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ARAŞTIRMA / RESEARCH

The evaluation of the early and intermediate age-related macular degeneration with optical coherence tomography angiography

Erken ve orta evre yaşa bağlı makula dejenerasyonunun optik koherens tomografi anjografi ile değerlendirilmesi

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Abstract

Purpose: To investigate superficial and deep retinal vessels, foveal avascular zone in patients affected by age-related macular degeneration (AMD) to find whether any association between features on retinal vessel density and stage of AMD.

Materials and Methods: Ninety-four patients enrolled in the study. Patients were divided according to AMD stages. Grade 1, no AMD; grade 2, early AMD; grade 3, intermediate AMD; grade 4 geographic atrophy (GA); and Grade 5, choroidal neovascularization (CNVM). All patients underwent an ophthalmologic evaluation, including optical coherence tomography angiography (OCTA). The main outcome measures were superficial vessel density, deep vessel density, foveal avascular zone (FAZ).

Results: In grade 3 AMD eyes; the deep vessel density values were lower than grade 1 and grade 2 eyes. The fellow eyes of the patients with CNVM, the deep vessel density values were lower in grade 3 eyes than grade 1 and 2 eyes, the other parameters were not statistically different. The fellow eyes of the patients with grade 3, the vessel density, FAZ, AI did not show significant difference.

Conclusion: Changes in retinal capillary vessel density, which can be detected with OCTA, begin at the intermediate stage AMD.

Keywords:. Age related macular degeneration, superficial vessel density, deep vessel density, foveal avascular zone

Öz

Amaç: Yaşa bağlı makula dejenerasyonu (YBMD) olan hastalarda yüzeyel ve derin kapiller pleksus ve foveal avasküler zonu değerlendirmek, YBMD evresi ile kapiller damar yoğunluğu arasında ilişki olup olmadığını araştırmak.

Gereç ve Yöntem: Çalışmaya 94 hasta dahil edildi. Hastalar YBMD evresine göre sınıflandırıldı. Evre 1: YBMD yok, Evre 2: erken YBMD, Evre 3: orta evre YBMD, Evre 4: jeografik atrofi, Evre 5: koroidal neovaskülarizasyon (KNVM) evresi. Tüm hastalar optik koherens tomografi anjiografiyi de içeren tam oftalmolojik muayeneden geçirildi. Yüzeyel ve derin pleksuslarda vasküler yoğunluk, foveal avasküler zon ana ölçüm değerleri olarak belirlendi.

Bulgular: Evre 3 YBMD hastalarında derin pleksusta vasküler yoğunluk evre 1 ve 2 ye göre azalmış olarak tespit edildi. KNVM hastalarının diğer gözlerinde evre 3 YBMD tespit edilenlerde derin pleksusta kapiller yoğunluk evre 1 ve 2 ye göre daha düşük düzeylerde idi. Diğer parametrelerde farklılık yoktu. Evre 3 YBMD olan hastaların diğer gözlerinde kapiller yoğunluk ve foveal avasküler zon değerleri arasında farklılık saptanmadı.

Sonuç: OKTA ile tespit edilen retinal kapiller damarlarda değişiklikler intermediate YBMD aşamasında başlamaktadır.

Anahtar kelimeler: Yaşa bağlı makula dejenerasyonu, yüzeyel kapiller yoğunluk, derin kapiller yoğunluk, foveal avasküler zon

INTRODUCTION

Age related macular degeneration (AMD) is the leading cause of blindness in people older than 60 years in developed countries. Drusen are a hallmark in eyes with AMD and are considered to be risk factors for late AMD including neovascular AMD and geographic atrophy (GA)[1,2].

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According to the Age-Related Eye Disease Study Group, AMD has been classified into two major categories as dry or neovascular AMD, based on the presence of choroidal neovascularization (CNVM). Dry AMD, especially at early and intermediate stages, has been characterized by the presence of retinal pigment epithelium changes, Bruch membrane alterations, drusen[3]. Increasing severity of baseline drusen characteristics and pigmentary changes have been shown to be important predictors for progression of AMD in white populations[4].

OCT-Angiography (OCTA) has become commercially available and is used for the noninvasive analysis of retinal and choroid vessel morphology and alterations. OCTA allows imaging from internal limiting membrane to the choroid, providing segmentation of the retina into different layers, as well as imaging of the choriocapillaris and of the choroid [5]. Vessel density (VD) and the foveal avascular zone (FAZ) have commonly been used to quantify vessel-specific characteristics on OCTA en face images.

In this study we want to investigate superficial and deep retinal vessels, FAZ, by means of OCTA, in patients affected by AMD to find an association between features on retinal vessel density and stage of AMD.

