Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia

Mehmet Bulut,[1] Fatma Kurtuluş,[2] Onursal Gözkaya,[3] Muhammet Kazım Erol,[1] Ayşe Cengiz,[1] Melih Akıdan,[1] Aylin Yaman[2]

[1]Department of Ophthalmology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Neurology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[3]Department of Ophthalmology, Antalya Private Life Hospital, Antalya, Turkey

Correspondence to
Dr Mehmet Bulut, Department of Ophthalmology, University of Health Sciences, Antalya Training and Research Hospital, Kazim Karabekir Caddesi 07 100, Antalya, Turkey; bulutme73@yahoo.com

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ABSTRACT

Background/Aims To identify the retinal vascular pathologies in patients with Alzheimer's type dementia (ATD) through optical coherence tomography angiography (OCTA) imaging.

Methods Our study included 26 patients in the patient group, and age-matched and sex-matched 26 subjects in the control group. A detailed ophthalmological and neurological examination was performed for all subjects included in the study. The retinal, choroidal vascular structures and choroidal thickness (CT) of all subjects were analysed in a detailed way with a commercial spectral domain OCTA. Moreover, all participants underwent detailed neurological examination including Mini Mental State Examination (MMSE) test to evaluate cognitive function.

Results In the group of patients with ATD, the MMSE score was significantly lower than that of the control group ($p<0.001$). The retinal vascular density was significantly lower than that of the control group in all zones ($p<0.05$). Foveal avascular zone (FAZ) was significantly enlarged compared with the control group ($p=0.001$). CT was significantly lower in the group of patients with ATD ($p<0.001$). Outer retinal and choroidal flow rates were lower in the group of patients with ATD, while the difference was not significant ($p>0.05$). Furthermore, significant correlation was found between the MMSE and all vascular density parameters, CT parameter and FAZ tested with OCTA imaging ($p<0.05$).

Conclusions In patients with ATD, retinal and choroidal vascular pathologies detected through OCTA imaging can be used as a new biomarker in the early diagnosis of the disease, follow-up of its progression and in investigating the efficacy of the drugs.

INTRODUCTION

Alzheimer's type dementia (ATD) is a chronic, progressive neurodegenerative disease and results in cognitive impairment. It is the most common cause of dementia (60%–70%). It affects memory, thinking, orientation, comprehension, calculation, learning capacity and language. In a cohort study, it was reported that the disease increased with age, and its prevalence was 1 in every 5 patients at age 85 (WHO 2012 Dementia Report).

ATD is characterised by deep brain atrophy due to the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFTs). Increased age is the most important factor while genetic predisposition is also an important risk factor for this disease. Moreover, diabetes, hypertension, smoking, depression, cognitive or physical inactivity and obesity increase the risk of ATD.[1]

ATD is a serious health problem that occurs at advanced age. The most important problem with this disease is related to diagnosis. Today, it can be diagnosed at the early stages of cognitive impairment. The diagnosis can be established after the other possible causes are ruled out by testing the mental and cognitive state of the patient.[2] Once it is diagnosed, the irreversible process that will lead to dementia starts. Therefore, early diagnosis of ATD is important before the irreversible process starts. The mean time from diagnosis to death is 4.6 years. The definitive diagnosis can only be established by postmortem brain biopsy.[3]

Studies on new diagnostic tools and biomarkers are ongoing in order to diagnose the disease earlier. Thanks to these studies, the disease will both be diagnosed early, and the efficacy of drugs in medical treatment and success of treatment will be determined.

