

News in Review

COMMENTARY AND PERSPECTIVES

ROP Telemedicine Passes Big Test

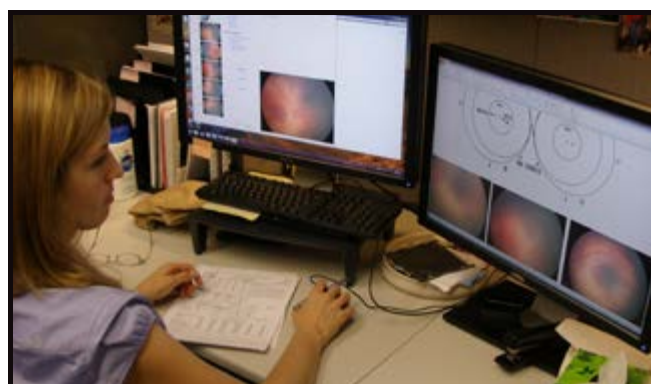
Trained nonphysician readers can reliably grade retinal images, obtained by nonphysician imagers in neonatal intensive care units (NICUs), for infants at risk for retinopathy of prematurity

(ROP).¹ In the NEI-sponsored e-ROP study, readings were compared with doctors' binocular indirect ophthalmoscopy exams of 1,257 premature infants in 13 North American study centers.

The goal of this study was to see whether the trained readers at a remote central reading center could identify infants with ROP severe enough to warrant evaluation by an ophthalmologist. Referral-warranted (RW) ROP was defined as zone 1 ROP, stage 3 ROP or worse, and/or plus disease—an outcome consistent with Type 1 and

Type 2 ROP severity as used in the Early Treatment for Retinopathy of Prematurity (ETROP) Study.

Validation. The study provides support for a telemedicine ROP screening system that relies less heavily on ophthalmologists, said Graham E. Quinn, MD, MSCE, principal investigator of e-ROP and professor of ophthalmology at Children's Hospital of Philadelphia. This is especially encouraging given a dearth of doctors available to repeatedly examine babies and the fact that less than 8 percent of at-risk infants ultimately require treatment.



REMOTE VIEW. Trained nonphysician reader scrutinizes fundus images of an infant at risk for ROP.

Of the 244 babies that doctors identified as having RW-ROP, 162 needed treatment. Among the treated babies, image readers correctly identified RW-ROP 98 percent of the time. Further supporting the study findings was the similarity in image evaluation between the trained readers and a panel of ROP experts.

When considering the presence of RW-ROP in both eyes, the researchers found that telemedicine screening by trained readers had a specificity of 87 percent and sensitivity of 90 percent. Missing 1 in 10 can't be considered ac-

ceptable, said Dr. Quinn. However, this finding must be seen in the light of an imaging schedule that, by necessity, mimicked a clinical exam schedule, he said.

Multiple advantages. In contrast, said Dr. Quinn, a telemedicine screening schedule could be set up weekly or even biweekly, enabling even better detection than that achieved in the study, where just three infants needing treatment were missed by image readers. In fact, telemedicine detected 43 percent of severe ROP cases on average about 15 days earlier than physician exams.

Telemedicine also allows for a more baby-centered approach, he said, with imaging being done when it's best for the baby, rather than shoehorned into a physician's busy schedule. It could also eliminate unnecessary transfer of babies, he said, since doctors can remotely check images for

progression of disease.

Moving forward. Although study results can be generalized to babies weighing less than 1,251 g in Level 3 nurseries, said Dr. Quinn, infants in Level 2 nurseries may stand to gain the most from a similar system. "That's because these nurseries don't have a large num-

ber of premature babies, so ophthalmologists may be less available than in Level 3 nurseries," he said.

If issues such as liability, cross-state licensing, and parent resistance can be resolved, said Dr. Quinn, ROP telemedicine using trained nonphysician imagers and readers may prove a

highly efficient strategy for evaluating infants at risk for ROP-related blindness.

