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Optical Coherence Tomography Angiography in the Evaluation of Macular Retinal Microvasculature in Patients in the Early Clinical Stage of Alzheimer's Disease – A Preliminary Report

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Abstract:

Introduction: Alzheimer's disease (AD) is a chronic neurodegenerative condition causing cognitive decline among elderly individuals. In addition to neurological deficits, a key role in the onset and subsequent progression of AD Alzheimer's disease-specific changes is attributed to vascular factors. Retinal microvasculature and cerebral small vessels share similar anatomical features and physiological characteristics, and damage to the retinal vascular bed can be observed at any stage of AD Alzheimer's disease. Retinal microvasculature can be visualized and assessed non-invasively using the technique of optical coherence tomography angiography (OCT-A).

Aim of study: Evaluation of macular retinal microvasculature in the superficial capillary plexus based on OCT-A optical coherence tomography angiography images in patients diagnosed with the mild stage of Alzheimer's dementia.

Material and methods: The study involved a total of 21 patients diagnosed with mild Alzheimer's dementia confirmed by neuropsychological tests and neuroimaging studies. optical coherence tomography angiography OCT-A was used to determine vessel density in the superficial retinal capillary plexus (SRCP), i.e. generate a density map within five-field ETDRS circles with diameters of 3 mm and 6 mm.

Results: Alterations in the macular retinal capillary network were noted in all eyes studied. In the majority of eyes, there was a marked reduction in vessel density reflected in the quantitative metrics in the density map around the FAZ in at least one of the scans obtained for a given eye (3 mm x 3 mm and/ or 6 mm x 6 mm) and in the macroscopic evaluation of the superficial and deep capillary plexuses, capillary thinning, and irregular area/mexpansion of the FAZ.

Conclusions: Optical coherence tomography angiography OCT-A has the potential to serve as a valuable tool for screening or monitoring the response to therapies in patients with Alzheimer's disease AD. However, further research is necessary to standardize study methodologies and determine whether impaired retinal microvasculature in patients with Alzheimer-type MCI or preclinical Alzheimer's disease AD correlates with the advancement of cognitive decline and loss of neurons and cerebral blood vessels in individual Alzheimer's disease AD patients and, hence, has clinical utility.

Key words: Alzheimer's disease (AD), mild cognitive impairment, optical coherence tomography angiography (OCT-A), retina, retinal microvasculature, vessel density.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia among the elderly population. AD affects more than 50 million people worldwide, but it is projected that this number will rise to 131 million by 2050 [1, 2]. In Poland, over 350,000 individuals suffer from AD. Dementia diseases, including AD, are widely acknowledged as one of the most pressing health concerns of the 21st century.

The hallmark pathologies in AD are the extracellular plaque deposits of amyloid beta (Aβ) and the intracellular neurofibrillary tangles made up of hyperphosphorylated tau proteins [1–3]. Pathological processes observed in AD encompass cerebral vascular angiopathy linked to amyloid build-up in microvessel walls, diminished capillary density and morphological abnormalities, athero- and arteriosclerosis, neuronal and synaptic loss, inflammation, and gliosis [1–3]. The impact of Aβ plaques and tau protein on synaptic dysfunction and neuronal survival increases as AD progresses from moderate to severe stages [3]. Therefore, early treatment initiation in AD is crucial to potentially slow down the progression of the disease and maintain cognitive function in patients. The primary clinical symptom observed in the initial stages of the condition is episodic memory impairment. As the disease progresses to its advanced stages, patients lose the ability to perform basic activities of daily living, such as walking and swallowing. Consequently, they become unable to live independently and function in society. Mild cognitive impairment (MCI) represents an intermediate phase between the natural aging of the body and dementia, causing only minimal interference with basic activities of daily living [2]. They manifest themselves, among others, with prolonged perception and deduction time, and problems with recalling events and names of objects. Alzheimer-type MCI is regarded as the initial clinical phase of AD and a risk factor for the rapid progression of dementia. The rising incidence of Alzheimer's disease – coupled with the absence of effective treatment options – have spurred efforts to identify biomarkers that would help detect the condition at its early stages, prior to the occurrence of irreversible brain lesions and the onset of clinical signs of dementia. Pathological processes in the brain causing neuronal and synaptic degeneration, and resulting in cogniti-

ve decline and dementia, typically begin at least a decade before clinical symptoms appear [3, 4]. The existing diagnostic methods for AD and MCI (MRI, CSF examination, amyloid PET imaging, genetic testing) are expensive, invasive, and time-intensive. Hence, there is a critical need for a rapid, more cost-efficient, and non-invasive diagnostic approach to effectively screen patients for the future risk of Alzheimer-type dementia.

Characteristic pathological changes seen in AD are not confined to the brain. They are also manifested in the retina and show a significant correlation across these locations. The retina is seen as an extension of the central nervous system, which leads to the assumption that it could offer valuable insights for the early diagnosis of AD. Thinning of the retinal nerve fiber layer (RNFL), along with the loss of retinal ganglion cells (RGCs), are closely linked to cerebral atrophy [1, 4, 5]. In addition to accumulating within the walls of cerebral blood vessels, amyloid β deposits also appear in neuronal structures, vessels, and perivascular retinal tissue [1, 4–6]. In animal models of AD, plaque deposits of Aβ were detected in the retina earlier than in the brain, and their build-up was linked to disease progression [1, 4]. In addition to neurological deficits, a key role in the onset and subsequent progression of AD-specific changes is attributed to vascular factors. Retinal arterioles and veins measuring between 100 to 300 μm in diameter exhibit similar anatomical features and physiological characteristics to small cerebral vessels [1–3]. Consequently, the retina serves as the only 'window' available for examination, enabling the assessment of latent pathologies within the cerebral microvascular bed. Retinal vascular bed damage may manifest at any stage of AD, presenting as diminished blood flow, narrowing of veins and arteries, increased venous tortuosity, loss/ apoptosis of pericytes in retinal blood vessels, decreased density/ thinning of macular retinal vasculature, and reduction in choroid thickness [1–4, 6].

