The Role of Peripheral Vasculature in AMD

Ultra widefield fluorescein angiography may provide clues in understanding why patients convert from dry to wet forms of this disease.

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In the past several years, our understanding of the exudative (wet) form of age-related macular degeneration (AMD) has increased substantially. We now know that the pathogenesis of AMD is a complex cascade of events not limited to the involvement of photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris. Genetics and chromosomal linkage, via complement factor H, have also been implicated in AMD. The role of inflammation and upregulation of vascular endothelial growth factor (VEGF), prostaglandins, and hyopxia inducible factors HIF1 and HIF2, have recently been in the spotlight as well.

Our understanding of nonexudative (dry) AMD, however, is limited, and we currently have no way of treating our patients with dry AMD or understanding how or why they convert to wet AMD.

At the annual meeting of the American Academy of Ophthalmology (AAO) this year, I presented a series of patients (n=128) for whom we reviewed ultra widefield angiograms, spectral domain optical coherence tomography (SD-OCT) scans, and fundus autofluorescence (FAF) images to assess the presence or absence of peripheral perfusion and/or ischemia and the correlation to wet AMD stage and rate of progression.[1] Our conclusion was that peripheral per-

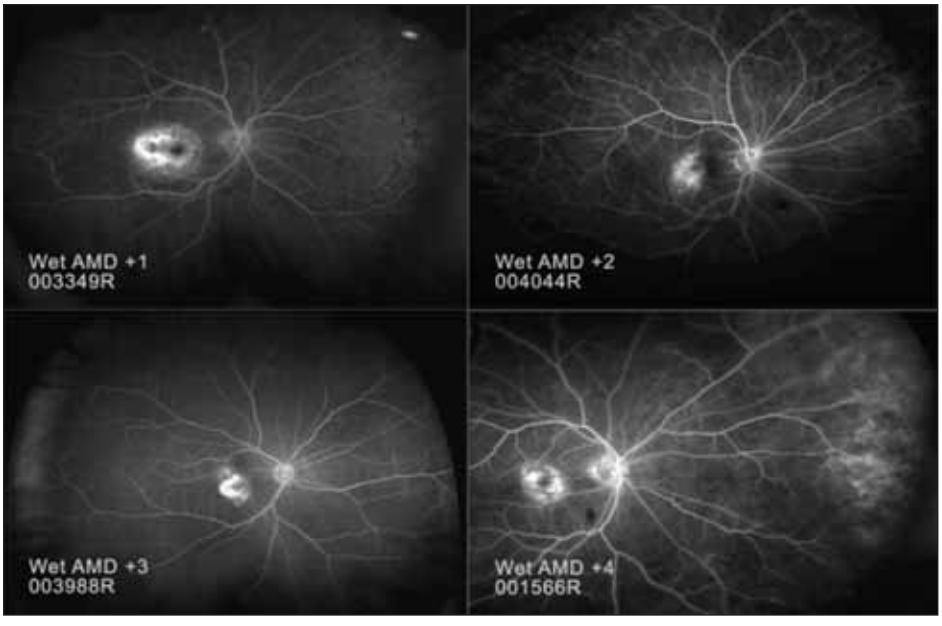

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Figure 1. Case examples of differences seen in luminescence intensity when grading gamma normalized standard peripheral angiography between stages 1, 2, 3, and 4 wet AMD.

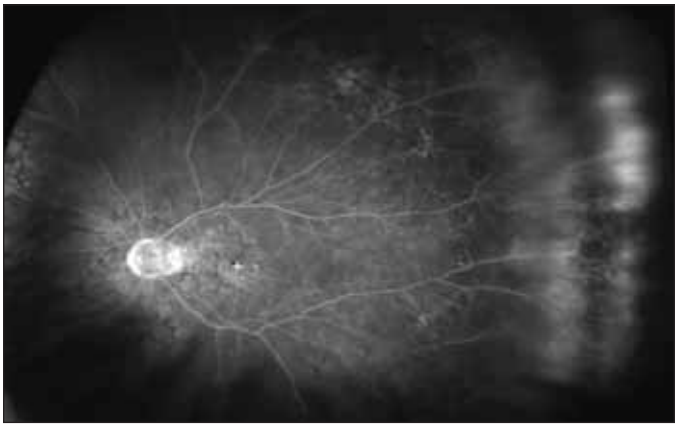

Figure 2. Blood vessels in the far periphery demonstrating hyperfluoresence with abnormally increased luminance.

