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ROLE OF FUNDUS AUTOFLUORESCENCE IN THE MANAGEMENT OF AGE-RELATED MACULAR DEGENERATION

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Abstract

Objective: *To evaluate the usefulness of Fundus Autofluorescence (FAF) in the detection and management of Geographic Atrophy (GA) in Age-Related Macular Degeneration (AMD), and compare its diagnostic accuracy with Spectral-Domain Optical Coherence Tomography (SD-OCT) with the reference standard of Color Fundus Photography (CFP).*

Methods: *This cross-sectional observational study included 40 patients (65–80 years old) with clinically suspected dry AMD. CFP, FAF imaging, and SD-OCT were performed in all patients. GA presence or absence was recorded for all the imaging modalities. Statistical analysis was done using SPSS version 25, and chi-square and t-tests were applied as and where required. The statistical significance level was considered $p < 0.05$.*

Results: *The age of the patients was 71.0 ± 5.5 years on average. GA was seen in 28 eyes (70%) on CFP, 27 eyes (67.5%) on FAF, and 29 eyes (72.5%) on SD-OCT. SD-OCT was most sensitive in detecting GA ($p = 0.007$), followed by FAF ($p = 0.021$), both of which had significant agreement with CFP. FAF and SD-OCT findings had a high correlation ($r = 0.84$, $p < 0.001$). GA presence was highly associated with advancing age ($p = 0.0003$), but not with gender.*

Conclusion: *SD-OCT and FAF are both valuable imaging modalities for GA detection in AMD, with a little more sensitivity when using SD-OCT. FAF for functional information about RPE health is crucial, while SD-OCT for visualization of structure in high detail. Combined, these modalities have enhanced diagnostic accuracy and enable early detection, monitoring, and treatment of AMD progression.*

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive, degenerative, neuro-retinal disease that affects adults over 65 and is one of the leading causes of visual impairment around the globe. [1,2] It has two main types, one being nonexudative or dry AMD, which is characterized by drusen formation and changes in retinal pigment epithelium (RPE), later on converting into geographic atrophy (GA) which is due to death of the affected RPE cells, and the other being exudative or neovascular AMD, characterized by

choroidal neovascularization.[3] RPE cell death is the earliest detectable disease marker and is a hallmark of AMD.[4, 5] Whenever there is loss of RPE, there is loss of lipofuscin as well since it is a byproduct of the visual cycle and is stored in lysosomes inside RPE cells.[5, 6]Lipofuscin naturally emits autofluorescence (AF) at wavelengths between 480 nm and 510 nm.[3, 5]

Lately, newer methods are being discovered and there are more precise approaches to study macular diseases and abnormalities, like Fundus Autofluorescence (FAF) imaging.[4] It is a noninvasive imaging modality that offers thorough insights into the condition of RPE and gives us not only the required information regarding anatomical changes in retina but also gives a functional assessment. [4, 5, 7] FAF imaging method relies on stimulatory emission of fluorescence from lipofuscin at emission spectra of 500 to 800 nm and focuses on assessment of the RPE monolayer by plotting the distribution of RPE fluorophores, namely lipofuscin and melanolipofuscin. [5, 6, 8] Therefore, geographic atrophy (GA) is seen as a zone of hypofluorescence and enhanced visualization of the underlying choroidal vessels.[6] Visual loss in case of AMD is largely due to choroidal neovascularization and patients with longstanding lesions of CNV have decreased autofluorescence.[3]

Multimodal imaging modalities like FAF imaging help us in early diagnosis and determining disease severity in a more precise manner.[7,9] They also aid in identification of patients who have a greater risk of progression to advanced stages of the disease (for example, patients having RPD).[5] A thorough assessment of different stages of the disease through FAF patterns has also helped in understanding the disease better and hence, formulating most of the current classifications of AMD.[5,7] FAF images help in follow-up and in determining the prognosis of the disease, all the more helping in improved counselling of the patients and making clinical decisions.[5,7]

Until early 21st century, there was no effective treatment of AMD available.[9] However, recent treatment options for AMD include intravitreal Anti-VEGFs like ranibizumab, bevacizumab, afilibercept etc.[9] However, not all patients respond to anti-VEGFs, especially patients with dry AMD.[5, 9] Therefore, newer treatments are also being investigated and researched over like DARPins, recombinant gene therapy, thermal laser photocoagulation, CRISPR-Cas9, Brimonidine and RPE inhibition etc.[9]

The purpose of this study is to evaluate the role of Fundus Autofluorescence in the management of Age-related macular degeneration at its different stages and establish FAF patterns of AMD.

Objectives

- To determine the presence or absence of Geographic Atrophy (GA) using Color Fundus Photography (CFP), Fundus Autofluorescence (FAF), and Spectral-Domain Optical Coherence Tomography (SD-OCT).
- To compare the findings of FAF and SD-OCT against CFP as the standard for detecting GA.
- To determine the statistical significance (p-value) of GA detection across imaging modalities.