In ATD, problems associated with the visual system have been known since 1970s while it was considered to have cortical origin. The studies conducted in the last two decades, however, demonstrated that ATD was also associated with visual problems such as colour vision, sense of depth, field of vision and contrast sensitivity due to its effects on the optical nerve and retina in addition to the brain.[4]

The most common vascular problems in ATD include impaired Aβ cleansing, impairment of blood–brain barrier, decreased vascular density, decreased vascular diameter and decreased blood flow.[5] Due to the similarity between the cerebral and retinal vasculature, the researchers focused on the use of investigating the intraocular vascular structures as a biomarker in ATD.[6]

In ATD and other neurodegenerative diseases, retinal imaging with optical coherence tomography angiography (OCTA) may give us additional input to understand the vascular deficits in the pathophysiology of these diseases. Therefore, in our study, we aimed at evaluating the retinal and choroidal vascular structures with OCTA imaging and identify an ocular biomarker that would help the early detection of ATD.

MATERIALS AND METHODS

Approval was obtained from the local ethics committee of University of Health Sciences, Antalya Training and Research Hospital, where the study was conducted and performed in compliance

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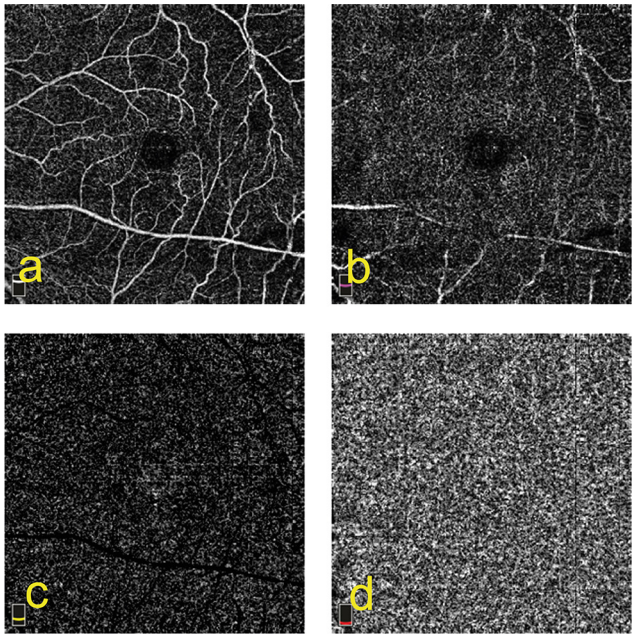

Figure 1 Optical coherence tomography angiography images of a 75-year-old patient with Alzheimer's type dementia: (A) superficial retinal vascular plexus, (B) deep inner retinal vascular plexus, (C) outer retina and (D) choriocapillaris.

with the ethical standards set out in the Declaration of Helsinki. Before the participants were included in the study, their written informed consent was obtained. Twenty-six consecutive subjects (11 male and 15 female), aged 55–85 years with ATD, and 26 cognitively healthy, age-matched and sex-matched volunteers (13 male and 13 female), were included in this study.

The participants with ATD were concordant with the criteria for dementia set out in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, and also the criteria for probable ATD proposed by the National Institute on Aging-Alzheimer's Association workgroups.[7 8] All patients were subjected to a detailed examination including neurological, Mini Mental State Examination (MMSE) and dementia screening tests; moreover, thyroid function tests as well as the routine biochemical tests for serum vitamin B_{12} and folate levels were performed, brain MRI was performed, after which ATD was diagnosed clinically. Dementia screening and neurological examination of all subjects without memory complaints in the control group were performed by the same neurologist.

A full ophthalmic examination that also included Goldmann applanation tonometry, central corneal thickness (CCT) measurements with optic pachymeter (Lenstar LS 900, Haag-Streit AG, Köniz, Switzerland), assessment of best-corrected visual acuity (BCVA), slit lamp examination of the anterior segment, gonioscopy examination, dilated fundus examination, axial length measurement with optical biometry (Lenstar LS 900) and OCTA measurements (RTVue XR100-2, Optovue, Fremont, California, USA) were performed for all participants.