MATERIALS AND METHODS

We retrospectively evaluated the medical records of consecutive patients who were diagnosed with AMD in at least one eye and had not received any treatment, including laser photocoagulation, photodynamic theraphy or intravitreal injection at the Adana City Training and Research Hospital between September 2018 and November 2019. All study protocols adhered to the tenets of the Declaration of Helsinki and it was approved by the Ethics Committee of the Adana City Training and Research Hospital (626-2019).

The inclusion criteria were; age>50 years, diagnosis of AMD in at least one eye; stable fixation required to allow OCTA examination. The exclusion criteria for the study were as follows; CNVM secondary to other macular disorders such as angioid streaks; a refractive error of> 6 diopters; amblyopia; media opacities; presence of other retinal diseases, ocular trauma, previous vitreoretinal surgery, presence of diabetes mellitus, uncontrolled hypertension.

All included patients had undergone comprehensive ophthalmological examinations, including measurement of best corrected visual acuity (BCVA), slit lamp biomicroscopy, OCT, OCTA. FFA was performed as needed. AMD stage was classified by clinical history, ocular examination, and all available imaging modalities, including color fundus photography, fluorescein angiography and OCTA. Grades were defined using the Clinical Age-Related Maculopathy Staging system; grade 1, no AMD (no drusen or a few small drusen <63 μm) ; grade 2, early AMD (intermediate size drusen 63-124 μm); grade 3, intermediate AMD (large drusen >125 μm); grade 4 GA; and Grade 5, CNVM. The both eyes of the patients were evaluated and graded.

SD-OCT (Retina Scan RS 3000 Advance, Nidek Inc, Gamagori, Japan) was used to measure the central retinal thickness (CRT). We captured the OCT scans using the macula line 12-mm horizontal scan. The scans consisted of 1,024 A-scans with high definition. Each image consisted of 120 averaged B-scans, with a 4-μm resolution. Before imaging, each subject's pupils were dilated with tropicamide and phenylephrine.

After pupil dilatation, macular retinal vascularization assessments were performed using OCTA (Optovue RTVue XR Avanti; Optovue Inc., Fremont, California). For the detection of erythrocyte movement, AngioVue uses the split-spectrum amplitude-decorrelation angiography (SS-ADA) algorithm. The 3x3 mm OCT angiograms were used to evaluate size of FAZ (mm2), acircularity index (AI), foveal density (%) (FD), and foveal and parafoveal vessel densities (%) in SCP and DCP. The AngioVue software provides automated FAZ boundary detection, applied on Retina slab (ILM to OPL +11μm). FD is defined as vascular density (%) in the circular area 300 microns distant from the FAZ. The AI of the phase is defined as the ratio of the FAZ circumference to the circumference of an equal area circle.

Using the integral software segmentation algorithm, the 'en face' image was automatically segmented to demarcate the SCP and DCP. In the segmentation of the SCP en face images, the inner boundary was the inner limiting membrane (ILM) and the outer boundary was 11 μm beneath the inner plexiform layer (IPL). In the segmentation of the DCP en face images, the inner boundary was 11 μm beneath the IPL and the outer boundary was 11 μm beneath the outer plexiform layer (OPL).

In the VD calculation, a binary image of the blood vessels was extracted from the grey-scale OCTA image using the AngioVue Analytics software and then a calculation was made of the percentage of pixels with a flow signal greater than the threshold in the defined region.To prevent diurnal fluctuations, all OCTA scans were administered in the mornings, and all scans were obtained by the same technician.

The OCTA scans were assessed for image quality. Any scans with quality index <6 or with residual motion artefacts, or segmentation errors were defined as poor quality and were excluded from the analysis. In cases of multiple OCTA scans, the highest quality image was used in the analysis.Segmentation errors, if present, were corrected manually in each patient.

Statistical analysis

Power analysis was performed by GPower version 3.1.9.2 (Universitaet Kiel, Germany). Different effect sizes were calculated for visual acuity, FAZ and superficial parafoveal density measurements obtained in a preliminary study. The minimum effect size was 0.492, the theoretical power and the type-1 error were considered as 0.85 and 5% respectively. Then the maximum sample size was calculated as 48 for three groups.

All statistical anaylses were performed by SSPS 20.0 (IBM Inc, Chicago, IL, USA). Descriptive statistics were presented as mean±SD for continuous variables since the variables except for visual acuity were distributed normally by Kolmogorov-Smirnov test. The median values were given additionally for BCVA only. The group comparisons were performed by Student t-test an done-way ANOVA for two independent and multiple groups. P<0.05 was considered a statistically significant result.

