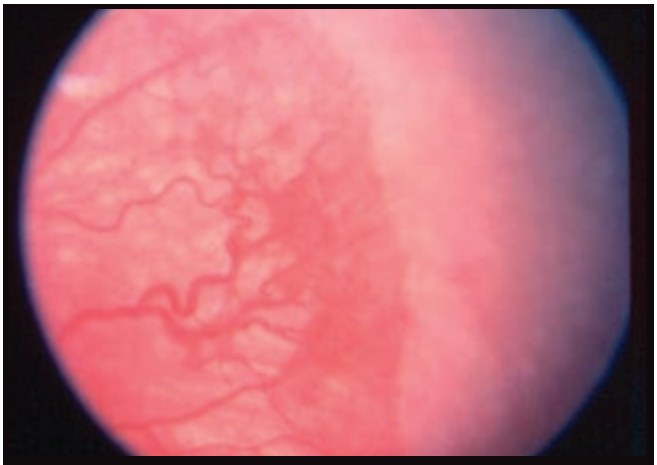
Severe ROP: Day Length a Predictor

Taking a cue from a mouse study, researchers at Cincinnati Children's Hospital Medical Center (CCHMC) conducted a single-center retrospective study of more than 300 premature infants.



STAGE 3 ROP. Maternal/fetal exposure to daylight during the first 90 days of pregnancy may reduce the risk of severe retinopathy of prematurity.

The investigators found that average day length (ADL), which is an estimate of maternal/fetal light exposure, was a statistically significant predictor of severe retinopathy of prematurity (SROP).[1]

This came as a surprise to lead author, Michael B. Yang, MD, pediatric ophthalmologist at the medical center. "I would have expected that early light exposure would be swamped by all the other variables that contribute to ROP risk," he said.

The mouse study. For normal eye development, fetal mice require exposure to light through the mother's body during early gestation. Reporting in *Nature*, a group led by Richard A. Lang, PhD, also of CCHMC, identified a fetal light-response pathway in mice involving melanopsin that regulates their number of retinal neurons and angiogenesis.[2]

The human study. Given that retinopathy of prematurity (ROP) affects the developing retinal vasculature of preterm infants, Dr. Yang's group then considered the mouse study findings and questioned whether day length during early human gestation could impact SROP. Results from their study of 343 premature infants—with 76 of 684 eyes developing SROP—showed ADL as a statistically significant predictor of SROP in three separate models.

Model 1 included all 684 eyes. During the first 90 days after the estimated date of conception (EDC), each additional hour of ADL decreased the likelihood of SROP by 28 percent. Other factors influencing the development of SROP in model 1 included birth weight, gestational age, multiple births, race, and per capita income in the mother's residence ZIP code. Model 2 included a subset of 468 eyes that developed any kind of ROP, and it produced results similar to model 1. Model 3 included a subset of 146 eyes that had developed prethreshold ROP. During the first 105 days after EDC, each additional hour of ADL decreased the chance of SROP by 46 percent.

Other analyses. The study also analyzed whether total light exposure over time (estimated by the

sum of day lengths during gestation) might influence outcome. "We found it was exposure to light during the first 90 days, rather than the entire gestational period, that was important," said Dr. Yang. He added that day 58, which falls in this period, theoretically correlates most closely to the light-sensitive period of vascular eye development in the mouse fetus (16 to 17 days). Calculating ADL during different time periods of early gestation, the researchers also found that 31 to 60 days and 61 to 90 days after EDC were most closely linked to SROP for model 1 and model 3, respectively.

Let there be light? Although day length stands out as an independent predictive factor in the current study, it doesn't necessarily prove a role for light exposure in the fetus, said Dr. Yang. ADL could be a surrogate for potential confounders—such as vitamin D deficiency, temperature, or activity of the mother. However, the basic research from the mouse makes a strong case that this light-response pathway is likely to exist in humans.

