Journal of Clinical & Experimental Ophthalmology
ISSN: 2155-9570

Franco et al., J Clin Exp Opthalmol 2018, 9:5
DOI: 10.4172/2155-9570.1000754

Research Article Open Access

Assessing Dry Age-Related Macular Degeneration in a Mexican Population with Fundus Autofluorescence and Spectral Domain Optical Coherence Tomography

Renata del Carmen García Franco, Marlon Rafael García Roa*, Veronica Romero Morales, Miguel Angel Vazquez Membrillo, Ximena Mira Lorenzo, Paulina Ramirez Neria, Charles Van Lansingh and Ellery Lopez Star

Instituto Mexicano de Oftalmología, I.A.P. (Mexican Institute of Ophthalmology), Queretaro, Queretaro, Mexico

***Corresponding author:** Dr. Marlon Rafael García Roa, Instituto Mexicano de Oftalmología, I. A. P, Circuito Exterior Estadio Estadio Corregidora S/N, Colinas Del Cimatario, Queretaro, Queretaro, Mexico 76090, Tel: +52 4422290776; E-mail: drmgroa@hotmail.com

Received date: September 26, 2018; **Accepted date:** October 09, 2018; **Published date:** October 16, 2018

Abstract

Purpose: To evaluate early and intermediate dry age-related macular degeneration (AMD) in a Mexican population using enhanced depth imaging spectral-domain optical coherence tomography (EDI SD-OCT) to determine fundus autofluorescence (FAF) patterns, choroidal thickness, and their correlations.

Methods: This cross-sectional study evaluated patients aged >50 y with early and intermediate dry AMD. Angiography and EDI SD-OCT were used to take digital retinal images, which were evaluated manually to determine the FAF pattern (using the Possible correlations with age and visual acuity (Log MAR) were investigated.

Results: Fifty-eight patients (84 eyes) were enrolled (mean age: 77 y; SD: 9 y); 72.4% were women (n=42). The mean visual acuity was 0.4 Log MAR (SD: 0.24). Reticular autofluorescence was the major pattern observed in 29.8% of eyes, followed by minimal change (23.8%), focal increased (19%), normal pattern (14.3%), linear (5.9%), patchy (3.6%), speckled (2.4%), and lacelike (1.2%). There was a statistically significant correlation between choroidal thickness (mean: 202.8 μm; SD: 69.8 μm) and 34 age (p<.01) and visual acuity (p=0.0243). The patchy pattern had the most reduced choroidal thickness (mean: 184.3 μm; SD: 104.6 μm), and the increased focal pattern had the lowest visual acuity (mean: 0.53 Log MAR: SD: 0.3 Log MAR).

Conclusions: Among a Hispanic population with early and intermediate dry AMD, the predominant autofluorescence pattern was reticular, with few cases of lacelike pattern observed. There was a tendency for choroidal thickness to decrease with age and visual acuity level.

Keywords: Early and intermediate dry age-related macular degeneration; Fundus autofluorescence (FAF) patterns; Choroidal thickness; Dry age-related macular degeneration in a Mexican population; Imaging spectral-domain optical coherence tomography (EDI SD-OCT); Fundus autofluorescence classification system

Introduction

Age-related macular degeneration (AMD) is the principal cause of blindness in developed countries [1-6]. The global prevalence rate of AMD is 8.7% and increasing with the aging population, with 196 million people projected to have AMD by 2020, which will potentially increase to 288 million in 2040 without the development of an effective treatment [1,7]. At least 1 in 10 Hispanics have AMD, which is slightly higher than the global rate [1]. Moreover, given that these epidemiological estimates were derived from historical AMD cases identified using fundus photographs, the prevalence rates may be underestimated, as the newer diagnostic modality of optical coherence topography (OCT) is much more precise in detecting AMD [7].