RESULTS

The records of 142 AMD patients were evaluated, 24 of these patients had history of at least one intravitreal injection, the OCTA image quality of 16 patients were not eligible for assessment, 6 patients had concomitant diabetic retinopathy findings, 2 patients had high myopia. There were totally 94 patients enrolled in this study. The mean age was 65.4± 8.12 years (range: 53-77). The rate of genders was approximately equal, but the rate of male patients was a little bit higher (52%; n=48).

Thirty-six patients had grade 3 AMD, thirty patients had grade 2 AMD and 28 patients had grade 1 AMD. The visual acuity of the patients with Grade 1 was statistically higher than grade 3 (p=0.001). In grade 3 AMD patients; the DFD and DPD values were lower than grade 1 and grade 2 patients. No significant difference was found between the grade 1 and grade 2 groups for AI, FAZ, SFD, SPD, DFD, DPD, and CMT measurements. (p>0.05) (Table 1)

Table 1. Comparison of the measurements between early and intermediate AMD stages

	Grade 1 AMD (n=28)	Grade 2 AMD (n=30)	Grade 3 AMD (n=36)	p
BCVA	0.80±0.15	0.64±0.15	0.47±0.23	0.001*
AI	1.15±0.03	1.16±0.03	1.15±0.05	0.707
FAZ	0.31±0.10	0.35±0.09	0.34±0.10	0.906
SFD	15.32±9.05	14.26±5.37	12.58±4.41	0.615
SPD	43.44±5.06	44.14±7.03	42.18±6.01	0.583
DFD	31.87±6.45	28.65±6.77	22.96±6.57	0.045*
DPD	53.28±4.56	52.30±3.75	45.99±5.48	0.047*
CMT	209.23±19.32	214.07±17.84	206.75±27.01	0.627

*:significant at p<0.05 level, independent sample Student t-test
BCVA: Best corrected visual acuity, AI:Acircularity index, FAZ: Foveal avascular zone, SFD: Superficial foveal density, SPD: Superficial parafoveal density, DFD: Deep foveal density, DPD: Deep parafoveal density, CMT: Central macular thickness.

Fourteen patients had CNVM in one eye, grade 1 AMD in the fellow eye. Sixteen patients had CNVM in one eye, grade 2 AMD in the fellow eye. Nineteen patients had CNVM in one eye, grade 3 in the fellow eye. When we compared the fellow eyes of the patients with CNVM, the DFD and DPD values were

lower in grade 3 patients, the other parameters were not statistically different. (Table 2) The visual acuity of the patients with grade 1 was significantly higher than grade 3 patients (p=0.021) and higher than grade 2 patients with insignificant result (p=0.371).

Ten patients had bilateral grade 3 AMD. Nine patients had grade 3 in one eye, grade 1 in the fellow eye. When we compared the fellow eyes of the patients with grade 3, the vessel density, FAZ, AI and CMT did not show significant difference. (Table 3)

Table 2. Comprasion of the fellow eye measurements in patients with Grade 5 AMD

	Grade 1 AMD (n=14)	Grade 2 AMD (n=16)	Grade 3 AMD (n=17)	p
BCVA	0.78±0.11[a]	0.67±0.10	0.53±0.23[a]	0.021*
AI	1.14±0.04	1.17±0.03	1.13±0.05	0.243
FAZ	0.24±0.11	0.35±0.09	0.30±0.10	0.115
SFD	18.20±8.37	15.56±5.57	13.20±3.93	0.297
SPD	43.95±5.59	40.11±6.94	39.61±5.97	0.329
DFD	32.90±8.95	30.14±7.61	24.88±6.23	0.035*
DPD	50.36±5.15	51.46±3.22	41.70±4.96	0.033*
CMT	228.62±22.83	211.50±17.80	219.37±36.68	0.459

*:significant at p<0.05 level, One way analysis of variance, * denotes the significant pairwise groups.
BCVA: Best corrected visual acuity, AI:Acircularity index, FAZ: Foveal avascular zone, SFD: Superficial foveal density, SPD: Superficial parafoveal density, DFD: Deep foveal density, DPD: Deep parafoveal density, CMT: Central macular thickness.

Table 3. Comprasion of the fellow eye measurements in patients with Grade 3 AMD

	Grade 1 AMD (n=9)	Grade 3 AMD (n=10)	p
BCVA	0.48±0.19	0.42±0.22[a]	0.421
AI	1.13±0.02	1.16±0.04	0.652
FAZ	0.37±0.11	0.35±0.11	0.600
SFD	12.48±5.13	11.80±4.54	0.787
SPD	47.25±6.38	28.97±7.61	0.576
DFD	25.98±8.95	30.14±7.61	0.784
DPD	51.52±3.72	48.99±4.99	0.301
CMT	206.5±24.1	202.6±18.5	0.241

*:significant at p<0.05 level, One way analysis of variance, * denotes the significant pairwise groups.
BCVA: Best corrected visual acuity, AI:Acircularity index, FAZ: Foveal avascular zone, SFD: Superficial foveal density, SPD: Superficial parafoveal density, DFD: Deep foveal density, DPD: Deep parafoveal density, CMT: Central macular thickness.