Retinal imaging modalities include optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A). OCT is a non-invasive and repeatable technique for intravascular imaging of retinal and choroidal structures based on optical scanning. The method makes it possible to acquire tissue sections consistent with histological examination, which is why it is referred to as real-time non-invasive high-resolution optical biopsy. OCT-A is an OCT-based non-invasive imaging modality developed to investigate the retinal vasculature. It enables visualization of blood flow within the retinal vessels and choriocapillaries without the use of contrast agents. Blood vessels are identified by tracking the motion of blood cells after isolating their signals from those of static tissues. OCT-A detects blood flow in the vessels at any time, and the resulting image is fixed (static method, as opposed to dynamic fluorescein angiography). OCT-A allows the visualization of retinal capillary plexuses that cannot be observed through fluorescein angiography. OCT-A automatically segments all layers of blood vessels within the retina, which provides an opportunity to analyze each plexus separately. At the posterior pole, the retinal capillary network comprises four layers:

– radial peripapillary capillary plexus (RPCP),
– superficial retinal capillary plexus (SRCP),
– intermediate capillary plexus (ICP),
– deep retinal capillary plexus (DRCP) [7].

The four capillary plexuses listed above are organized into two main plexuses: superficial vascular complex (SVC) and deep vascular complex (DVC). The SVC comprises the RPCP and SRCP, while the DVC consists of the ICP and DRCP and is regarded as a singular vascular system. The SRCP is located in the ganglion cell layer of the retina and consists of arterioles and venules radiating from the superior and inferior vascular arcades. They are linked together by transverse capillaries. The vessels converge centripetally towards the fovea [7] (Fig. 1).

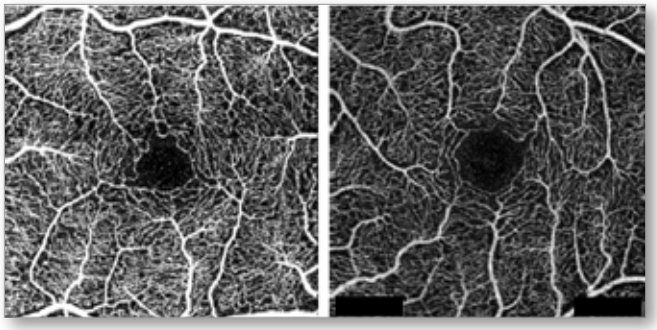

Fig. 1. OCT-A image of the superficial retinal capillary plexus (SRCP).

The ICP and DRCP are visualized as individual vascular networks. The ICP occupies the space between the inner plexiform layer (IPL) and the inner nuclear layer (INL), while the DRCP is located between the INL and the outer plexiform layer (OPL). Both deep plexuses are composed of densely interwoven capillaries of constant thickness, with multiple horizontal and vertical junctions. The vascular pattern is distributed around the FAZ. Both the ICP and DRCP are supplied via vertical anastomoses from the SVP [7] (Fig. 2).

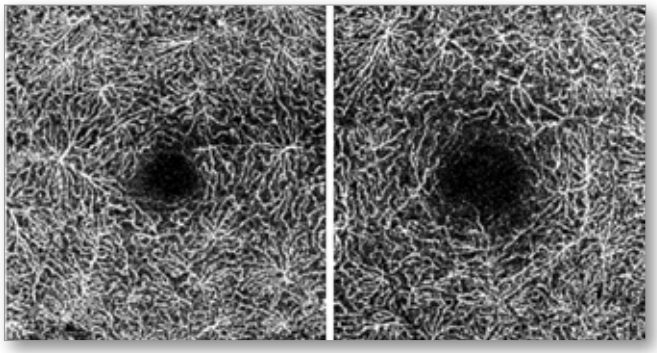

Fig. 2. OCT-A image of deep retinal capillary plexus (DRCP), 6 mm x 6 mm and 3 mm x 3 mm scans.

In healthy individuals, the outer retina is avascular. No vascular elements should be present within this area, with no signs of vascular perfusion seen on OCT-A [7] (Fig. 3).

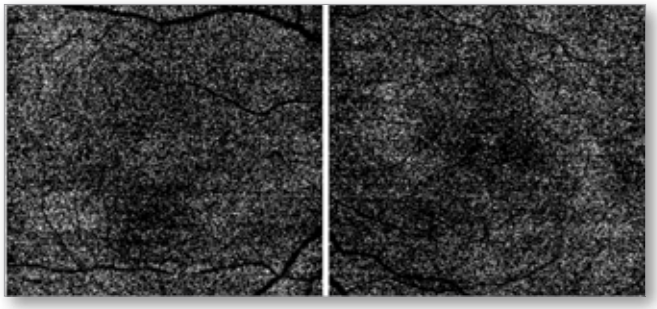

Fig. 3. OCT-A image of normal outer retina in both eyes.