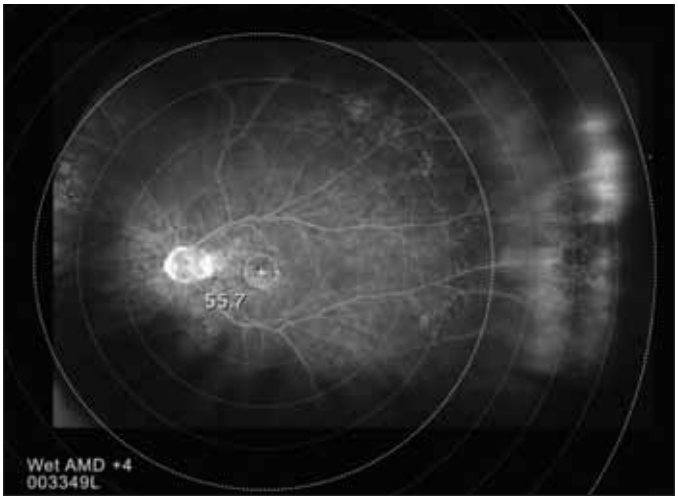

Figure 3. The macula was isolated and the brightest pixel was measured with an intensity of 55.7. Standardized centipetal arcs were used to register and ultimately calculate the peripheral luminance.

fusion or lack thereof may be a key marker for the relative AMD disease state. Further, measuring peripheral angiographic perfusion and understanding this potential source of VEGF might be important in developing new AMD therapy and/or adjusting regimens with current therapies.

We hope to be able to apply this knowledge to dry AMD to better understand the factors that determine when and why patients convert.

ULTRA WIDEFIELD (PERIPHERAL) FA

Figure 1 shows case examples of differences seen in luminescence intensity when grading standard peripheral angiography between stage 1, 2, 3, and 4 wet AMD. Figure 2 is an ultra widefield image that shows a good deal of leakage and hyperfluorescence in the periphery. This might cause us to question whether there is something more to macular disease than leakage in the center to midperipheral field and whether some sort of peripheral end-artery ischemia is causing problems. The following case is presented to discuss the correlation between leakage seen out in the periphery and the reasons why the patient with dry AMD converted to wet AMD.

CASE EXAMPLE

Our patient was a 72-year-old man, with an ex-smoker, had a history of alcohol use, hypertension, previous angina, and a myocardial infarction several years prior. He was taking medications for blood pressure and hypertension. His visual acuity was fluctuating wildly from visit to visit, and his OCT scans demonstrated variable neurosensory retinal edema; there was no evidence of choroidal neovascularization on fluorescein angiography (FA) or indocyanine green imaging. It was not until we took images using the ultra widefield Optos P200A (Optos, Fife, Scotland) and reviewed his FA Optomap (Optos) image that we saw zones of peripheral late vascular leakage. Out in the far periphery of Figure 2, it is clear that the blood vessels at approximately 2:00 to 3:00 are leaking profusely.

The patient recently converted to wet AMD, and treatment with anti-VEGF medications has been started.

Had the chronic small vessel disease, alcohol and tobacco use, hypertension, high blood pressure, and heart disease led to a relative hypoxia or ischemia that drove the patient's conversion to wet AMD?

DISCUSSION

We looked at a large series of wet AMD patients in the study presented at the AAO.[1] After looking at the peripheral angiograms of 123 patients, we noted that 80% of them showed some evidence of hyperfluorescence and leakage in the periphery.

To attempt to answer the question posed above, we have gone further and normalized the gamma on each of the angiograms and measured the pixel luminence using a computer software program that we are currently developing. With this program, we are able to assign a numeric value (relative intensity and area) to a region of interest on the image, allowing us to quantify and numerically follow suspicious angiographic activity over time.