DISCUSSION

AMD is a progresive disease leading to severe late-stage retinal and choroidal damage. Many factors have been implicated in AMD pathogenesis and progression, such as inflammation, oxidative damage, ageing, genetic predisposition and environmental elements. The time of progression from early to late AMD differs from patient to patient. An analysis based on the Beaver Dam Eye Study demonstrated that, in subjects aged 43–86 years with signs of early AMD in both eyes, the cumulative 15-year incidence is 13.5% for GA and 14.8% for CNV [6]. We analyzed the foveal microvasculature in AMD patients in this study. Late AMD may exhibit low repeatability of

OCT measurements because of GA or choroidal neovascularization and segmentation errors. Thus, we studied only patients with early and intermediate AMD.

The widespread nature of dry AMD and the unpredictability of its progression to choroidal neovascularization, geographic atrophy, or both with sight threatining implications, continues to draw the interest of many investigators to better understand its pathogenesis. The association of dry AMD with CNVM and GA, which are the late AMD stages, has been the subject of various studies and it is predicted that there are possible 'associated' vascular abnormalities in the pathogenesis[7-10]. Advances in imaging techniques have facilitated the high quality of in vivo imaging, enabling us to further assess dry type AMD, identifying the high risk properties that may be present in the progression to GA and CNVM.

Several recent studies on OCTA have reported retinal vascular changes in eyes with early AMD and subretinal drusenoid deposits are risk factors for CNVM and GA[11,12]. Recently, several studies have reported vascular factors play an important role in the pathogenesis of AMD. Indeed, there is increasing evidence that choroidal and retinal blood flows are reduced in AMD[13-15]. Grunwald et al found a significant reduction of blood volume by 33% and of blood flow by 37% as well as a higher, but not statistically significant different blood flow pulsatility by 6% in subjects with nonexudative ARM when compared with age-matched controls[16].
In that study, the decrease in the capillary blood flow at an early stage of AMD was also indicated but the results were not statistically significant. Remsch et al reported raised macular retinal capillary blood flow in patients with the exudative form of late AMD, which may be caused by an autoregulative vascular response due to a compromised metabolism [13]. Patients with disciform late AMD showed a significant reduction of macular retinal capillary blood flow, which is supposed to be an autoregulative response to the breakdown of central retinal metabolism and substitution of photoreceptor cells by scar tissue.

Several study showed that both inner and the outer retina were thinner in patients with AMD[17,18]. In our study there was statistically difference between the groups in patients with early, intermediate AMD in according to the deep capillary plexus. But we did not find difference in the superficial vascular plexus between the groups.

It has been shown that retinal vasculature and choroidal vasculature are detrimented in AMD eyes and that this destruction may contribute to AMD progression[13]. Recent studies with OCTA has also attempted to describe abnormal retinal structures in AMD but definitive findings have been conflicting. Patients with non-exudative AMD disclosed relative retinal thinning, particularly at the GCL level, associated with significant retinal vascular loss (more pronounced in those featuring reticular pseudo-drusen and outer retinal atrophy).

Toto et al demonstrated that both superficial and deep retinal plexus are altered among patients affected by early-intermediate stage AMD. Superficial vessel density was significantly decreased only in intermediate AMD eyes. They reported that vascular damage starts immediately at the intermediate stage[15]. Trinh et al showed that vascular density of the SCP significantly decreased in eyes with intermediate AMD compared with healthy subjects[19]. Cicinelli et al on the other hand reported a significant reduction in vascular density in the deep plexus only[20].

Lee et al found that significant change in both vascular layers in early AMD eyes where the fellow eye had progressed to neovascular AMD [21]. In our study it was found that vascular density was significantly decreased in the DCP but not in the SCP.

Trinh et al showed that no difference in FAZ parameters in AMD eyes compared with normal eyes. Shin et al reported that in dry AMD patients FAZ was larger, FAZ circularity index was smaller and VD was signicantly lower than normal controls [22]. In our study there was no statistically significant difference between the groups in terms of FAZ, acircularity index.

Our study has several limitations; retrospective design, small number of included eyes, small number of eyes of subgrup's, no comparison on follow-up, no comparison with eyes with geographic atrophy and CNVM.

Our study evaluated OCTA features in early and intermediate AMD eyes in order to identify associated findings with a higher risk of progression to advanced disease. Results indicate that vascular injury starts at the intermediate stage AMD, and the DCP is more susceptible to vascular injury than superficial capillary plexus.

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