OCT is a reproducible, noninvasive modality that produces a 3-dimensional, cross-sectional, high-resolution image of the retina *in vivo* [8]. OCT used with fundus autofluorescence (FAF) is the current standard diagnostic and monitoring modality to detect dry AMD and follow up on its progression [9]. Enhanced depth imaging (EDI) spectral-domain OCT (SD-OCT) examines the eye at a closer distance to produce an inverted image of the retina, which provides an even more detailed visualization of the choroid and the deeper layers of the retina [8-13].

Impaired choroidal circulation is thought to have a role in the development of AMD, by producing vascular endothelial growth factor that causes the retinal pigment epithelium to become hypoxic and ischemic, resulting in choroidal neovascularization [8,14-16]. Decreased blood volume and progressively impaired circulation have been observed in eyes with dry AMD, as the disease progresses, [8,14,17,18] and are thought to result from choroidal thinning, the narrowing of the choriocapillaries lumen, and cellularity loss [8,14].

Given the difficulty in measuring choroidal thickness and circulation, their relationship with the development of AMD has not been confirmed. However, the use of EDI SD-OCT allows for a more accurate evaluation of the effect of choroidal thickness on the development of dry AMD [10,19-21]. EDI SD-OCT has shown that the choroidal thickness decreases with aging [11,19,22]. Studies have observed increased choroidal thinning in eyes with early AMD [11,23] and late AMD [24-26]. Eyes with dry AMD with reticular pseudodrusen (RPD) have been reported to have significantly reduced choroidal thickness and vessel density [27]. Choroidal thickness has also been found to be inversely correlated with drusen load (r=-0.35, p=0.04) [10] and related to the severity and progression of dry AMD [28]. In both normal and unhealthy eyes, choroidal thickness has been found to be associated with better visual acuity [29]. Choroidal thickness also appears to be related to visual acuity in dry AMD [10,28].

To the best of our knowledge, the relationship between choroidal thickness and FAF alterations has not yet been examined. FAF maps the density of lipofuscin, the excessive accumulation of which is known to be a factor in the development of retina diseases [30-34]. Abnormal FAF changes have been evaluated in AMD [30,35,36]. Eight phenotypic patterns of FAF have been identified in early dry AMD: normal, minimal change, focal increased, patchy, linear, lacelike, reticular, and speckled [30].

The purpose of this study was to evaluate early and intermediate dry AMD in a Mexican population using EDI SD-OCT to determine FAF patterns, choroidal thickness, and their relationships with each other, age, and visual acuity levels.

Methods

Study design and patient recruitment

This descriptive, observational, cross-sectional study was carried out over a 19- month period at the Instituto Mexicano de Oftalmología, I.A.P. (IMO, Mexican Institute of Ophthalmology) among first-time patients aged 50 y or older attending the retina department, who received a diagnosis of early and intermediate dry AMD determined by 4 ophthalmologists training to be retinal specialists *via* a comprehensive ophthalmic examination (done by biomicroscopy with slit lamp and dilated fundus examination using slit lamp and indirect ophthalmoscope). An experienced vitreoretinal specialist confirmed the diagnosis.

Early dry AMD was defined as cases with less than 20 medium-sized drusen (63-124 µm) or with pigmentary anomalies. Intermediate dry AMD was defined as eyes presenting with geographic atrophy (GA) that did not extend under the macula or those with large drusen (at least 125 µm), or at least 20 medium-sized, irregular drusen, or at least 65 medium-sized, defined drusen. There was no defined sample size calculated for this study, given the intent to capture the most first-time patients possible during the study period. Patients were excluded from this study if they had:

- Eye surgery performed within 2 months prior
- A preexisting choroidal disease
- Glaucoma
- Media opacities
- Myopia greater than 6 diopters
- Wet AMD in both eyes
- Another macular disease different than dry AMD.

Patients, who met the above inclusion criteria, were willing to have FAF and EDI-OCT performed, and who provided their signed informed consent after explanation of the nature and possible consequences of the study were consecutively enrolled.

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the IMO Clinical Research Committee.