The exclusion criteria for all groups were as follows: BCVA <20/40; refractive error >±4 spherical equivalent; axial length <22 mm and >26 mm; poor image quality <60 due to severe cataracts or unstable fixation; intraocular pressure (IOP) >21 mm Hg; closed angle on gonioscopy; pre-existing macular pathologies such as age-related macular degeneration, epiretinal membrane or macular hole; other retinopathies such as retinal vascular occlusion or retinal dystrophy; pre-existing ocular diseases such as glaucoma, optic neuropathy or uveitis; previous intraocular surgery or laser treatment except for cataract surgery performed at least 12 months before enrolment; ocular trauma; currently being a smoker; and history or showing evidence of other neurological or psychiatric disorders, other types of dementia except ATD, diabetes mellitus, systemic arterial hypertension, cardiovascular diseases and cancer.

OCTA measurements

The imaging of all subjects was performed with a commercial spectral domain OCTA that had a scan rate of 70 000 A-scans/s, scan beam wavelength of 840±10 nm and bandwidth of 45 nm. This device can do the volumetric scans of 304×304 A-scans at 70 000 A-scans/s in around 3.0 s.[9] All measurements were performed between 09:00 and 11:00 on the same day. The participants were told not to take caffeine for a minimum of 12 hours before the examination. At each site, two consecutive measurements of OCT were performed for 2 days, after which the average values were calculated. For the scans to be included in data analysis, the requirement was to to have a signal strength of a minimum of 60.

To evaluate the vascular structures, 6×6 mm OCT angiogram software was used. Two B-scans were captured at each fixed position before proceeding to the next sampling location, and two orthogonal OCTA volume scans were used to minimise motion artefacts and fixation changes. The software automatically segmented these full-thickness retinal scans into the superficial and deep inner retinal vascular plexuses, outer retina and choriocapillaris (figure 1A–D). The projection of the vasculature in the superficial and deep inner retina is demonstrated by the OCTA segmentation. The vascular density in superficial retinal vascular zone was calculated automatically by this software and the foveal avascular zone (FAZ) was also automatically identified

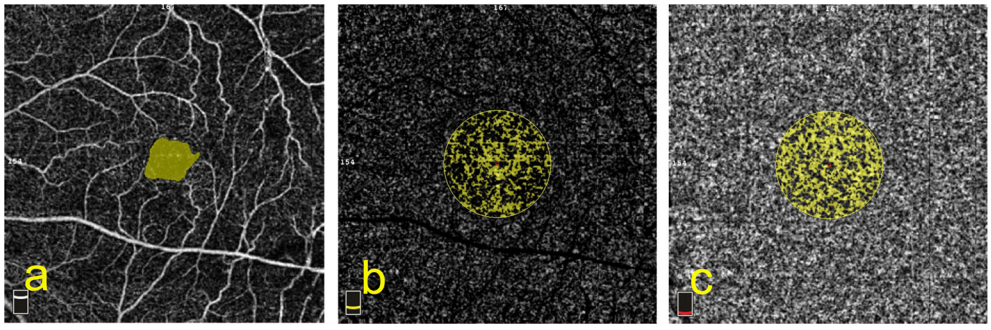

Figure 2 Optical coherence tomography angiography images of a 75-year-old patient with Alzheimer's type dementia: (A) foveal avascular zone, (B) outer retinal flow and (C) choroidal flow.

Table 1 Demographic and clinical characteristics of the study subjects

	Patients with ATD (n=26 eyes of 26 subjects)	Control subjects (n=26 eyes of 26 subjects)	p Value
Age	74.23±7.55	72.58±6.28	0.156
Sex (M/F)	11/15	13/13	0.578
IOP (mm Hg)	15.16±3.25	15.32±1.84	0.993
CCT (µm)	557.81±27.77	548.69±33.61	0.292
AXL (mm)	23.27±0.73	23.23±0.71	0.826
MMSE score	16.92±7.39	26.81±2.20	<0.001*

Data reported as mean and SD with p values from Mann-Withney U tests (age, IOP and MMSE score), χ^2 test (sex) and independent t-tests (CCT and AXL).
*Significant at p<0.05.
ATD, Alzheimer's type dementia; AXL, axial length; CCT, central corneal thickness; IOP, intraocular pressure; M/F, male/female; MMSE, Mini Mental State Examination.