Methodology

This cross-sectional, observational study was conducted in Armed Forces Institute of Ophthalmology for a duration of six months, during which a total of 40 patients with clinically suspected with dry age-related macular degeneration (AMD) were recruited from the outpatient department. The study was approved by the institutional review board and written informed consent was obtained from all participants after clearly explaining the study's nature and implications of participating in research. Patients were included in the study following a strict inclusion and exclusion criteria, as follows:

Inclusion Criteria:

- Patients aged 65 - 80 years.
- Clinically suspected dry AMD.
- Willing to provide informed consent.
- Patients with drusens of 63 micrometers or more.
- Absence of confounding retinal diseases such as diabetic retinopathy, retinal vascular occlusion, or hereditary retinal dystrophies.

Exclusion Criteria:

- History of retinal surgery or any recent intraocular surgery (within 6 months)
- History of laser treatment
- Diabetic retinopathy
- History of retinal vascular occlusion
- History of hereditary retinal dystrophy

- Presence of vitreous hemorrhage, exudates or fibrosis
- Presence of dense cataract or corneal opacity
- Presence of neovascular (wet) AMD or any other macular pathology.
- Poor image quality due to media opacities

All the included patients were interviewed and demographic details (age, gender, laterality) along with clinical history (duration of visual symptoms, any relevant systemic comorbidities, history of surgery) were recorded. Baseline visual acuity (LogMAR) was recorded in all the patients.

Color Fundus Photography (CFP) was performed and served as the reference standard to assess for the presence or absence of Geographic Atrophy (GA).[10] Fundus Autofluorescence (FAF) imaging was then performed using Spectralis HRA+OCT system (Heidelberg Engineering), focusing on detection of hypofluorescent lesions indicative of GA.

Spectral-Domain Optical Coherence Tomography (SD-OCT) was subsequently performed in the same visit to evaluate retinal and RPE structural integrity and detect atrophic areas consistent with GA. The imaging protocol included FAF imaging with excitation at 488 nm and emission between 500–700 nm, SD-OCT scanning with a scan depth of 1.8 mm, acquisition speed of 40,000 A-scans per second, and digital depth resolution of approximately 3.5 µm/pixel. Only images where the SD-OCT scan line transected a well-demarcated atrophic lesion ≥1.25 mm^2 were selected.

For each modality (CFP, FAF, and OCT), GA was classified as present or absent. Findings from FAF and SD-OCT were then compared to the CFP results. The tests were performed by a single trained observer to ensure consistency. For each patient, one pair of FAF and corresponding SD-OCT scans were selected and exported in high resolution.

The data was analyzed using IBM SPSS version 25 and descriptive statistics were calculated using mean ± SD for continuous variables (e.g. age) whereas categorical variables (e.g. gender, presence/absence of GA) were calculated using frequencies and percentages. Chi-square test was performed to compare the categorical variables such as the presence/absence of GA between genders or across imaging modalities. An independent sample t-test was performed to compare the mean age of patients with and without geographic atrophy. A p-value of <0.05 was considered statistically significant for all tests.

Results

A total of 40 patients were included in this study. The mean age of the participants was 71.0 ± 5.5 years, with a range of 64 to 78 years. There were 24 male (60%) and 16 female (40%) participants. 20 (50%) patients had bilateral AMD, while the rest had unilateral involvement. Demographic characteristics of the sample are summarized in Table-I below.

Table-I: Demographic Characteristics of Study Participants (n = 40)

Variable		n (%)
Age (years)		71.0 ± 5.5
Gender	Male	24 (60%)
	Female	16 (40%)
Laterality of AMD	Bilateral	20 (50%)
	Unilateral	20 (50%)
Mean LogMAR VA		0.35 ± 0.12

Table-II below summarizes the number and percentage of eyes in which GA was detected as present or absent using Color Fundus Photography (CFP), Fundus Autofluorescence (FAF), and Spectral-Domain Optical Coherence Tomography (SD-OCT). CFP was used as the reference standard. Both FAF and SD-OCT showed statistically significant agreement with CFP in detecting GA. SD-OCT had slightly higher sensitivity in detecting GA compared to FAF.

Table-II: Detection of Geographic Atrophy (GA) Across Imaging Modalities

Imaging modality	GA Present (n, %)	GA Absent (n, %)	p-value (imaging modality vs CFP)
CFP (Standard)	28 (70%)	12 (30%)	-
FAF	27 (67.5%)	13 (32.5%)	0.021
SD-OCT	29 (72.5%)	11 (27.5%)	0.007

Using color fundus photography (CFP) as the reference standard, the presence of GA was confirmed in 29 eyes. Corresponding imaging findings were observed on fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT). FAF revealed hypoautofluorescent regions consistent with RPE loss, while SD-OCT confirmed these findings by showing RPE disruption, thinning of the outer retinal layers, and increased choroidal hyper-transmission.