Study intervention

Participants had 1 study visit, during which the study ophthalmologists measured their visual acuity using a Snellen chart, which was later converted to logarithm of the minimal angle of resolution (Log MAR) for statistical analysis. Patient age and sex were also recorded. An OCT-certified technician examined each participant 3 times with the SD-OCT instrument (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) set to the EDI mode. A 488 nm excitation wavelength and 500 nm barrier filter were used. Three retina images per participant were also captured using the same instrument set to the scanning laser fundus imaging modality (BluePeak-Blue Laser).

Pattern	Definition
Normal	· Homogeneous background
	· Yellow macular pigment casts a masking effect that results in a gradual decrease in the inner macula toward the foveola
	· Soft or hard drusen may be present
	· Abnormal alterations may be absent
Minimal Change	· Minimally irregular decrease or increase of background FAF
	· No obvious topography
Focal Increased	· ≥ 1 area of <200 µm diameter present
	· Markedly increased and brighter FAF, which may be surrounded by a darker halo
	· Well-defined borders, with no gradual decrease between the areas with focal increased FAF and the background
	· Areas may correspond to drusen or focal hyperpigmentation
Patchy	· ≥ 1 spot of >200 µm diameter present of increased, brighter FAF
	· Less defined borders with a gradual increase between the FAF and the background
	· Areas may correspond to hyperpigmentation or large, soft drusen
Linear	· ≥ 1 area of increased FAF
	· Well-defined borders
	· No decrease between the background and linear structure of FAF
	· Linear structures usually correspond to hyperpigmentation
Lacelike	· Increased FAF forms multiple-branching linear structures
	· Less defined borders
	· Gradual decrease of FAF from the center of the linear areas toward the background can be observed
	· Areas may correspond to hyperpigmentation or no visible change
Reticular	· >1 areas of <200 µm diameter of decreased FAF present
	· Less defined borders with a decrease in FAF from the center of the areas toward the background.
	· Found in both macular and superotemporal areas

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	· Areas may correspond to small, soft, hard, drusen, reticular pseudodrosen, pigmentary alterations, or no visible changes
Speckled	· >1 small punctuate or linear areas of irregularly decreased and increased FAF present beyond the macular area and potentially covering the entire posterior fundus
	· Visible alterations correspond to hyper- and hypopigmentation and subconfluent and confluent drusen

Table 1: Fundus autofluorescence (FAF) patterns, based on descriptions defined by the International Fundus Autofluorescence Classification Group [30].

For each participant, the vitreoretinal specialist selected the FAF image with the best quality and examined it to determine the patterns based on those previously described by the International Fundus Autofluorescence Classification Group (Table 1) [30]. She also manually measured the subfoveal choroidal thickness using the guidelines of the International Nomenclature for Optical Coherence Tomography Panel, which describes the structure of the retinal pigment epithelium and choroidal-scleral interface [37].

Statistical analysis

The study ophthalmologists collected the study data and recorded them in an Excel database. The Statistics Department at the IMO analyzed the data using Stata 13 (StataCorp LLC, College Station, TX, USA. The qualitative variables are shown as absolute and relative frequencies, while the quantitative variables are shown as measures of central tendency and dispersion according to the distribution of the data, which was evaluated by the Shapiro-Wilk test. Descriptive statistics were used to analyze patient clinical and demographics data.

To determine the correlation between visual acuity and subfoveal choroidal thickness, the Spearman correlation coefficient was used, given the nonnormality of the variable visual acuity. The correlation between the variables age and subfoveal choroidal thickness was determined by the Pearson correlation coefficient, given the normality of both variables. In all cases a p-value less than 0.05 was considered statistically significant.

Results

This study took place from February 2016 through August 2017. The ophthalmologists screened 256 patients with AMD; 161 patients were excluded due to having wet AMD, 11 were excluded for having the advanced atrophic stage, and 26 with early and intermediate dry AMD were excluded due to also having cataracts (n=9), epiretinal membrane (n=3), pterygium (n=2), glaucoma (n=8), proliferative diabetic retinopathy (n=2), myopia greater than 6 diopters (n=1), and choroidal melanoma (n=1). Fifty-eight patients were enrolled, 26 (44.8%) of whom had dry AMD in both eyes; therefore, 84 eyes with early and intermediate dry AMD were evaluated in this study. The majority of participants were female (n=42; 72.4%). Among participants, the mean age was 75 y (SD: 8.4 y), and the mean visual acuity level was 0.4 Log MAR (SD: 0.24).