(figure 2A). The same software also calculated the flow index rates in a central circular zone of 3.144 mm² in the outer retina and choriocapillaris segments (figure 2B,C).

Furthermore, OCT was also applied for the measurement of the choroidal thickness (CT) with high definition (HD) protocol. CT was imaged by the same independent technician with enhanced deep imaging OCT based on a technique developed previously.[10]

Statistics

The statistical analysis was performed using SPSS V.20 package software. One eye from each subject was randomly selected for the analyses. To compare the groups, independent t-test and Mann-Whitney U test were applied. The normality assumption for the independent variables was checked with Shapiro-Wilk test. The variables that were compliant with the normality assumption were subjected to independent t-test, while those that do not meet the normality assumption were subjected to Mann-Whitney U test. For the analysis of correlation, Pearson correlation coefficient and Spearman correlation coefficient were used. The independence between the variables was analysed with χ^2 test.

Table 2 Relationship of vascular density, foveal avascular zone, outer and choroidal flow rate and choroidal thickness with ATD and control subjects

	Patients with ATD (n=26 eyes of 26 subjects)	Control subjects (n=26 eyes of 26 subjects)	p Value
Vascular density (%)			
Whole	45.50±3.85	48.67±3.29	0.002*
Fovea	29.04±7.17	34.80±6.76	0.004*
Parafovea	47.96±4.86	51.12±4.10	0.015*
Foveal avascular zone (mm²)	0.47±0.18	0.33±0.08	0.001*
Outer retina flow rate	0.38±0.03	0.39±0.03	0.302
Choroidal flow rate	0.59±0.22	0.60±0.02	0.084
Choroidal thickness (µm)	198.27±49.09	251.88±29.93	<0.001*

Data reported as mean and SD with p values from Mann-Whitney U tests (foveal avascular zone and choroidal thickness) and independent t-tests (vascular density and flow rate).
*Significant at p<0.05.
ATD, Alzheimer's type dementia.

RESULTS

As table 1 presents, both groups were similar in age, sex, IOP, CCT and axial length values (p>0.05). MMSE scores were found to be significantly lower in the group of patients with ATD than in the control group (p<0.001).

The comparison of the vascular density between the groups revealed that the group of patients with ATD had a significantly lower density in whole macular zone (p=0.002), foveal (p=0.004) and parafoveal (p=0.015) zone separately compared with the control group. Outer retinal flow rate (p=0.302) and choroidal flow rate (p=0.084) were found to be slightly lower in the group of patients with ATD while the difference was not significant. However, the FAZ area was found to be significantly enlarged in the patient group compared with the control group (p=0.001). Moreover, the CCT was lower in the group of patients with ATD than in the control group (p<0.001) (table 2).

The correlation between the MMSE score and age, retinal and choroidal parameters was evaluated. The correlations between the MMSE score and all these parameters are shown in table 3. Figure 3 also shows the correlation between MMSE score and whole vascular density and FAZ area.

DISCUSSION

The optical nerve and retina develop as a direct extension of diencephalon during the embryonic development stage. The inability of endpoint arterioles to make anastomosis in the retinal arterioles and venules, barrier function and autoregulation are similar to relatively lower flow and high oxygen transport function.[11] The studies on patients with ATD conducted in the last three decades showed that the pathophysiology of the disease included the neurodegenerative changes due to the accumulation of abnormal Aβ and tau proteins in the amyloid plaques and NFTs.[12 13]

Vascular problems leading to ATD were demonstrated to be associated with the impairment in Aβ cleansing, resulting in impaired blood–brain barrier. Moreover, decreased vascular density, decreased vascular thickness and decreased blood flow are observed.[4] It is suggested that imaging the retinal vasculature may play an important role for the follow-up of ATD due to the similarity between the cerebral and retinal vasculature.[5] Therefore, previous studies using laser Doppler imaging demonstrated that patients with ATD had narrower retinal veins and lower venous blood flow compared with