"If we can confirm our initial findings in more than one center and rule out these confounders," said Dr. Yang, "we can be more confident that light plays a role during gestation to decrease the risk of severe ROP." Even then, rather than prescribing light therapy for all pregnant women, identifying women at greatest risk for giving birth prematurely may be the best starting point, he added.

—Annie Stuart

***Dr. Yang** reports no related financial disclosures.*

1 Yang MB et al. *Ophthalmology.* 2013 Oct. 16. [Epub ahead of print].
2 Rao S et al. *Nature.* 2013;494 (7436):243-247.

Refractive Report

AMD Risk Varies by Refractive Status

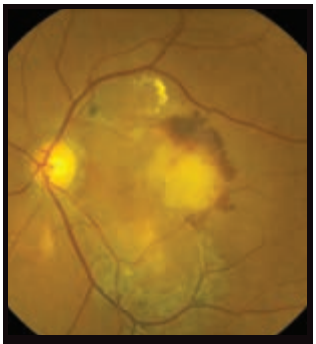
Finally some good news for myopes. A systematic review and meta-analysis reports that people with myopia are less likely to have age-related macular degeneration (AMD), whereas hyperopes may have an increased risk.[1]

Risk factors for AMD have proved difficult to find. Only cigarette smoking has been consistently identified in most studies. "New risk factors that are consistently associated with AMD have eluded researchers," said study author Tien Yin Wong, MD, PhD. Until now.

Background. A couple of studies in the past decade suggested a correlation between refractive error—in particular, hyperopia—and AMD. "When this was first reported, I think some people dismissed the association, reasoning that it was a chance finding," said Dr. Wong, professor and executive director at Singapore Eye Research Institute, chairman of ophthalmology at the National University of Singapore, and group director of the SingHealth Office of Research.

Indeed, the data from the literature over the years were somewhat conflicting and inconclusive. "Then one or two more high-quality studies reported the same link between hyperopia and AMD risk. That's when we thought there may be something to this association," Dr. Wong said. "So we reviewed the literature and summarized the strongest studies we could find in a meta-analysis to look at the robustness of this association."

Study findings. The analysis concluded that refractive error, when analyzed as a continuous variable for each diopter toward hyperopia, is associated with a 6 to 9 percent increased risk of both prevalent and incident AMD. "The absolute risk itself was not very high, but the association was strong," said Dr. Wong.



AMD. Wet AMD with hemorrhage in a hyperopic patient (+2.00), right eye.

It is noteworthy that the analysis included several studies that also looked at axial length, a more precise measurement than refraction. Shorter axial length was associated with an increased risk of AMD, whereas longer axial length was associated with a decreased risk of AMD. "If we only found the association for refractive power, not for axial length, we might not be so confident in the findings," Dr. Wong said.

One caveat is that there were not enough prospective studies to include in the analysis; accordingly, there were insufficient incident AMD cases over time to detect a significant relationship between refractive status and new AMD, even if a relationship was present. The authors therefore could not establish a temporal or causal relationship.

"Our findings have opened doors for people to think about new ocular mechanisms involved in AMD," Dr. Wong said. The current epidemiology literature cannot tell us that.

The authors offered several possible explanations for their findings, one of which is that VEGF may become more concentrated in hyperopic than myopic eyes. They noted that this and other possible explanations require further study.

—Gabrielle Weiner

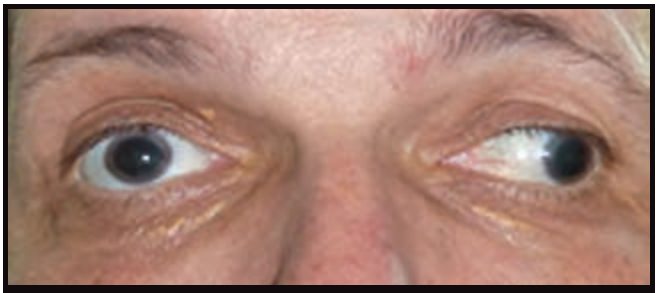
1 Pan C et al. *Ophthalmology.* 2013;1209(10):2058-2065.