The most frequent FAF pattern found in study eyes was reticular (n=25, 29.8%), followed by minimal change (n=20, 23.8%), focal increased (n=16, 14.3%), normal (n=12, 14.3%), linear (n=5, 5.9%), patchy (n=3, 3.6%), speckled (n=2, 2.4%, and lacelike (n=1, 1.2%). Figures 1-3 show examples of the most frequent FAF patterns observed in this study: reticular (Figure 1), minimal change (Figure 2), and focal increased (Figure 3).

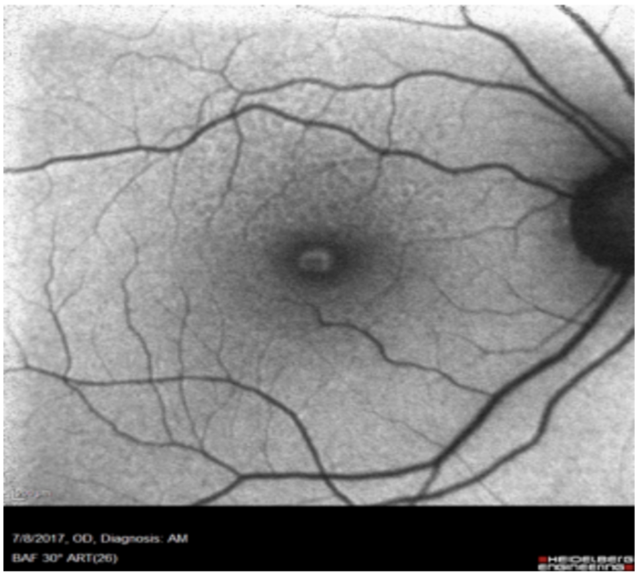

Figure 1: An example of the reticular pattern observed in an eye affected with dry age-related macular degeneration using autofluorescence.

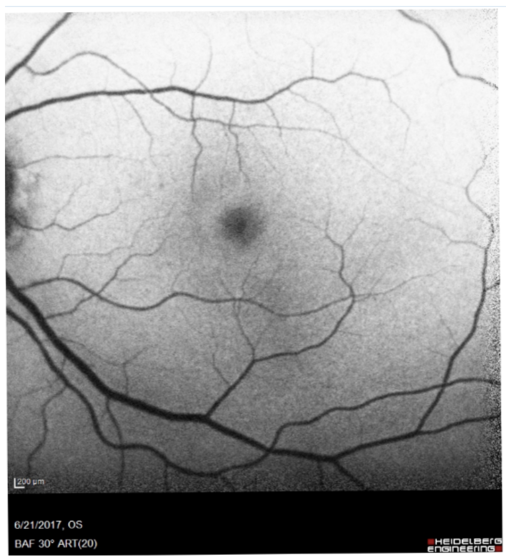

Figure 2: An example of the minimal change pattern observed in an eye affected with dry age-related macular degeneration using autofluorescence.

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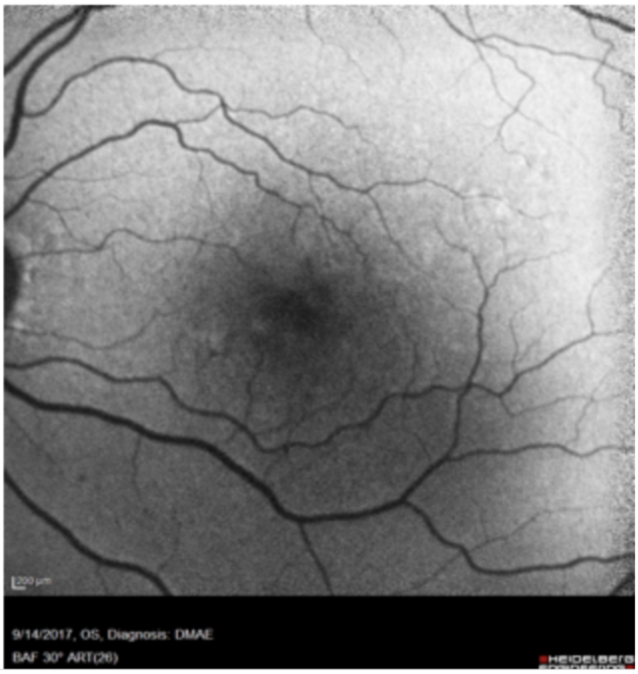