Table 3 Correlation between MMSE score and age and OCTA parameters

	r Value	p Value
Age	−0.340	0.014*
Vascular density		
Whole	0.438	0.001*
Fovea	0.450	0.001*
Parafovea	0.370	0.007*
Foveal avascular zone	−0.531	<0.001*
Outer retina flow rate	0.124	0.380
Choroidal flow rate	0.253	0.070
Choroidal thickness	0.556	<0.001*

p Values with Spearman's correlation coefficient tests (age, foveal avascular zone and choroidal thickness) and Pearson correlation coefficient tests (density and flow rate).
*Significant at p<0.05.
MMSE, Mini Mental State Examination; OCT, optical coherence tomography.

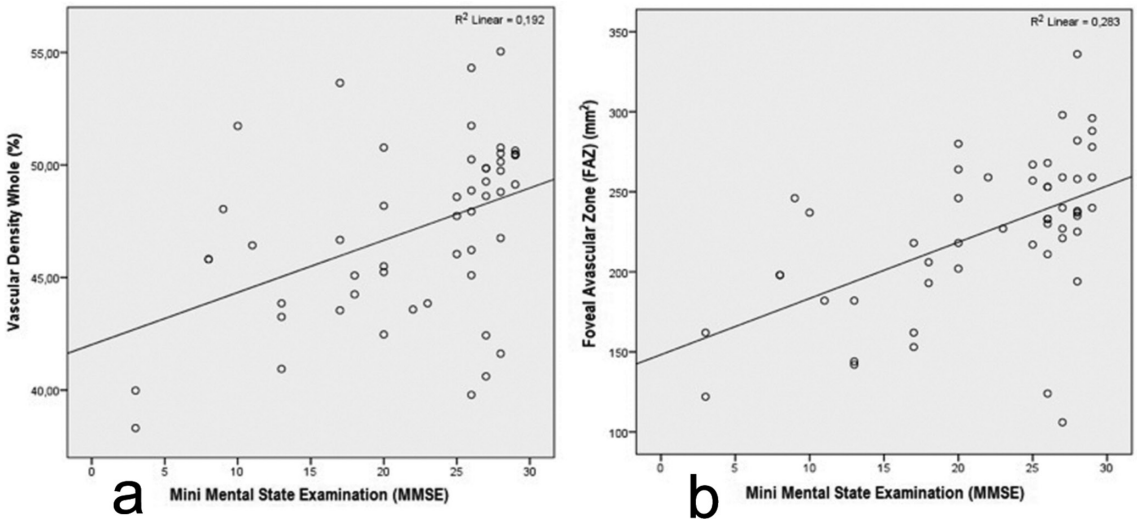

Figure 3 This figure shows the correlation between Mini Mental State Examination (MMSE) scores and (A) whole vascular density and (B) foveal avascular zone area.

the healthy individuals.[6 13] These researchers argued that Aβ deposits accumulated in the internal vessel walls leading to stenosis in the lumen. In a study using fundus photography and automated vessel segmentation software, it was shown that the patients with ATD had a lower retinal diameter, lower fractal dimension and increased vascular tortuosity.[14]

In our study, we aimed at detecting the retinal and choroidal vascular changes in ATD. We found that the vascular density was significantly lower in all retinal zones in the ATD group than in the control group according to the superficial vascular density measurements performed with OCTA ($p<0.05$). In the previous studies, it was demonstrated that the decreased vascular density in ATD was associated with the decreased angiogenesis due to the binding of vascular endothelial growth factor (VEGF) to Aβ and its confinement in the plaques.[15 16] In our study, we could detect only superficial retinal vascular density, because of insufficiency of software for calculating deep vascular density, in ATD with OCTA imaging, which is an easy non-invasive imaging method.