***Dr. Wong** is a consultant for and is on the advisory boards of Allergan, Bayer, and Novartis.*

JASON S. CALHOUN

Strabismus Update

Strabismus May Affect Social Interactions



STRABISMUS. Sample image of a strabismic eye that was viewed by study participants.

A team of Swiss researchers reports that cosmetically obvious strabismus generates negative feelings in observers, which can actually be measured in the brain.[1]

Thirty-one healthy volunteers underwent functional magnetic resonance imaging to assess and compare their response to images of both strabismic and normal eyes. The strabismus images led to significant activation of the amygdala and hippocampus in 30 observers. (The observer with no reaction was an ophthalmologist who helped design the study.) Earlier studies have shown that amygdala activation plays an important role in processing emotions that are negative, fearful, and aversive, leading the researchers to conclude that healthy individuals respond negatively to strabismus.

This study, among the first to consider strabismus from the observer's point of view, asked participants: Did the pictures evoke any emotions? Surprisingly, more than one-fourth claimed a neutral response, despite the clear organic effect. This suggests that the response in the brain did not reach the level of consciousness but likely would influence behavior, said Hanspeter E. Killer, MD, study coauthor and professor of ophthalmology, Kantonsspital Aarau and University of Basel.

He hopes that the findings will convince reluctant insurers to pay for strabismus surgery. He also wants ophthalmologists to take strabismus more seriously. Some doctors try to talk patients out of surgery on the grounds that it is merely a cosmetic concern, but this study proves it is more than that, he said. "I will definitely listen more carefully to the complaints of adults with strabismus."

—Miriam Karmel

1 Berberat J et al. *Ophthalmology.* 2013;120(10):2125-2129.

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

Retina Report

Oral Drug for AMD?

The topical form of pazopanib, an anti–vascular endothelial growth factor (VEGF) drug, has not shown the promise in treatment of wet age-related macular degeneration (AMD) that researchers had hoped for.[1] But the oral formulation shows early signs of efficacy.[2]

Oral pazopanib was used in a two-part trial in which 15 patients with neovascular AMD took 15 mg of the drug daily for 28 days, and 72 healthy participants took pazopanib (5 to 30 mg) or a placebo daily for 14 days to test for safety and tolerance. Jason S. Slakter, MD, clinical professor of ophthalmology at New York University School of Medicine and director of the Digital Angiography Reading Center in Manhattan, led the trial's image analysis.

Nine of the AMD patients completed the trial without needing adjunct intravitreal injections. All nine showed improvement in best-corrected visual acuity (average, 8 letters), central retinal lesion thickness (average, −50.94 µm), and central retinal thickness (average, −50.28 µm). Six of the nine who improved had the *CFH* Y402H TT or CT genotype.

"Rescue" anti-VEGF injections were needed by six other patients to control their AMD; all had the *CFH* Y402H CC genotype, which is associated with higher AMD risk. The researchers concluded that the T allele may predict which patients will respond well to oral pazopanib.

No participants withdrew from the study due to adverse health events. All tolerated the drug well, indicating that doses up to 30 mg daily may be safe.

"The results suggest that an oral agent targeting the VEGF pathway may potentially control the exudative changes in choroidal neovascular AMD so that fewer injections would be needed," said Dr. Slakter. "Also, there may be a connection between a patient's genotype and his or her response to an AMD therapy. Further research is required to confirm the potential contribution of pazopanib or similar agents."

—Mary Wade

1 Csaky K et al. A phase 2b dose-ranging study of pazopanib eye drops vs. ranibizumab intravitreal injections for the treatment of neovascular AMD. Presented at: Retina Subspecialty Day; Nov. 15, 2013; New Orleans, La.
2 McLaughlin MM et al. *JAMA Ophthalmology.* 2013 October 10. [Epub ahead of print].

***Dr. Slakter** received grant research support for image analysis in this clinical study. He also serves as a consultant to GlaxoSmithKline for the pazopanib program.*