Figure 3: An example of the focal increased pattern observed in an eye affected with dry age-related macular degeneration using autofluorescence.

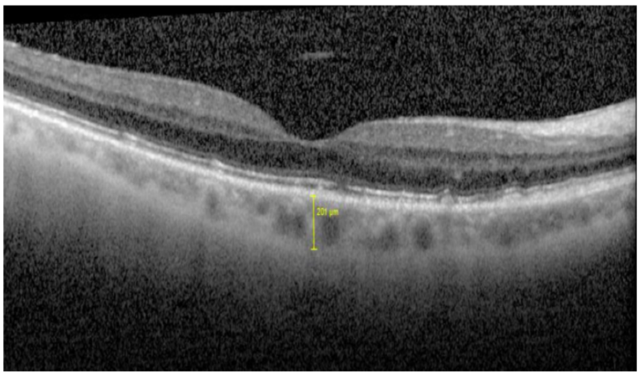

Figure 4: A manual take of choroidal thickness, measuring at 201 µm.

An example of the choroidal thickness of an eye measured manually at 201 µm is provided in Figure 4. The mean subfoveal choroidal thickness was 209.7 µm (SD: 69.8 µm). There was a weak, negative Pearson correlation between visual acuity and subfoveal choroidal thickness (r=-0.2457; Figure 5), which was statistically significant (p=0.0243).

There was a moderate, negative Spearman's rank correlation between age and subfoveal choroidal thickness (r=-0.3560, Figure 6), which was statistically significant (p<0.01).

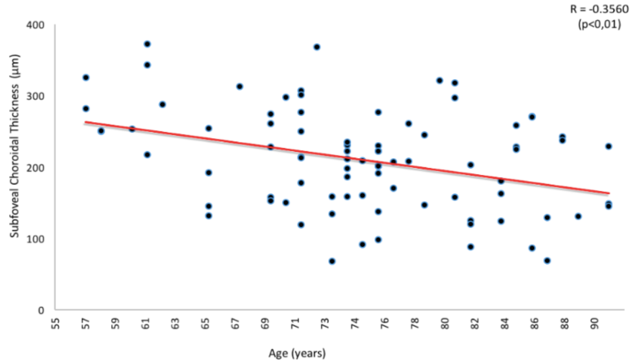

Figure 5: Pearson correlation of visual acuity with subfoveal choroidal thickness in eyes with early and intermediate dry age-related macular degeneration.

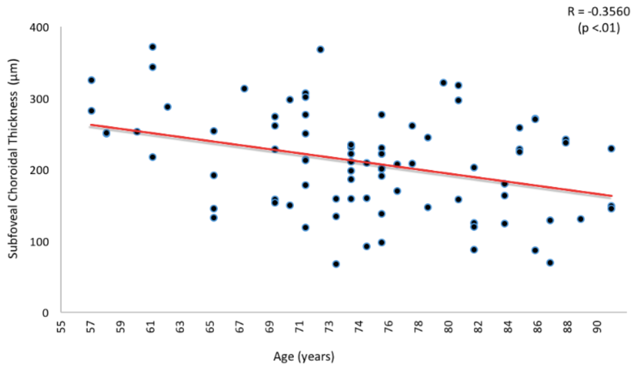

Figure 6: Spearman's rank correlation of age with subfoveal choroidal thickness in eyes with early and intermediate dry age-related macular degeneration.

