Peripheral manifestations in age related macular degeneration

A Review of Imaging and Findings

Andrew Pivovar, BA
Patrick Oellers, MD

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population of developed countries worldwide. Rapidly evolving ultra-widefield imaging modalities and approaches have aided in analysis of peripheral manifestations in AMD.

METHODS

This is a literature review of all notable publications focused on the relationship between AMD and the retinal periphery conducted within the last two decades, with a focus on novel approaches to grid analysis.

RESULTS

NOTEABLE STUDIES	Findings
Shuler, 2008[9] Seddon, 2009[10] Munch, 2010[11]	Peripheral pigmentary changes and drusen in AMD associated with complement factor H polymorphisms
Rudolf, 2008[12]	Varying morphology & composition of drusen in the macula (soft type) vs the periphery (compound type)
Reznicek, 2012[13]	FAF imaging produces greater peripheral and central signal in AMD patients
Heussen, 2012[14]	Higher prevalence of peripheral atrophic, hemorrhagic, and drusenoid AF abnormalities in AMD patients
Witmer, 2012[15]	Peripheral granular, patchy, and reticular AF changes found in AMD patients
Tan, 2013[16]	Granular, mottled, and nummular FAF abnormalities more common in exudative AMD
Suetsugu, 2016[17]	Further evidence in support of Tan, 2013
Domalpally, 2017[18]	Drusen more prevalent in mid and far periphery of AMD eyes
Laíns, 2018[28]	Peripheral reticular pigmentary changes found to be associated with delayed dark adaptation
Tsunoda, 2019[29]	Association between late-onset night blindness and trickling subtype of AMD as evidenced by peripheral FAF patterns
Forshaw, 2019[31]	Meta analysis of UWF studies confirming peripheral lesions to be more prevalent in AMD

Table 1. Summary of notable findings in early and recent studies of peripheral manifestations of AMD.
(FAF = fundus autofluorescence, AF = autofluorescence, UWF = ultra-widefield)

Peripheral pigmentary changes, drusen deposits, and autofluorescence abnormalities are more prevalent in AMD patients. Studies are beginning to understand the implications of these findings in development of disease. However, there exists a significant discordance in how we characterize ultra-widefield imaging findings. The newly proposed Boston Grid analysis aims to set a new standard by which to characterize UWF findings by introducing a novel zone and helping to correct for visual distortion.

	Grid Characteristics	Evolution
Reznicek, 2012[13]	7-ring grid	Total 48 zones of optic disk length
Heussen, 2012[14]	Four quadrant analysis	Superior, inferior, temporal, nasal
Tan, 2013[16]	Four quadrant analysis	Centered on fovea with added peripheral zone outside central 30° (clock hour documentation of peripheral abnormalities
Nomura, 2015[19]	Added mid-peripheral zone (area between 3 and 9 papilla diameter circles)	
Lengyel, 2015[20]	5-zones	Zone 1-3: standard macular grid as established by international classification Zone 4 as mid periphery & zone 5 as far periphery (both zones further subdivided into 4 quadrants)
Suetsugu, 2016[17]	Four quadrant analysis with central 30° centered on macula	
Guduru, 2017[23]	Four quadrant analysis	
Domalpally, 2017[18]	3-zone grid centered on midpoint between optic disk and fovea (*only grid not centered on fovea*)	Zone 1: posterior retinal pole (3 optic disk diameters) divided into 4 quadrants Zone 2: area between 3 and 9 optic disk diameters divided into 4 quadrants Zone 3: region anterior to zone 2 divided into superior and inferior hemispheres
Bae, 2017[25]	Four quadrant analysis (clock hour documentation of peripheral abnormalities)	
Oellers, 2017[2]	***Boston Grid***: 12-zone grid composed of 3 concentric circles and crosshairs centered on fovea (Figure 1)	Circle 1: encompasses macula + vascular arcades (adopted from AREDS study) Circle 2: encompasses perimacular + temporal arcades (new zone around central macula with high prevalence of pathology) Circle 3: divides mid and far periphery based upon location of vortex veins Grid corrected for peripheral distortion
Küçükiba, 2020[26]	3-zone grid based on Domalpally, Nomura, and Tan studies	

Table 2. Evolution of grid analysis methods for peripheral retinal changes in AMD eyes.