—Annie Stuart

1 Quinn GE et al. *JAMA Ophthalmol.* 2014 June 26. [Epub ahead of print.]

Dr. Quinn received NEI support for e-ROP.

Retina Report

CATT Conundrum: Vision Loss Despite Tx

In every clinical study of anti-VEGF therapy to treat neovascular age-related macular degeneration (AMD), there has been a small cohort of patients who lose significant amounts of vision, leaving clinicians to ponder the reasons why. In May 2014, investigators from the Comparison of AMD Treatments Trials (CATT) reported a new analysis of their 24-month outcomes.¹ They found that 61 patients (5.9 percent) among the 1,030 patients participating at the end of two years had developed sustained visual loss, defined as loss of 15 or more EDTRS letters from baseline at the last two trial visits. These losses occurred despite regular intravitreal injections with bevacizumab or ranibizumab.

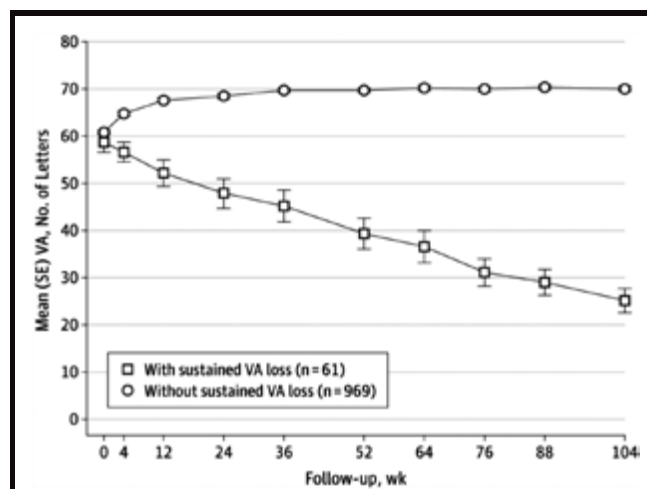
Characterizing the loss. In more than 80 percent of the affected patients, the researchers attributed the visual deterioration to foveal scarring (44.3 percent), pigmentary abnormalities

(27.9 percent), or foveal geographic atrophy (11.5 percent)—conditions commonly associated with wet AMD prior to the advent of anti-VEGF drugs, said Daniel F. Martin, MD, who chaired the CATT studies.

"But what surprised me was that the decrease in visual acuity was, for the most part, linear over time," said Dr. Martin, chairman of the Cleveland Clinic Cole Eye Institute.

"The majority of these patients [75.4 percent] did not experience any improvement after treatment began and, instead, had a steady, slow deterioration to lower levels of vision," he said.

Factors beyond VEGF. These findings highlight the fact that other cytokines, apart from VEGF, are involved in progression of neovascular AMD. Some researchers propose that platelet-derived growth factor (PDGF) is an important contributor to the development of subretinal fibrosis. PDGF is thought to



LINEAR DECLINE. The lower line shows results over two years for the patients who had visual loss in CATT.

support the health of pericytes that surround blood vessels, possibly shielding CNV from the effects of anti-VEGF therapy.²

Combined therapy may help. Though the vast majority of patients do very well with a VEGF inhibitor, said Dr. Martin, a small percentage still wind up with visual loss. A drug that worked synergistically with anti-VEGF agents by decreasing subretinal scarring might provide a solution.

A phase 2b trial of this approach, using ranibizumab plus PDGF inhibitor Fovista (Ophthotech), found that combined therapy produced 62 percent more improvement than therapy with ranibizumab, Ophthotech reported. In this

study, said Dr. Martin, some of the neovascular lesions became smaller over time, and there appeared to be less subretinal fibrosis than expected.

"If those findings are confirmed in the phase 3 trial, it may be very promising news for those patients who have a propensity to develop subretinal scarring and decreased vision during the treatment of neovascular AMD," he said.

—Linda Roach

1 Ying GS et al. *JAMA Ophthalmol.* 2014 May 29. [Epub ahead of print.]

2 Jo N et al. *Am J Pathol.* 2006; 168(6):2036-2053.

Dr. Martin reports no related financial interests.