Retinal vessel density (VD) on OCT-A represents the macular capillary network. The parameter is acquired by OCT-A to identify changes in the macular retinal microvasculature during the early stages of retinopathy and neurodegenerative conditions. VD appears to be significantly reduced in the superficial retinal capillary plexus (SRCP), though some studies show thinning of the capillary network in the deep retinal capillary plexus (DRCP) and expansion of the foveal avascular zone (FAZ). Small microvessels within the DRCP might be more prone to disease development

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compared to the larger vessels in the SRCP. Alternatively, their thinning, scarce number, and irregularities could stem from the physiological aging of the body. There have been reports of increased VD in patients with subclinical AD, which may be due to heightened blood flow secondary to hypoxia [1, 8]. Retinal vascular parameters appear to correlate significantly with cognitive outcomes. Macular retinal vascular abnormalities, such as a decrease in VD detected via OCT-A, could potentially serve as a marker for monitoring disease progression. The role of pathologies in the macular retinal microvasculature in the early stages of AD is still under study.

Key findings for the current analysis:
- multiple recent studies have demonstrated the benefits of OCT-A in the early diagnosis of AD [1–5, 8],
- changes in the FAZ and VD of the superficial retinal capillary plexus may reflect the progression of changes observed in AD patients (decreased density/ thinning of macular retinal vasculature, expansion of the FAZ) [1–3, 8–9],
- there is a correlation between retinal capillary changes and cerebral angiopathy associated with amyloid plaque deposition and the patient's clinical condition [1–3],
- accumulation of amyloid β and tau protein deposits in the retina precedes similar changes occurring in the brain [1, 4],
- changes in the retinal circulation in patients with AD – reduced density/ thinning of macular retinal vasculature, diminished blood flow, narrowing of arterial and venous vessels, increased venous tortuosity, and loss/ apoptosis of pericytes in retinal vessels [1–6, 8].

Aim of study – evaluation of macular retinal microvasculature in the superficial capillary plexus seen in OCT-A images in patients diagnosed with mild Alzheimer's dementia.

Could alterations in the density of small blood vessels in the retina mirror the changes occurring in small cerebral blood vessels before the onset of dementia?

Can OCT-A be useful for the early detection of AD risk and subsequent monitoring of disease progression?

Material and methods

Ophthalmological examinations were performed in a total of 21 patients receiving routine care at the Alzheimer's Outpatient Clinic at the National Medical Institute of the Ministry of Internal Affairs and Administration in Warsaw. All the patients included in the analysis attended the ophthalmological assessment following a diagnosis of mild Alzheimer's dementia established according to the NINCDS-ADRDA criteria. The diagnosis was further confirmed by neuropsychological and neuroimaging examinations (CT or MRI of the brain).

Out of the 21 patients assessed, there were 13 women and 8 men, ranging in age from 52 to 75 years. The following patient exclusion criteria were adopted:
- diabetes,
- uncontrolled arterial hypertension,
- ischemic stroke,
- myocardial infarction within 6 months prior to eye examination,
- glaucoma,
- ocular hypertension (IOP ≥ 25 mmHg),
- age-related macular degeneration and other maculopathies,
- optic nerve diseases,
- thromboembolic changes in retinal blood vessels,
- amblyopia,
- lack of patient compliance,
- poor scan quality/ artifacts.

One patient (two eyes) was excluded from the analysis due to age-related macular degeneration, and five eyes because of difficulties encountered during OCT/ OCT-A procedures and secondary artifacts preventing reliable evaluation of the scans. In addition, the researchers excluded one eye with a primary narrow angle due to the potential risk of acute angle closure following diagnostic pupillary dilation.

The artifacts in the findings, which hindered or even entirely prevented a reliable and meaningful assessment of OCT-A scans, stemmed from the challenges faced by a proportion of patients during the scanning process because of their underlying disease, such as an inability to sustain a forced head position or maintain constant fixation of the examined eye on the center of the camera's field of view, and frequent blinking.

Ultimately, the results obtained via OCT and OCT-A evaluations of 34 eyes were analyzed.

The ophthalmological examination comprised a range of parameters including:
- best corrected near and distance visual acuity,
- intraocular pressure,
- examination of the anterior eye segment,
- fundus examination after pupillary dilation with 1% tropicamide eye drops,
- color fundus photography,
- optical coherence tomography (OCT) – macula, optic nerve head, ganglion cell complex (GCC)
- optical coherence tomography angiography (OCT-A) – 3 mm x 3 mm and 6 mm x 6 mm scans.

OCT and OCT-A examinations were performed using the Swept Source DRI OCT (Deep Range Imaging OCT) Triton from Topcon after pupillary dilation with 1% tropicamide eye drops.

The parameter measured in the study was **vessel density in the superficial retinal capillary plexus (SRCP), determined by generating a density map within five-field ETDRS circles with diameters of 3 mm and 6 mm.**

Density map determines the ratio of the measured macular area to the blood vessels occupying that area. In the Swept Source DRI OCT Triton device, it corresponds to the VD parameter in the SRCP [3].

Other assessed parameters that are beyond the reported scope:
- subfoveal central retinal thickness (CRT),
- retinal nerve fiber layer (RNFL) thickness around the optic nerve head,
- macular retinal ganglion cell complex (GCC) thickness,
- choroidal thickness (CT).

Results

The study assessed the density map parameter determined by OCT-A (Swept Source DRI OCT Triton device from Topcon) in a total of 34 eyes of patients diagnosed with mild Alzheimer's dementia.