Figure 3 shows how we mapped the macula with the computer program. We then chose the brightest pixel luminence within the normal vascular channel. Based on

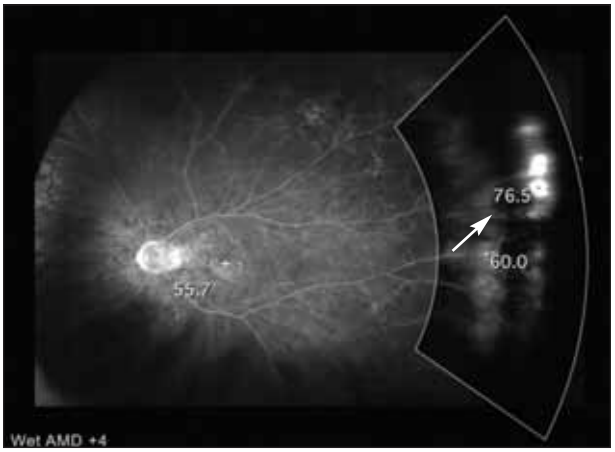

Figure 4. One of the brightest areas measured that was particularly hot measured a luminance value of 76.5, and another vessel was also hyper-intense in comparison to the normal first-order vessel.

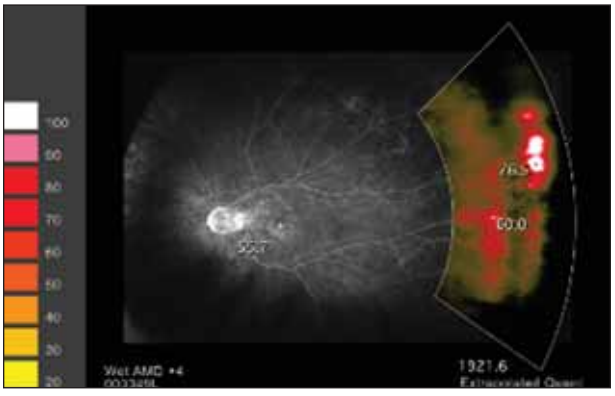

Figure 6. The summation of the extrapolated quantitative value to total 1921.6, which is considerably higher than the 257 average quantitative value that was measured in the "normal" non-AMD control population.

the pixel intensity, values were assigned and graded between 1 and 100 in luminance value. In normal vasculature, the dye should go out to the periphery, stay relatively dark, and then re-circulate. Any areas that are brighter than what appears in the normal first-order vessels indicates clinical leakage. In Figure 3 we measured all the pixels in the main arcades, and the brightest pixel was assigned a luminance value of 55.7. After isolating the zone of brightness out in the periphery that was demonstrating relative hyperfluorescence, we calculated and summated each pixel within the entire grid. One of the brightest areas measured that was particularly hot measured a luminance value of 76.5, and another area that appeared rather bright was measured at a luminance value of 60.0, which is brighter than anything that

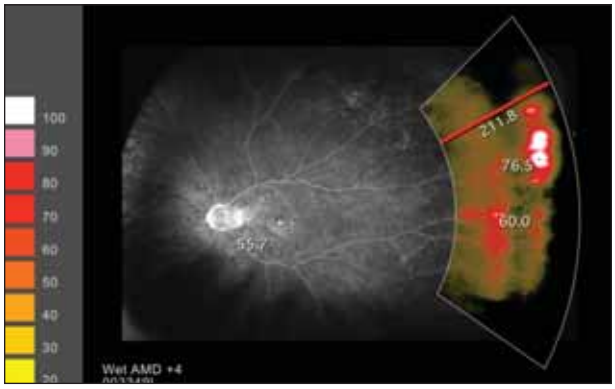

Figure 5. One slice during the calculation of the extrapolated quantification value. Each radial slice was calculated and summated to reach final extrapolated qualitative luminance value.

we saw within the normal blood value columns (Figure 4). Figures 5 and 6 shows how a calculation of a percentage of how much illuminance actually existed, similar to an OCT—with yellow at the lower end of the spectrum of leakage, red being more intense, and white exceeding all anticipated values.

SUMMARY

Could it be that events in the peripheral vasculature are capable of catalyzing the conversion of AMD from dry to wet? The factors that have been implicated in the pathophysiology of AMD thus far—VEGF, inflammation, genetics and chromosomal linkages, and HF1 and HF2—may be only some of the factors that will help predict how AMD progresses. Our study found that peripheral vasculature may provide an indication that a patient is at risk for converting to wet AMD. In our opinion, further research is warranted in a larger group of patients to answer this question. ■

Third party image analysis on the Optos ultra widefield images were performed by W. Kent Demaine of Retina Metrics, LLC.

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1. Bennett MD. wide field angiography and documentation of peripheral perfusion and/or ischemia in patients with wet AMD. Presented at: the Annual Meeting of the American Academy of Ophthalmology. October 25, 2009; San Francisco.