News in Review

COMMENTARY AND PERSPECTIVE

NEUROSCIENCE

Microglia Can Repopulate Retinas After Depletion

RESEARCHERS AT THE NATIONAL EYE Institute (NEI) have discovered that the eye has the potential to regenerate the intraretinal immune cells that it needs to keep retinal synapses functioning properly.[1]

The finding represents the first time that neuroscientists have been able to observe the regeneration of these immune cells, called microglia, directly in a living animal and demonstrate that the repopulated cells can do their normal job within a neural system, said the study's lead investigator, Wai T. Wong, MD, PhD, at the NEI.

It also suggests that targeted control of these cells might one day allow ophthalmologists to tamp down destructive inflammation in diseased retinas without the use of corticosteroids, Dr. Wong said.

Rethinking neurodegeneration. "In the business of trying to save neurons from dying, people have been trying to directly sustain the neurons," Dr. Wong said. More recently, however, researchers have recognized that "many diseases in which neurons degenerate actually involve a maladaptive, maladjusted immune system within the brain or retina."

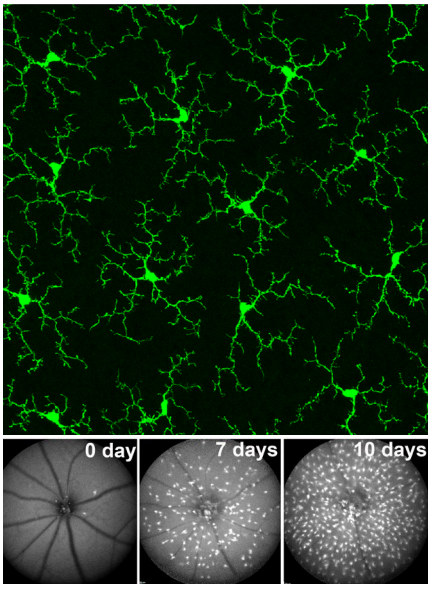
As a result, "finding ways in which the immune cells behave and can change, as well as discovering the agents that can manipulate them, is a new way of thinking about cures to neurodegeneration," he explained.

Road to repopulation. In this animal study, Dr. Wong and his colleagues were following up on their own and other scientists' work showing that microglia in the brain and the retina are essential to synaptic functioning of the neurons. "This is something that is quite recent in the field. We had studied this question a few years ago and found that, in the prolonged absence of microglia, the fidelity of the transmission of the signal between retinal neurons begins to break down. It's like having a bad electrical connection. You still get some transmission, but the amount is decreased," he said.

The researchers used the investigational drug PLX5622 (Plexxikon), an inhibitor of the colony-stimulating factor 1 receptor, to almost entirely deplete the microglia in the inner and outer plexiform layers of mouse retinas. When they withdrew the drug 1 week later, the few surviving cells began multiplying and, over subsequent weeks, redistributed themselves across the plexiform layers into the same functional, mosaic arrays that existed before the drug treatment, they reported.

"We were actually able to witness the repopulation process by looking into the eyes of living animals and document it in a video," Dr. Wong said.[2]

Looking ahead. Dr. Wong said that reversibility of microglial depletion suggests that targeted delivery of PLX5622 or another drug with similar action might someday be used to temporarily suppress microglia from sending inflammatory signals that would eventually lead to photoreceptor malfunction or death.



RECOVERY. *Top: Healthy microglia in an adult mouse retina. Bottom: Mouse eyes after being treated with a drug that nearly eliminates microglia. On Day 0, almost all microglia are gone, except for a few near the optic nerve head. By Day 7, the microglia have migrated across the retina, and by Day 10, they have increased in number.*

However, more research is needed to understand how to time and deliver the treatment in each disease scenario, he cautioned. Because the molecule is not soluble, intravitreal injection would require a special formulation or delivery device, Dr. Wong said. Human research on the drug is limited but ongoing; www.ClinicalTrials.gov lists only 2 PLX5622 clinical studies, both safety trials in patients with rheumatoid arthritis, and the outcomes have not been published.

For now, much research remains to be done, Dr. Wong said. "We were aiming at a proof of concept. So this

Neuron-Glia Interactions in Retinal Diseases Section, NEI

is a step toward understanding what the retina's immune system is capable of and how to control and manipulate that for therapeutic purposes," he said.

—Linda Roach

1 Zhang Y et al. *Sci Adv.* 2018;4(3):eaap8492.
2 See http://advances.sciencemag.org/cgi/content/full/4/3/eaap8492/DC1. (Note: Three movies are toward the bottom of the web page.)
Relevant financial disclosures—Dr. Wong: None.