Among the five ETDRS circle fields in the macular retina of the examined eyes, variable values were noted in the central field, encompassing the zone surrounding the FAZ. Importantly, the values could vary within the same eye, depending on scan size (3 mm x 3 mm and 6 mm x 6 mm).

The findings obtained for the eyes of study subjects were compared with the OCT-A results and density maps of individuals aged older than 65 years, without cognitive impairment (Fig. 4).

Alterations in the macular retinal capillary network were noted in all eyes analyzed. Of the 34 eyes included in the analysis, in 18 eyes there was a marked reduction in vessel density reflected in the quantitative metrics in the density map around the FAZ in at least one of the scans obtained for a given eye (3 mm x 3 mm and/ or 6 mm x 6 mm) and capillary thinning as well as irregular area/ expansion of the FAZ in the macroscopic evaluation of the superficial and deep capillary plexuses (Fig. 5–12 and 13–20].

In the remaining 16 eyes studied, vessel density around the FAZ, reflected in the quantitative metrics in the density map's central field, was found to be no worse than in the controls. However, there was a discrepancy between the quantitative metrics in the density map's central field and the macroscopic evaluation of the superficial and deep retinal capillary plexuses in the 3 mm x 3 mm and/ or 6 mm x 6 mm OCT-A scans. In the macroscopic evaluation of vessel density within the superficial and deep retinal capillary plexuses, some of the scans, corresponding to normal quantitative metrics in the density map, showed capillary thinning/ loss around the FAZ along with the expansion/ irregular outline of the FAZ (Fig. 21).

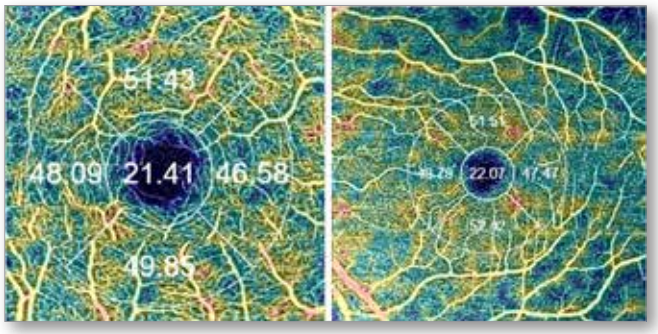

Fig. 4. Example of control OCT-A image – 3 mm x 3 mm and 6 mm x 6 mm density maps in patients over 65 years of age without a diagnosis of AD, MCI, or any other form of dementia, and without cognitive impairment.

Conclusions

Based on the literature reports, disorders in the retinal microvasculature and neuronal microstructures begin to appear during the preclinical stage of Alzheimer's disease. Therefore, damage to the retinal microvasculature can be observed across all stages of AD, even in the early phases when the clinical signs of the condition are not yet apparent. Recent reports indicate reduced density/ thinning of macular retinal vasculature in the SRCP and DRCP, and expansion of the FAZ among individuals with AD or Alzheimer-type MCI [1–4, 8]. Macular retinal vascular parameters can be assessed in a repeated and non-invasive manner using the relatively new diagnostic method of OCT-A. Abnormalities in macular capillary network density appear to correlate with cognitive impairment observed in AD patients [1–3, 8–9]. In the reported analysis, changes in the macular retinal capillary network were found in all OCT-A-examined eyes. They included a marked decrease in vessel density reflected in the quantitative metrics in the density map around the FAZ in at least one of the scans per eye (3 mm x 3 mm and/ or 6 mm x 6 mm) and capillary thinning/ loss shown in the macroscopic evaluation of the superficial and deep capillary plexuses, accompanied by the irregular area/expansion of the FAZ even when the quantitative metrics in the density map fell within the range observed in the healthy eyes used as controls. Damage to the retinal vasculature, manifested as decreased density of the macular microvasculature seen on OCT-A, could serve as an objectively measurable marker for assessing the prognosis in AD patients and for monitoring disease progression. OCT-A-

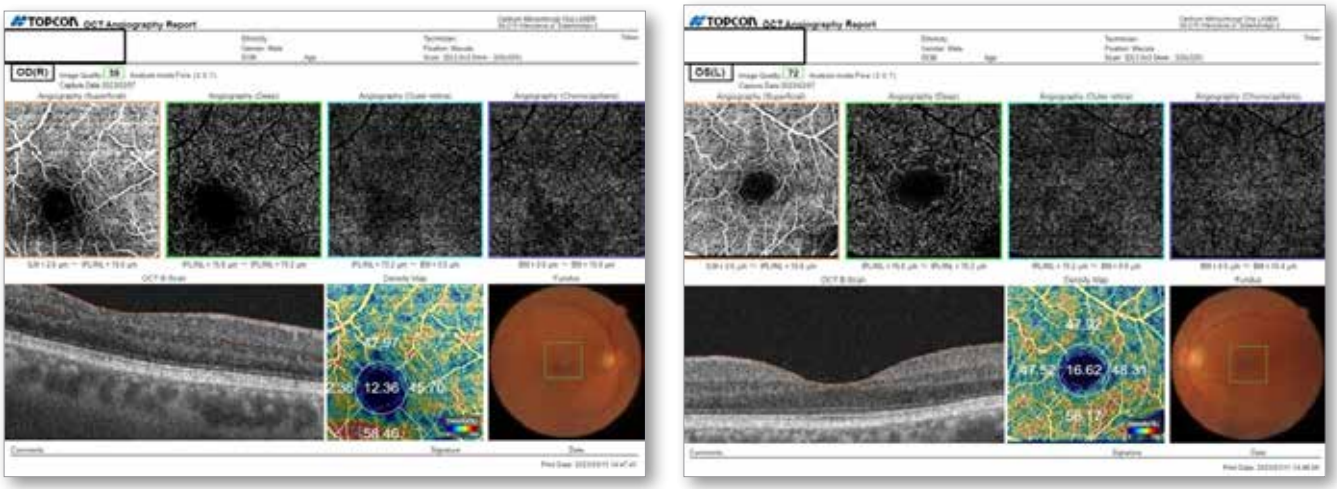

Fig. 5. Patient 1. OCT-A report 3 mm x 3 mm OD and OS.