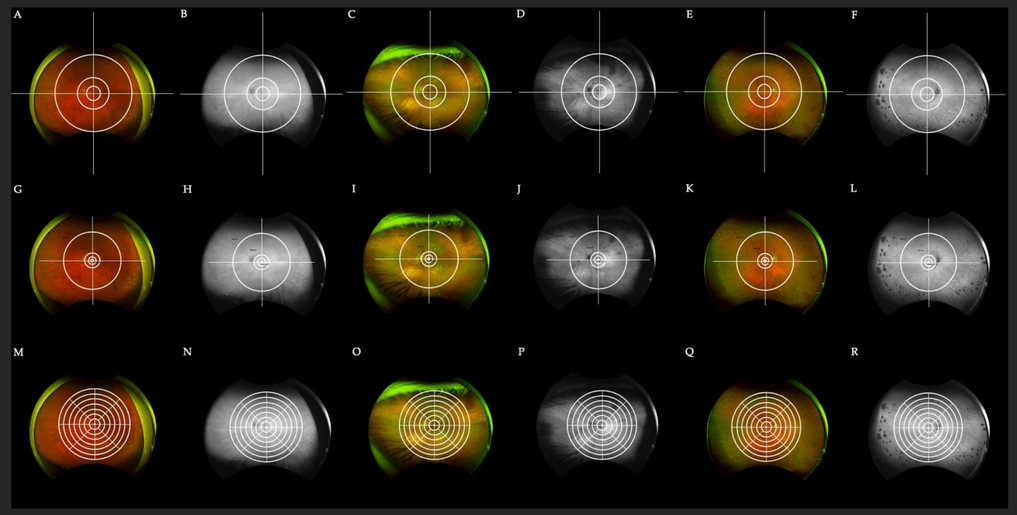

Figure 1. A comparison of the Boston Grid to two other discussed grids for a total of 3 patients with AMD. **(A-F)** Fundus pseudocolor and autofluorescence imaging of 3 patients diagnosed with AMD with the Boston Grid overlay. Fundus imaging of the first patient is depicted in (A), (B), (G), (H), (M), and (N). Peri-macular drusen in (C) is best captured by the Boston Grid when compared with the Lengyel (I) and Reznicek (O) grids. Similarly, central drusen in (E) is best circumscribed by the Boston Grid. **(G-L)** The exact same photos as in (A-F) with the recreated grid by Lengyel et al. superimposed. In comparison to the Boston Grid, the Lengyel grid lacks comprehensive peri-macular and mid-peripheral zones, with zones 1-3 found strictly in the macula and zone 4 encompassing both the mid-periphery and peri-macular area. **(M-R)** An overlay of the recreated Reznicek et al. grid on the images presented previously. The 48 partitions seen here do not clearly distinguish the mid-periphery from the far-periphery and peri-macular areas of the retina, but create much further detail which might be helpful in select cases. For instance, the peri-macular drusen in (O) can be found in approximately 12 zones as opposed to one or few distinct zones. Grids were recreated based on instructions detailed elsewhere.[13,20]

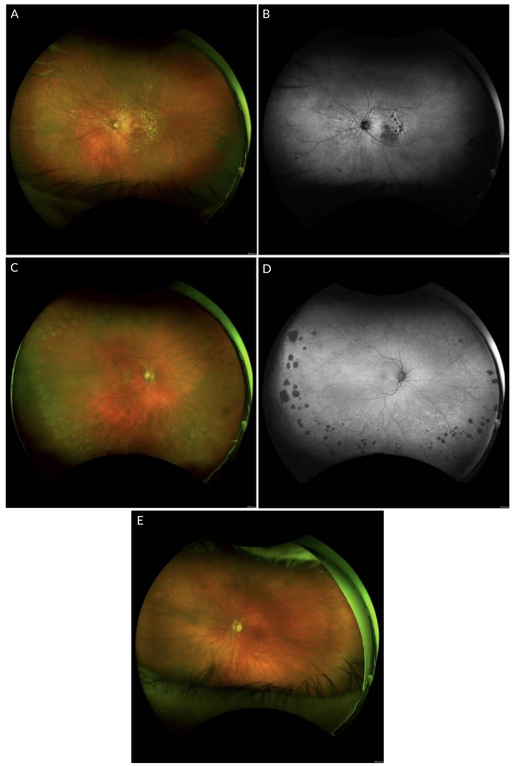

Figure 2. Exemplary ultra-widefield images of eyes with macular degeneration and peripheral abnormalities. Pseudocolor and corresponding autofluorescence of a left eye demonstrating multifocal retinal pigment epithelium (RPE) atrophy and drusen in the macula with peripheral drusen and multifocal RPE atrophy, especially nasal to the optic nerve. Note there is a glaucomatous disk hemorrhage and a peripheral retinal tear status post laser retinopexy **(A,B)**. Another example demonstrates a right eye with macular drusen and peripheral drusen and multifocal atrophy in the far periphery **(C,D)**. A left eye with macular drusen and pigment changes and drusenoid bodies and mild reticular pseudopigmentation in the periphery. Note eyelash artifact inferior **(E)**.

CONCLUSIONS

UWF imaging and analysis has evolved over the years to become an essential mode by which we make new discoveries and broaden our horizons of understanding for AMD pathology. The Boston Grid was developed with an effort to standardize image analysis and improve data comparability. Nevertheless, there is still much work to be done in optimizing study protocols to further unveil the peripheral manifestations in AMD.

References

Please refer to the QR code linking the full paper containing the complete list of numerically-coinciding references.

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