RETINA

Evidence Review: Lasers for PDR

SINCE THE EARLY TREATMENT OF Diabetic Retinopathy Study (ETDRS), argon laser photocoagulation has been the gold standard for treating proliferative diabetic retinopathy (PDR). And, in recent years, there have been attempts to modify the technique and introduce new laser technologies. But do these strategies provide safe and effective alternatives? A team from the United Kingdom reviewed the literature and found a significant gap in the evidence.[1]

Intervention review. To assess the effects of different lasers and different laser protocols, the U.K. researchers identified and evaluated 11 randomized controlled trials proposing alternative laser modalities for the treatment of PDR. These trials compared a variety of modifications to the ETDRS standard of care, including different laser types, a variety of pulse intensities and durations, and altered scatter distributions for laser burns.

"After assessing and grading the overall certainty of the results, we found that these trials provide limited evidence with respect to the efficacy and safety of alternative laser systems or strategies," said Tanya Moutray, MB BCh, BAO, FRCOphth. In particular, the review found, the trials were small in size, poorly conducted, and poorly reported. They also contained a high risk of bias and failed to clearly define study outcomes.

Potential for confusion. The ETDRS standard of care calls for a single-spot treatment—specifically, an initial treatment of midperipheral scatter laser consisting of 1,200 to 1,600 burns, 200- to 500-µm spot size, and an argon pulse duration of 100-200 ms with power titrated to produce moderate-intensity burns.

However, guidelines set by the Royal College of Ophthalmologists (RCO) contradict this standard, stating that "technological advances in new laser technology using multispot and micropulse abilities have widened clinical

NEURO-OPHTHALMOLOGY

Measuring Intracranial Pressure: Is Ultrasound Acceptable?

A STUDY BY RESEARCHERS AT JILIN UNIVERSITY IN Changchun, China, furthers the case for orbital/optic nerve ultrasound's potential as an alternative to lumbar puncture for measuring changes in intracranial pressure (ICP).[1] Previously, the researchers confirmed that ultrasonographic measurements of optic nerve (ON) sheath diameter could be used to identify patients with elevated ICP.[2]

Dynamic assessments. For this study, the researchers measured both ON sheath diameter and ICP in 60 patients who had been admitted for lumbar puncture. Of those, 37 were found to have elevated ICP, most caused by cerebral infection. One month later, following treatment, the 25 patients not lost to follow-up underwent an additional round of measurements.

In both situations—upon admission and after treatment—the ON sheath diameter and lumbar puncture measurements were strongly correlated. What's more, there was no difference in mean ON sheath diameter between patients with higher or lower levels of elevated ICP.

The researchers speculated that the elasticity of the ON sheath may explain why sheath diameter examinations can be used to dynamically assess variations in ICP. They also noted that the technique is easy to learn, has high interobserver reliability, and may be generalizable and applicable in a variety of potential clinical settings.

Clinical implications. "This study adds further evidence [supporting] the sensitivity and specificity of ultrasonography for the purpose of determining in a noninvasive manner whether or not there is elevated ICP," said Andrew G. Lee, MD, at the Blanton Eye Institute at Houston Methodist Hospital.

In fact, Dr. Lee said in an accompanying editor's note, he has used orbital ultrasound as either an adjunct or surrogate to actual direct measurement of ICP in a number of common clinical circumstances.[3] Among them: differentiating difficult cases of pseudopapilledema from papilledema, and following patients who either refuse or cannot undergo lumbar puncture.

Nevertheless, Dr. Lee noted that the technique "is still in development." And he agreed with the researchers that larger studies are needed, in part to determine whether the results are generalizable at ICP levels outside the study's parameters. The maximum ICP value in the study was 400 mm H_2O, so the accuracy of the technique at higher levels is not clear.

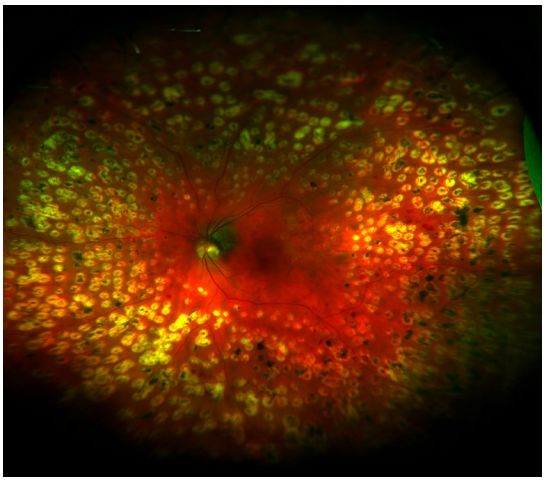
Despite ultrasonography's potential as a noninvasive alternative to lumbar puncture, Dr. Lee said, "Direct measurements of ICP remain the gold standard."