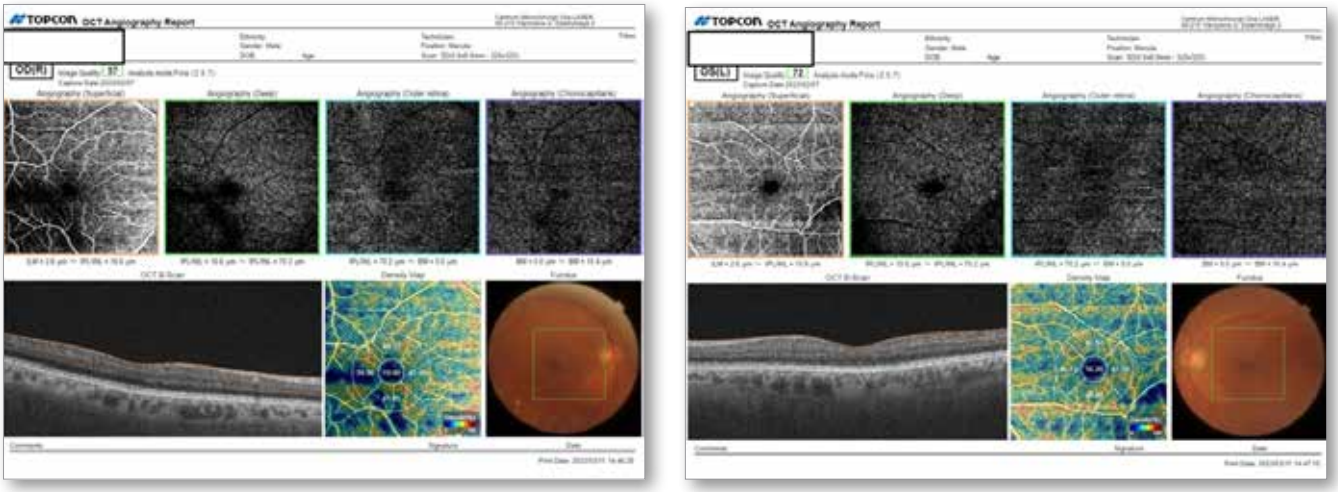

Fig. 6. Patient 1. OCT-A report 6 mm x 6 mm OD and OS.

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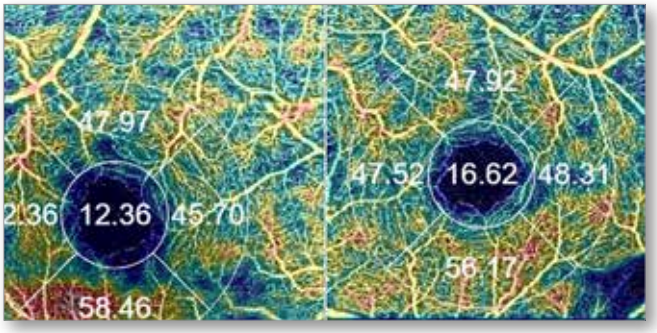


Fig. 7. Patient 1. Density map 3 mm x 3 mm OD and OS.

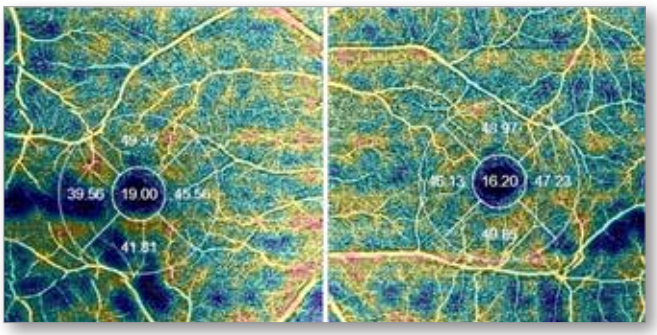


Fig. 8. Patient 1. Density map 6 mm x 6 mm OD and OS.

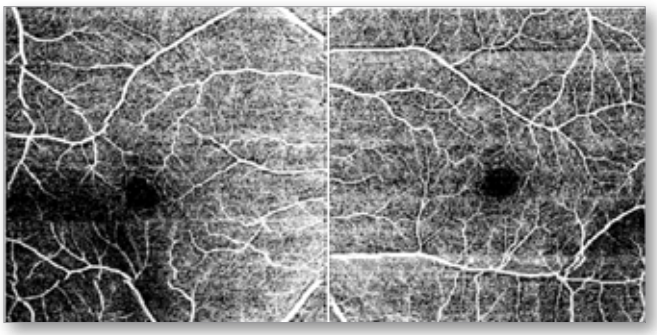


Fig. 9. Patient 1. OCT-A images, OD and OS, superficial capillary plexus, 6 mm x 6 mm scans.