Comprehensive Update

Evidence Builds for Education-Myopia Link

A study from Germany linking education to myopia adds to the body of literature suggesting that environmental factors play a strong role in the pathogenesis of shortsightedness.¹ Among 4,658 participants drawn randomly from the Gutenberg Health Study, both the prevalence and the magnitude of myopia increased with each consecutive year of education.

Genetics yields to education. Genetics had little

effect compared with education, according to a statistical analysis of 45 myopia-related single-nucleotide polymorphisms (SNPs). Lead author Alireza Mirshahi, MD, FEBO, a senior lecturer at University Medical Center in Mainz and head of Dardenne Eye Hospital in Bonn, said, “In our study, every single SNP associated with myopia accounted for only 0.01 diopters in spherical equivalent.”

On the other hand, level



SCHOOL AND SHORTSIGHTEDNESS. A new study corroborates prior reports on the association of education and myopia.

of education made a big difference. Secondary school graduates had a mean spherical equivalent of -0.5 D compared with $+0.2$ D for those who never finished school. Moreover, 50.9 percent of secondary school

graduates were myopic compared with 26.9 percent of those who never graduated. That pattern held in comparisons of various levels of higher education.

Findings across populations. Dr. Mirshahi said a similar association between education and myopia was reported earlier in an Asian population. “Our study corroborates this finding in Caucasians.” He added the association may be universal across ethnic groups.

—Miriam Karmel

1 Mirshahi A et al. *Ophthalmology*. 2014 June 16. [Epub ahead of print.]

Dr. Mirshahi reports no related financial interests.

Neuro Notes

Factors in Recovery From Acute Optic Neuritis

A father's concern for his daughter's sight was the origin of a study elucidating factors in the severity of, and recovery from, acute optic neuritis (AON) in multiple sclerosis (MS), said Tanuja Chitnis, MD. When the father asked about the 15-year-old girl's chance of recovering vision, Dr. Chitnis reviewed the literature and found little helpful information.

Prompted by this unmet need, Dr. Chitnis, director of Partners Pediatric MS Center and associate professor of neurology at Harvard Medical School, and colleagues embarked on a study

to identify demographic and clinical factors associated with AON in adults and children with MS.¹

Demographic factors studied included age, sex, race, and ethnicity. In addition, use of steroids and disease-modifying therapy and levels of serum vitamin D were analyzed.

Vitamin D and severity. Neither steroid use nor demographic factors studied were associated with severity of the attack, as measured by loss of visual acuity. However, vitamin D emerged as a significant predictor: Participants with lower seasonally adjusted

serum vitamin D levels were more likely to have severe attacks. Dr. Chitnis said that although vitamin D is sometimes used as a disease-modifying therapy in MS, this is the first study that focused on the vitamin in connection with ON.

Demographics and recovery. In her practice, Dr. Chitnis had observed anecdotally that children fared better than adults. The study supported this observation: 94.7 percent of the pediatric patients experienced full visual recovery, compared with 79.8 percent of adults. She said, “This is consistent with a number of studies now demonstrating that children in general have more resilience in the central nervous system.”

The news was not so positive for men, who had a significantly worse chance of recovery than women (odds ratio, 2.27; $p = .03$).

Clinical implications.

Among the manifestations of MS, “Optic neuritis is a particularly good example to study because we actually have a number by which we can measure both severity and recovery,” said Dr. Chitnis, adding that findings from ON could potentially be extrapolated to other types of MS attacks. Further, “This study reminds us that it's important to pay particular attention to male patients, who might need treatment or other intervention if they have optic neuritis.”

—Peggy Denny

1 Malik MT et al. *Neurology*. 2014;82(24):2173-2179.

Dr. Chitnis has been an advisor for Biogen Idec, Novartis, Sanofi-Aventis, and Teva; and received grant support from Guthy-Jackson Charitable Foundation, Merck Serono, National MS Society, NIH, and Novartis.