FAF Pattern	Mean (µm)	Standard Error (µm)	Median (µm)	Minimum (µm)	Maximum (µm)
Normal	221.8	52.9	213.5	132	301
Minimal Change	219	78.5	229.5	68	372
Linear	213	40.9	225	158	261
Reticular	199.3	62.4	201	119	343
Focal Increased	208.6	90.2	220	69	368
Speckled	204.5	64.4	204.5	159	250
Lacelike	228	N/A	228	N/A	N/A
Patchy	184.3	104.6	163	92	298

Table 2: Summarizes the choroidal thickness findings for each FAF pattern.

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Table 2 summarizes the choroidal thickness findings for each FAF pattern. The distribution of choroidal thickness among FAF patterns is shown in Figure 7. Study eyes with the autofluorescent patchy patterns had the thinnest choroidal thickness (mean: 184.3 μm; SD: 104.6 μm), while the eye with the lacelike pattern had the greatest choroidal thickness at 228 μm.

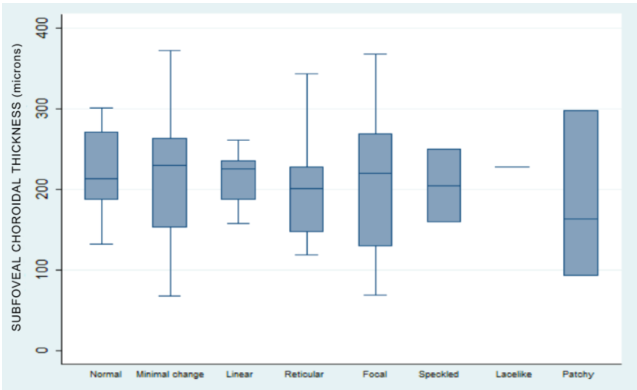

Figure 7: Distribution of choroidal thickness among fundus autofluorescence patterns in eyes with early and intermediate dry age-related macular degeneration.

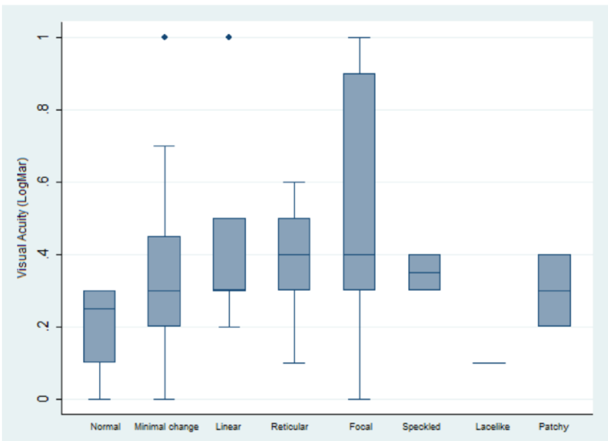

Figure 8: Distribution of visual acuity levels among fundus autofluorescence patterns in eyes with early and intermediate dry age-related macular degeneration.

Table 3 summarizes the visual acuity level findings among FAF patterns. Figure 8 shows the distribution of visual acuity levels among FAF patterns. Study eyes with the focal increased pattern had the worst visual acuity level, while the eye with the lacelike pattern had the best visual acuity level at 0.1.

FAF Pattern	Mean (µm)	Standard Error (µm)	Median (µm)	Minimum (µm)	Maximum (µm)
Normal	0.2	0.13	0.25	0	0.3
Minimal Change	0.35	0.23	0.3	0	1
Linear	0.46	0.32	0.3	0.2	1
Reticular	0.38	0.14	0.4	0.1	0.6
Focal Increased	0.53	0.36	0.4	0	1
Speckled	0.35	0.07	0.35	0.3	0.4
Lacelike	0.1	N/A	0.1	N/A	N/A
Patchy	0.39	0.1	0.3	0.2	0.4

Table 3: Summarizes the visual acuity level findings among FAF patterns.