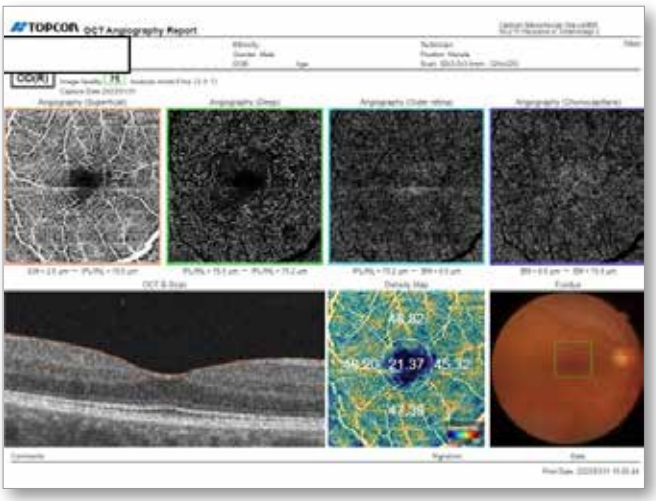


Fig. 13. Patient 2. OCT-A report 3 mm x 3 mm, OD and OS.

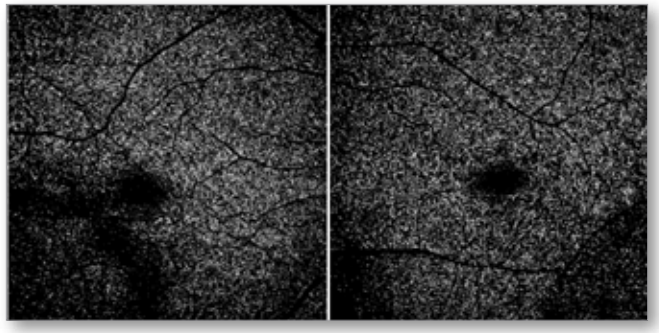


Fig. 10. Patient 1. OCT-A images, OD and OS, deep capillary plexus, 6 mm x 6 mm scans.

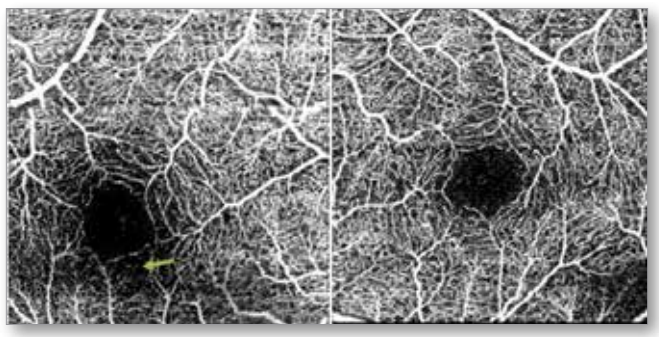


Fig. 11. Patient 1. OCT-A images, OD and OS, superficial capillary plexus, 3 mm x 3 mm scans. Green arrow indicates capillary thinning/ loss around the FAZ.

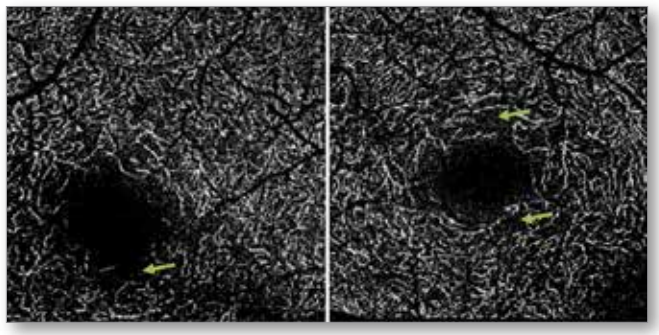
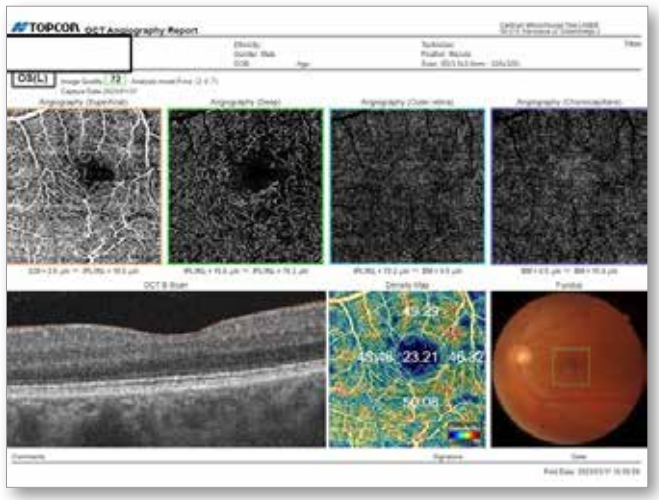


Fig. 12. Patient 1. OCT-A images, OD and OS, deep capillary plexus, 3 mm x 3 mm scans. Green arrows indicate capillary thinning/ loss around the FAZ.