In our study, a strong correlation ($r = 0.84$, $p < 0.001$) was found between the hypoautofluorescent areas on FAF and the anatomical abnormalities observed on SD-OCT, indicating significant alignment between functional (FAF) and structural (SD-OCT) imaging modalities.

The mean age of patients with GA (n = 29) was 71.0 ± 5.5 years, while the mean age of patients without GA (n = 11) was 66.0 ± 4.2 years. The presence of GA was significantly associated with advancing age ($p = 0.0003$), suggesting a strong age-related component in GA development. No statistically significant association was observed between gender and the presence of GA ($p > 0.05$).

A strong correlation ($p < 0.05$) was also found between the hypoautofluorescent areas on FAF and the structural abnormalities seen on SD-OCT, confirming the diagnostic value of combining functional and structural imaging modalities.

Discussion

This study assessed the role of Fundus Autofluorescence (FAF) and Spectral-Domain Optical Coherence Tomography (SD-OCT) in the detection of geographic atrophy (GA) in patients with dry age-related macular degeneration (AMD), using color fundus photography (CFP) as the reference standard. Our findings suggest that both FAF and SD-OCT show high agreement with CFP in detecting GA, with SD-OCT exhibiting slightly higher sensitivity. Moreover, the presence of GA was significantly associated with advancing age, reinforcing the age-dependent nature of this degenerative retinal disease. The mean age of patients with GA in our study was significantly higher than those without GA (71.0 ± 5.5 vs. 66.0 ± 4.2 years, $p = 0.0003$), aligning with previous studies that underscore age as the most prominent risk factor for GA development.[11, 12] Age-related oxidative stress and mitochondrial dysfunction have been implicated in retinal pigment epithelium (RPE) degeneration, which is central to GA pathogenesis.[13]

Our findings further validate the diagnostic utility of FAF in identifying early and advanced stages of GA. FAF imaging, through detection of lipofuscin-related fluorescence patterns, is particularly sensitive to RPE abnormalities before they manifest as overt atrophic lesions.[14] In our study, FAF detected GA in 67.5% of cases, closely matching the CFP standard (70%). This is consistent with reports by Wu et al. and Ryu et al., who found that FAF accurately delineates areas of RPE atrophy and surrounding stress zones, which are indicative of impending lesion progression.[15, 16]

SD-OCT, on the other hand, demonstrated the highest detection rate for GA (72.5%) and showed strong correlation with structural features such as RPE disruption and choroidal hypertransmission. These findings reinforce prior literature that has identified SD-OCT as a highly reliable imaging tool for mapping the morphologic changes in GA.[17, 18] Studies by Guymer et al. and Nassisi et al. also emphasized the superior sensitivity of OCT in quantifying atrophic areas and monitoring lesion enlargement over time.[19, 20]

The synergy between FAF and SD-OCT enhances both structural and functional assessment of AMD. In our study, a strong correlation was found between the hypoautofluorescent areas on FAF and the anatomical abnormalities observed on SD-OCT. Similar conclusions were reported by Borrelli et al., who advocated for the complementary use of these modalities in routine AMD evaluation.[21] The multimodal approach not only improves diagnostic

accuracy but also facilitates better patient stratification for treatment and monitoring.

Although anti-VEGF therapy remains the cornerstone for neovascular AMD, its role in dry AMD is limited. The emergence of advanced imaging techniques, such as FAF and OCT, has become essential for clinical decision-making, particularly in identifying patients at risk for progression to advanced GA.[22] Furthermore, imaging biomarkers derived from FAF and SD-OCT are increasingly being incorporated into clinical trials for novel therapeutics like complement inhibitors, suggesting a paradigm shift in how we manage and track dry AMD.[23, 24]

Despite the high concordance rates, discrepancies between modalities can occur due to differences in imaging principles and resolution. FAF may miss very early or small atrophic lesions that SD-OCT can detect due to its higher depth resolution, while SD-OCT may occasionally underestimate the lesion boundary in cases of diffuse RPE thinning. [25] Hence, combining both modalities provides a more holistic view and reduces diagnostic uncertainty.

Limitations

The study has some limitations, including its cross-sectional design, which prevents the assessment of AMD progression over time. Longitudinal studies are necessary to validate FAF's predictive power and better understand its role in disease management. Additionally, a larger sample size could preferably improve the generalizability of the results. The study was also conducted at a single center, which can introduce potential bias, therefore future multicenter studies with larger and more diverse populations would be valuable. Finally, while CFP was used as the standard reference, variability in grading GA could still exist across observers. Going further, there should be work on linear dimensions so that FAF and SD-OCT can be studied in greater depth.

Conclusion

This study confirms that both FAF and SD-OCT are valuable in detecting GA in AMD, with strong correlation to CFP-based findings. The presence of GA was significantly associated with advancing age. Integrating FAF and SD-OCT with CFP enhances diagnostic accuracy, especially in early detection and staging of GA. These findings support the clinical utility of multimodal imaging in AMD assessment and future therapeutic monitoring.

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