—Miriam Karmel

1 Wang L et al. *JAMA Ophthalmol.* 2018;136(3):250-256.
2 Wang L et al. *PLoS One.* 2015;10(2):e0117939.
3 Lee AG. *JAMA Ophthalmol.* 2018;136(3):256.
Relevant financial disclosures—Dr. Lee: None.

knowledge and treatment options."[2] Dr. Moutray voiced concern regarding the RCO guidelines, noting that "our review was unable to find evidence to definitively support these alternative modalities."

Advancing the discussion. Even so, physicians and clinicians should not ignore newer photocoagulation strategies because of the quality of these trials, said Dr. Moutray. Instead, she said, she hopes that her team's work will set a framework for future research.



PHOTOCOAGULATION. *After panretinal laser treatment.*

"New clinical trials focusing on PDR management and modern laser therapies can build on the research by using our findings and recommendations. This will help avoid research waste and encourage researchers to conduct studies that are large enough to provide definitive answers and evaluate the long-term outcomes most relevant to patients," she said. —*Mike Mott*

1 Moutray T et al. *Cochrane Database Syst Rev.* 2018;3:CD012314. doi:10.1002/14651858.CD012314.pub2.

2 https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-301-FINAL-DR-GUIDELINES-DEC-2012-updated-July-2013.pdf. Accessed April 17, 2018.

Relevant financial disclosures—Dr. Moutray: None.

WORLD HEALTH

Visual Symptoms in Diplomats Posted to Cuba

HOW AMERICAN DIPLOMATS IN Havana, Cuba, came to suffer a constellation of symptoms characteristic of neurotrauma remains as mysterious today as it was when first reported in 2016 and 2017. But the first comprehensive clinical study of a cohort of "Havana syndrome" patients has concluded that their oculomotor and other neurological symptoms look a lot like those of a well-established diagnosis: persistent concussion.

A team of experts assembled by the University of Pennsylvania's Center for Brain Injury and Repair reached this conclusion after extensive examinations of 21 diplomats (mean age, 43 years) referred by the U.S. State Department for evaluation, treatment, and rehabilitation.[1]

"Much to our surprise—and even though a lot of people on the team were a little skeptical that someone without history of a head impact could display symptoms similar to concussion—one by one, each member of our multidisciplinary panel felt that these symptoms really did look like persistent concussion," said Douglas H. Smith, MD, who directs the center, which is located in Philadelphia.

What caused it? Eighteen of the 21 diplomats told the physicians that they heard a localized, intensely loud sound, with pure and sustained tonality, just as their symptoms began. Most of the patients also reported that the sound was accompanied by pressurelike or vibratory sensory stimuli.

Visual symptoms. Examinations at the Philadelphia center began an average of 203 days (range, 3-331 days) after exposure.

In addition to having cognitive difficulties, the patients exhibited an array of oculomotor and visual problems similar to those seen in persistent concussion, Dr. Smith said. These symptoms included convergence insufficiency (n = 11, 52%); abnormal smooth pursuits (n = 11, 52%); saccadic dysfunction (n = 10, 47%); and impairment of the vestibulo-ocular reflex (n = 15, 71%). In addition, the patients complained of light sensitivity (n = 13, 62%); difficulty reading (n = 12, 57%); and eye strain (n = 11, 52%), particularly with reading, and associated with headaches, disequilibrium, and nausea.

Need for rehab. The majority of the patients required intervention by multiple rehabilitation experts, including those specializing in oculomotor evaluations, for their symptoms to subside. "In contrast to patients with classic concussions, most Havana syndrome patients exhibited significant impairment that persisted for months [and they experienced] no significant improvement until rehabilitation was initiated," the researchers wrote.

What's next? The origin of the sound and the apparently coincident mechanism through which the patients' brains were injured remain unknown, Dr. Smith said. Neuroimaging was performed on all 21 patients, 18 of whom had conventional findings well within the normal limits. Findings for the other 3 were nonspecific. Thus, he said, the researchers hope to use advanced neuroimaging techniques to look for structural and functional alterations in the brain that might account for the various symptoms of Havana syndrome.

Networks of axons in the visual system are especially sensitive to any injury that disrupts their serial communication, he pointed out. "So, for instance, eye tracking requires a really complex system of the brain to work together just correctly, at 100 meters per second. At each node the information has to be processed and sent on, and finally at the end the muscles can move the eyes back and forth to track motion." —*Linda Roach*

1 Swanson RL II et al. *JAMA*. 2018;319(11):1125-1133.

Relevant financial disclosures—Dr. Smith: None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.