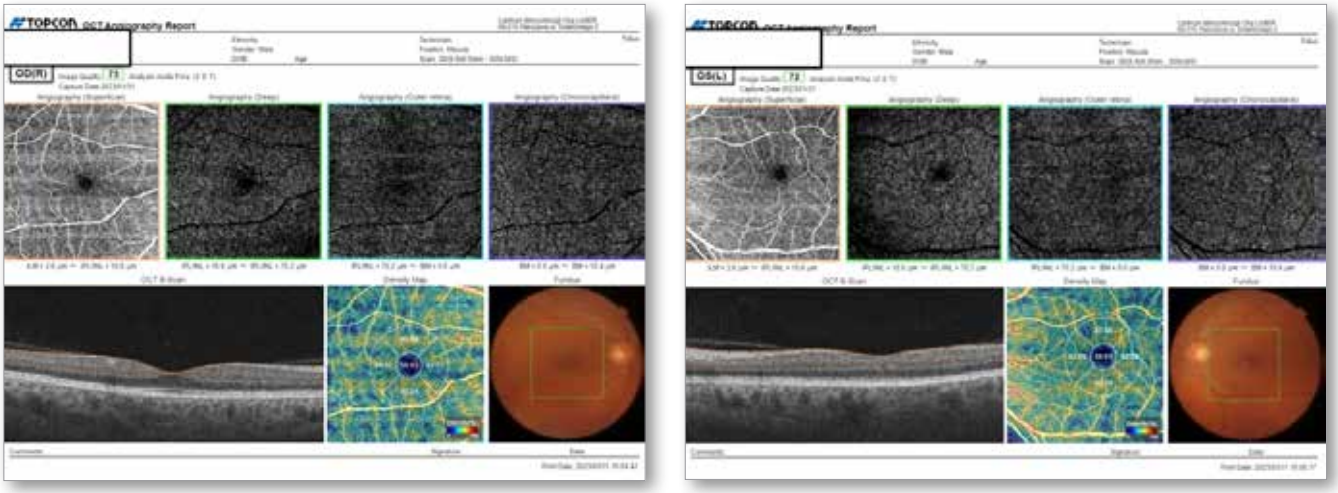


Fig. 14. Patient 2. OCT-A report 6 mm x 6 mm, OD and OS.

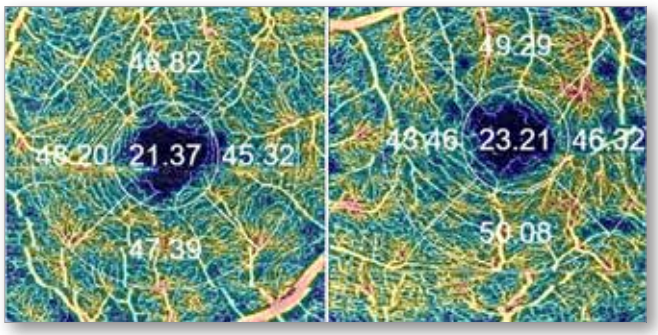


Fig. 15. Patient 2. Density map 3 mm x 3 mm, OD and OS.

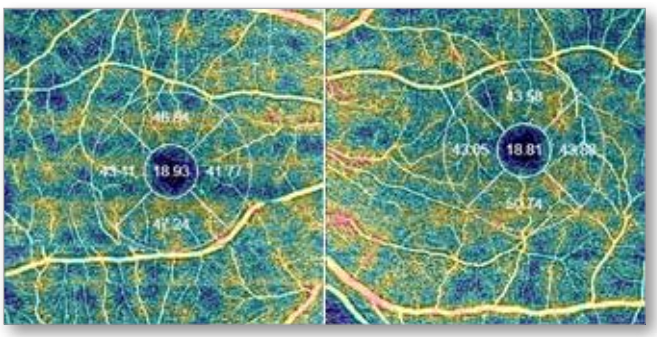


Fig. 16. Patient 2. Density map 6 mm x 6 mm, OD and OS.

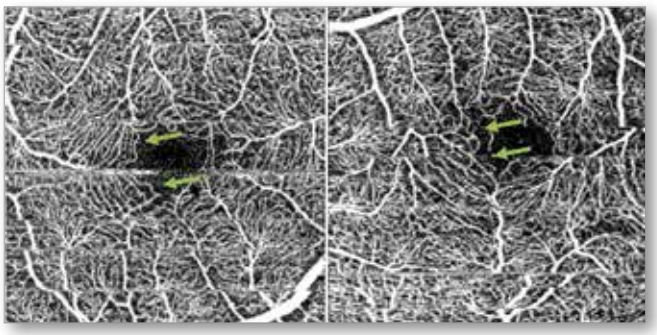


Fig. 17. Patient 2. OCT-A images, OD and OS, superficial capillary plexus, 3 mm x 3 mm scans. Green arrows indicate capillary thinning/ loss around the FAZ.

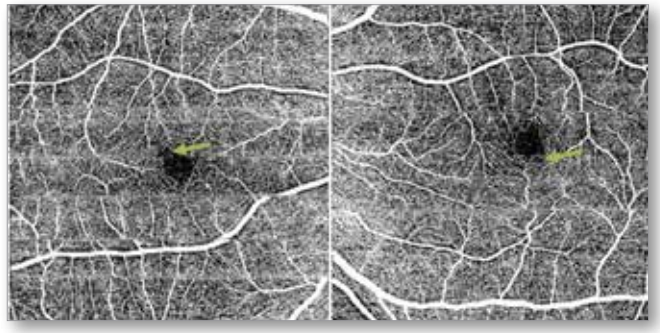


Fig. 18. Patient 2. OCT-A images, OD and OS, superficial capillary plexus, 6 mm x 6 mm scans. Green arrows indicate capillary thinning/ loss around the FAZ.