Retinal vasculature includes three structures: radial peripapillary capillary, superficial vascular and deep vascular plexuses. These vascular structures feed the retinal nerve layer, ganglion cell layer and inner nuclear layer.[17] Superficial and deep plexuses create a capillary-free area in the foveal zone, which is named foveal avascular zone.[18] FAZ is susceptible to ischaemia. Enlargement of FAZ is a sign of ischaemia while previous studies showed that it is enlarged in such cases as diabetic retinopathy and macula vein branch occlusion especially using FFA.[19 20] With FFA, only superficial vascular structures can be scanned. With OCTA, however, each of the three structures can be imaged; therefore, it provides more valuable information about FAZ.[21] In our study, FAZ was found to be statistically significantly enlarged in the ATD group compared with the control group.

Our study is the first in the literature to evaluate the vascular density and FAZ in ATD through OCTA imaging. We suggest that the decreased retinal vascular density and enlarged FAZ we found in patients with ATD could be associated with the decreased angiogenesis due to the binding of VEGF to Aβ and its confinement in the plaques and also the accumulation of Aβ deposits in the internal vessel walls, leading to occlusion of the vascular structures and decreased blood flow, as also underlined in previous studies.[6 13]

Although we found a slightly lower outer retinal and choroidal flow rate in the group of patients with ATD, the difference was not statistically significant. This might be due to the limited number of subjects in our study. We think that there is a need for larger studies on this matter. Previous studies used retinal laser Doppler flowmetry to determine the retinal flow rate. However, retinal laser Doppler flowmetry has a limited capability to determine the blood flow in large blood vessels and deoxygenated blood. Therefore, retinal blood flow rate results reported by the studies using retinal laser Doppler flowmetry in ATD are limited.[6 13] In a review conducted by Koustenis *et al*[22] regarding OCTA, they argued that imaging with OCTA for retinal flow measurement could yield better results. Our study is the first in the literature also on this matter.

Choroid is an important tissue of the eye with a vascular structure located between the retina and the outer coat of the eye. There are previous studies on CT considered as a biomarker in ATD.[23 24] In parallel to these studies, we also found statistically significantly lower CT in patients with ATD. Since choroid is a dense vascular structure, thinner choroidal tissue than the normal thickness was a result that we expected.

As the severity of cognitive impairment can be measured with MMSE score, the association between the OCT parameters and this cognitive test can give us useful information for the clinical valuation and monitoring of patients with ATD.[25] In our study, we found a significantly higher positive correlation between the MMSE score and superficial retinal vascular density and CT. However, we found a significantly higher negative correlation between the MMSE score and FAZ measurement zones. The correlation we found between the retinal vascular density and FAZ measurement zones and MMSE scores is the first one in the literature in this area. Moreover, we found a correlation between the CT value and MMSE score in a previous study similar to this present one[23]; another study conducted on this subject did not find any correlation.[24]

Our study had some limitations. One of the most important limitations was the low number of patients. Our study can be supported with larger studies including higher number of

patients. Another important limitation was that it took slightly longer time to perform OCTA imaging than the normal spectral domain optical coherence tomography (SD-OCT) imaging; thus, scans of patients with advanced stage ATD resulted in artefacts especially due to fixation problem. Therefore, evaluation of the retinal structures in advanced stage AD with OCTA may not provide healthy results. We excluded patients with artefacts in OCTA scans from our study, which is one of the reasons why we had a low number of patients.

In conclusion, retinal and choroidal microvasculature deficits in ATD can be detected early with OCTA imaging. In these patients, due to the close association between retinal and cerebral circulations deficits, microvasculature deficits detected early with OCTA can be used as a new biomarker in the early detection of ATD, monitoring of its progression and in the evaluation of the efficacy of drugs used for its treatment.

Contributors MB and FL carried out the study. MB, MA, AC, FK and AY finished data collection and statistical analysis. MB, OG and MKE wrote the paper and revised the manuscript.

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Patient consent Obtained.

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