ANGIOGENESIS, EXUDATION, AND DEGENERATION 2021—VIRTUAL EDITION

New findings around iRORA and cRORA.

AN INTERVIEW WITH DAVID SARRAF, MD, AND PHILIP J ROSENFELD, MD, PHD; BY MATTHEW R. STARR, MD

The Angiogenesis, Exudation, and Degeneration 2021—Virtual Edition meeting was packed with groundbreaking reports. Recently, the topic of identifying patients with lesions that could predict the development of geographic atrophy (GA) has attracted interest. Such lesions may prove to be biomarkers for clinical trials and evidence physicians can use to counsel patients on their long-term visual prognoses.

For this article, Matthew R. Starr, MD, a vitreoretinal fellow at Wills Eye Hospital, interviewed David Sarraf, MD, of UCLA Stein Eye Institute and Philip J. Rosenfeld, MD, PhD, of Bascom Palmer Eye Institute about their presentations at the 2021 Angiogenesis meeting. Both presenters detailed new findings on two types of lesions that may serve as useful GA biomarkers: incomplete retinal pigment epithelial (RPE) and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA).

MATTHEW R. STARR, MD: PLEASE BRIEFLY DESCRIBE THE IMPORTANCE OF DETECTING IRORA OR LESIONS PREDATING THE DEVELOPMENT OF IRORA.

David Sarraf, MD: OCT provides a more granular grading system of atrophy so that we can better identify earlier thresholds of intervention and prevention. Therapies in clinical trials for GA aim to reduce the rate of progression of disease. Targeting patients at earlier stages of intervention and aiming to reduce the development of end-stage GA and central blindness are critical because we cannot reverse this disease. OCT provides the opportunity to do this.

Philip J. Rosenfeld, MD, PhD: A group of retina providers are interested in identifying changes on OCT that predate GA. How you view fundus and en face images influences how you view that OCT. Depending on the type of OCT machine, some retina physicians rely on dense raster scans, maps, and en face imaging, whereas others rely on averaged B-scans.

The first notion of identifying these predictive lesions in nascent GA came in 2014 with a report by Robyn Guymer, AM, FAHMS, and colleagues in which they detailed changes within the outer plexiform layer and inner nuclear layer as well as hyporeflective wedge-shaped bands within the outer retina. Those authors, however, did not include hypertransmission defects in the choroid. We believe these defects indicate that the RPE is dying—but not dead yet.

Prof. Guymer's work led to the development of the Classification of Atrophy Meeting group. This consensus group eventually developed the belief that hypertransmission defects are important markers predating the development of cRORA. However, the notion of nascent GA does not take into account these hypertransmission defects, and thus iRORA is a more encompassing term. Detection of these lesions may allow better clinical guidance for patients who have yet to develop GA.

DR. STARR: DR. SARRAF, WHY WERE ONLY EXTRAFOVEAL LOCATION AND INTRARETINAL HYPERREFLECTIVE FOCI FOUND TO BE ASSOCIATED WITH PROGRESSION TO CRORA, WHEREAS OTHER STUDIES HAVE SHOWN FEATURES SUCH AS SUBRETINAL DRUSENOID DEPOSITS AND HYPOREFLECTIVE FOCI WITHIN THE DRUSEN CORE TO BE ASSOCIATED WITH LATE AMD DEVELOPMENT?

Dr. Sarraf: These may be the most important risk factors. Subretinal drusenoid deposits and hyporeflective foci are likely also important, but our study may not have been powered to show that.

DR. STARR: DR. ROSENFELD, DO TRANSIENT HYPERTRANSMISSION DEFECTS SEEN ON EN FACE OCT IMAGES CORRELATE WITH THE DEVELOPMENT OF GA, OR IS IT PRIMARILY PERSISTENT DEFECTS?

DETECTION OF THESE LESIONS MAY ALLOW BETTER CLINICAL GUIDANCE FOR PATIENTS WHO HAVE YET TO DEVELOP GA.

Dr. Rosenfeld: iRORA has a very high probability of leading to GA. Once iRORA is identified, GA will most likely develop within 1 to 2 years. Once you have this, you are beyond recovery and on the way to GA. The ability to identify hypertransmission defects larger than 250 µm and the significant association of these patients to develop cRORA indicates the clinical utility these lesions present for clinical trials and physicians.

DR. STARR: ARE THERE OTHER IMAGING MODALITIES THAT MAY PREDICT CRORA PROGRESSION?

Dr. Sarraf: iRORA and even milder subtypes of cRORA may not be detected with fundus autofluorescence (FAF) or fluorescein angiography, which supports OCT as perhaps the most granular classification system available. The OCT biomarkers may therefore be the best way to predict GA. Choroidal flow deficit analysis with OCT angiography has the potential to predict atrophy, and this was recently validated by the Sadda group at UCLA.

Dr. Rosenfeld: Hypertransmission defects precede any FAF findings. Once they are seen on FAF, it is GA. Until there is a dark spot on FAF, there is no GA. There are two large-scale studies—SWAGGER, evaluating swept-source imaging of GA, and IMPACT, evaluating the natural history of drusen—seeking to identify early multimodal imaging findings in patients without cRORA who later go on to develop GA and cRORA.

DR. STARR: DO YOU BELIEVE STUDIES NOW EVALUATING GA PROGRESSION MAY BE ABLE TO TARGET IRORA LESIONS AS WELL AND PERHAPS PREVENT OR SLOW CRORA DEVELOPMENT?

Dr. Rosenfeld: Hypertransmission defects lead to a 68% increase in the risk of developing GA compared with patients with intermediate AMD. This is extremely important for new clinical trials seeking to evaluate disease progression. Trials can use this in identifying how to slow the development of GA.

This concept of using hypertransmission defects on OCT will allow clinical trials to enroll patients without crossing the threshold of GA development and will allow studies to present earlier readouts of findings, perhaps at 6 or 12 months, to identify high-risk patients. Both of these metrics are useful in counseling patients and in designing clinical trials.

Dr. Sarraf: Yes, GA trials are now using iRORA and cRORA as thresholds for intervention and prevention. By preventing the development of cRORA, we may be able to better preserve central visual acuity as opposed to preventing GA, which may be a later, more end-stage outcome of atrophic AMD more commonly associated with central blindness.

DR. STARR: WHAT ARE THE NEXT STAGES IN EVALUATING IRORA LESIONS?

Dr. Sarraf: We are hoping to define subcategories of iRORA better to more precisely and accurately identify earlier and later stages of iRORA.

Dr. Rosenfeld: We hope to gather longer-term data, beyond 3 years, and further solidify hypertransmission defects on OCT as metrics for cRORA progression. ■

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