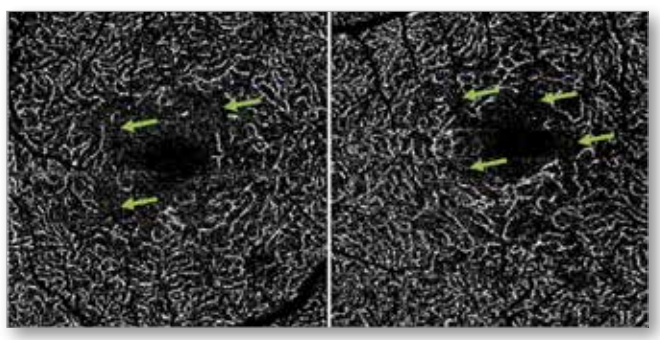


Fig. 19. Patient 2. OCT-A images, OD and OS, deep capillary plexus, 3 mm x 3 mm scans. Green arrows indicate capillary thinning/ loss around the FAZ.

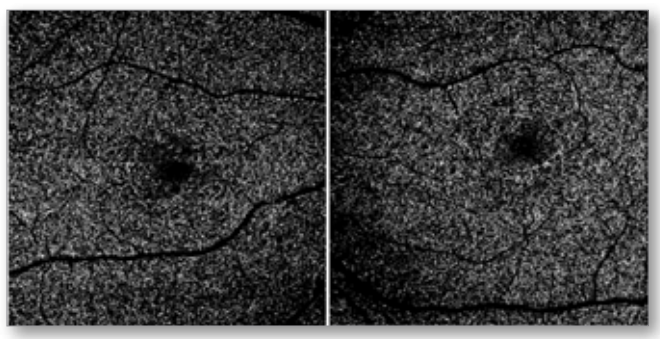


Fig. 20. Patient 2. OCT-A images, OD and OS, deep capillary plexus, 3 mm x 3 mm scans.

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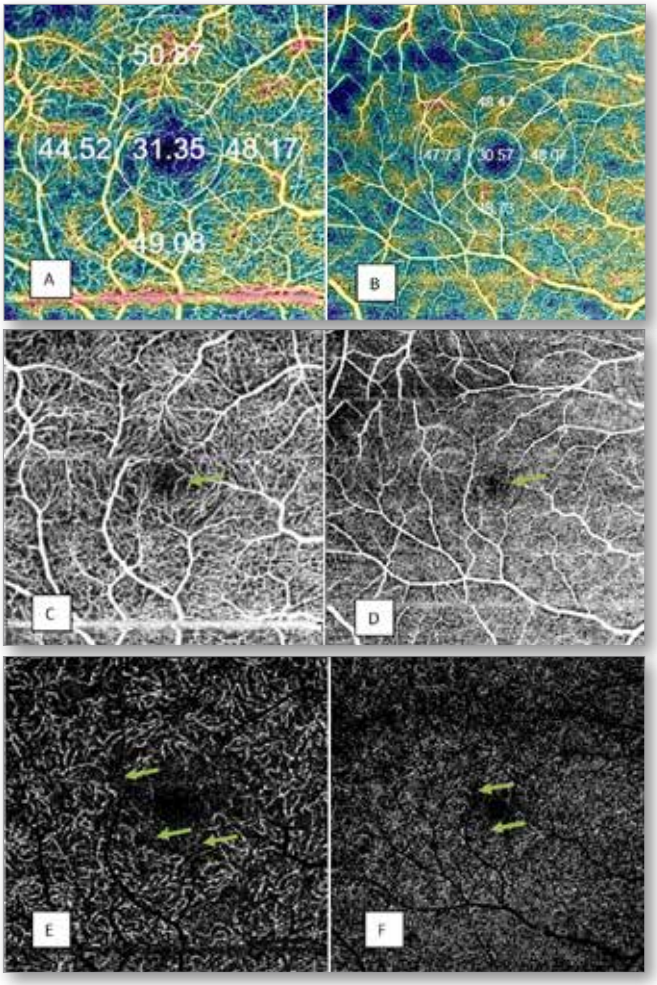

Fig. 21. OCT-A image of the right eye in a patient with AD. A. – density map, 3 mm x 3 mm scan, normal quantitative metrics in the five-field ETDRS circle. B. – density map, 6 mm x 6 mm scan, normal quantitative metrics in the five-field ETDRS circle. C. – superficial capillary plexus, 3 mm x 3 mm scan. D. – superficial capillary plexus, 6 mm x 6 mm scan. E. – deep capillary plexus, 3 mm x 3 mm scan. F. – deep capillary plexus, 6 mm x 6 mm scan. Green arrows indicate capillary thinning/ loss around the FAZ (Fig. 21).

-based imaging of the macular retinal microvasculature has the potential to serve as a valuable tool in population-based screening or for monitoring the response to therapies initiated in patients with AD. Due to variations in the OCT-A devices used across the studies conducted to date, lack of standardized measurement field for macular retina, and application of diverse software for image and data processing, some findings showed no significant differences across the AD, MCI, and control groups. Research is needed to determine whether impaired retinal microvasculature seen in patients with MCI or preclinical AD correlates with the advancement of cognitive decline, and with the loss of neurons and cerebral blood vessels in individual patients with AD. To ensure reliability and repeatability in the evaluation of the macular retinal microvasculature via OCT-A, it is crucial to standardize the terminology and anatomical boundaries of the examined areas of the macula and optic nerve head. Moreover, standardization is needed in the calculation methods used for the VD algorithm.

Disclosure

The authors declare no conflict of interest.

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