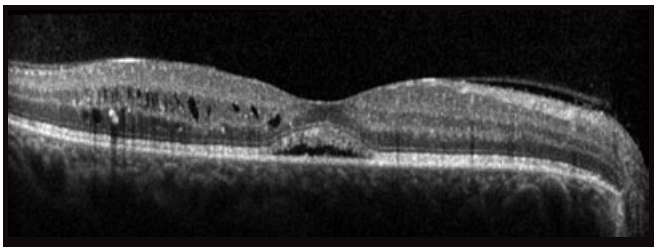
—Laura B. Kaufman

1 Ehlken C et al. *Arch Ophthalmol.* 2012;130(9):1226-1227.

***Dr. Ehlken** reports no related financial interests.*

Diabetes Update

Sleep Apnea May Play a Role in Diabetic CSME



DIABETES. Clinically significant macular edema in a diabetic patient with type 2 disease.

Could screening for and treatment of sleep apnea help protect against retinal complications in patients with diabetes? This was a question considered by Oxford researchers who recently found a high prevalence of sleep-disordered breathing (SDB) in patients with diabetic clinically significant macular edema (CSME).[1]

Eighty diabetic patients with CSME consented to have a home sleep study, which found an oxygen desaturation index of 10 or greater in 54 percent of participants and an apnea-hypopnea index of 15 or greater in 31 percent—both signs of SDB. "In previous studies of patients with diabetes, the prevalence of sleep apnea is higher than normal, but not as high as this," said coauthor Victor Chong, MD, head of the Oxford Eye Hospital at the University of Oxford in the United Kingdom.

Without the benefit of a closely matched group, said the study authors, it is not possible to know for certain whether this increased prevalence is specifically linked to CSME or simply due to the greater age (64.7 years) and obesity of CSME patients, which in turn is linked to various features of sleep apnea.

Patients in the study had, on average, a neck circumference of 40.4 cm and body mass index of 30.2 kg/m^2—both of which correlated strongly with the oxygen desaturation index and, in the case of neck circumference, with the apnea-hypopnea index, according to the authors.

Dr. Chong also emphasized that patients with more severe symptoms might have influenced the study results by introducing patient enrollment bias. However, the study found that, despite the high prevalence of SDB, the majority of patients were normal on the Epworth sleepiness scale.

It is also notable that the study did not find a relationship between the severity of SDB and degree of macular thickness, measured by spectral-domain OCT, and the nature or severity of retinopathy, evaluated by fundus photography.

If SDB plays a role in the pathophysiology of CSME, its mechanism remains a mystery. The study authors hypothesized that blood pressure spikes and oxygen desaturation from sleep apnea may be jointly to blame. These likely work hand in hand, but which comes first presents a chicken-and-egg question, said Dr. Chong.

—Annie Stuart

1 Mason RH et al. *Retina.* 2012;32(9):1791-1798.

***Dr. Chong** reports no related financial interests.*

Glaucoma Update

Exfoliation Glaucoma: Caffeine a Risk Factor?

People who drink three or more cups of caffeinated coffee a day may be at greater risk of developing exfoliation glaucoma (EG) than non-coffee drinkers, particularly if they have a family history of glaucoma.[1] It's still too soon, however, to advise patients to skip that extra cup of joe.

Other studies will have to confirm this finding, which is from the first exploration of a possible relationship between caffeinated coffee and EG risk, said Jae H. Kang, ScD, assistant professor of medicine at Brigham and Women's Hospital in Boston.

The prospective study spanned more than two decades and examined two cohorts: 78,977 women from the Nurses' Health Study and 41,202 men from the Health Professionals Follow-Up Study. Heavy coffee drinking increased the risk 1.66-fold for developing EG or being an EG suspect.

The trend did not extend to other caffeinated products—soda, tea, and chocolate. It didn't hold up with decaffeinated products, either, which leaves the precise etiologic factor a mystery. "We do not have enough powerful data to clearly discern whether the effect is due to caffeine or noncaffeinated coffee factors or both," said Dr. Kang.

Caffeine was the focus of this study because several randomized clinical trials have linked its consumption to elevated homocysteine levels in the plasma, aqueous humor, and tear fluid of EG patients. One theory holds that elevated homocysteine may enhance formation of exfoliation material.

—Miriam Karmel

1 Pasquale LR et al. *Invest Ophthalmol Vis Sci.* 2012; 53(10):6427-6433.

***Dr. Kang** reports no related financial interests.*

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