Discussion

In this study of FAF patterns in a Hispanic population with early and intermediate dry AMD, the most frequent pattern observed was the reticular pattern (29.8%). The least frequent pattern was lacelike (1.2%). In a Turkish study of 178 eyes with dry AMD, the authors also found that the most frequent pattern among 26% of eyes was reticular [38]. The reticular pattern has a greater risk of developing neovascularization at 30 months in 20% of cases [38]. From among 100 FAF images of eyes with early AMD, Bindewald et al. [30] found that the speckled pattern was the most frequent (26%), which only appeared in 2.4% of eyes in our study. However, the lacelike pattern was also the least frequent in both studies, with Bindewald et al. observing this pattern in 2% of eyes.

Structural and functional changes to the choroids are known to occur during the aging process. SD-OCT has shown that the mean subfoveal choroidal thickness in normal, healthy eyes is 278 μm, which decreased 15.6 μm each decade in 30 patients with a mean age of 50.4 years [19]. Another study found that choroidal volume decreases by 0.54 mm^3 every decade of life [21]. Choroidal thickness (mean=209.7 μm) had a moderate, negative correlation with age in our study (r=-0.3560, p=0.009). Manjunath et al. found that the mean choroidal thickness in eyes with dry AMD measured with SD-OCT was similar to our study's at 213.4 μm, but there was a stronger, statistically significant correlation with age (r=-0.703; P=0.002) [8]. Ko et al. did not find that the relationship between choroidal thickness and age was statistically significant [10]. It is not understood why choroidal thickness is variable in eyes with AMD [8]. To the best of our knowledge, our study was the first to examine the relationship between choroidal thickness and FAF patterns. The patchy pattern showed the most reduced choroidal thickness at 184.3 μm.

The mean visual acuity in this study was 0.4 LogMAR, which tended to be better with greater choroidal thickness. This relationship was statistically significant (r=-0.2457, p=0.0243), similar to findings previously reported [8]. Previous studies did not look at the relationship between visual acuity and FAF patterns. We found that the focal increased pattern had the worst visual acuity at 0.53 Log MAR.

Limitations

This study was limited by its single-center, cross-sectional design with a small sample size. As also observed by Ko et al. [10] the small sample size in this study resulted in greater bias with increased standard error when analyzing the different variables. However, obtaining a larger sample size was a challenge in this study, given the low prevalence rate of the disease. A recent Mexican analysis of 39,280 fundus images taken with a nonmydriatic camera of 16,939 eyes from 9,280 patients from 17 states in Mexico, including Queretaro, found that 7% of eyes (n=1,189) had AMD [43]. It is not known how many eyes had dry AMD, but we can assume that there were some cases. Furthermore, the retina department of the IMO saw 9,523 patients of the retina department at IMO in 2017, which includes both first-time and repeat patients for all retina diseases, which is why we chose not to work with a predefined sample size, with the hopes of recruiting the greatest number of patients with dry AMD possible for this study.

The cross-sectional design and the fact that the duration of dry AMD was unknown among the study participants, who were first-time patients at the IMO, also weakens our conclusions, as we do not know if there were changes in choroidal thickness over time [8]. In our study, only 1 assessor interpreted the FAF images, which also increases the bias of our results. A final limitation of this study was that Snellen charts were used to collect visual acuity data [39-42], whereas Early Treatment Diabetic Retinopathy Study charts are the preferred tool to measure visual acuity in AMD trials, with better visual acuity consistently reported [40,43].

Conclusion

The most frequently observed AF pattern in this study of early and intermediate dry AMD in a Hispanic population was the reticular pattern, while the lacelike pattern was only observed in 1 eye. Choroidal thickness was weakly correlated with age and moderately correlated with visual acuity. The patchy pattern had the most reduced choroidal thickness, while the focal increased pattern had the worst visual acuity level.

Funding

The Instituto Mexicano de Oftalmología, I.A.P. funded this study.

Acknowledgements

The authors would like to thank Kristen Eckert, independent consultant, (San Antonio Tlayacapan, Jalisco, Mexico) for her assistance in writing, translating, and editing this manuscript.

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