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Diagnosis of Alzheimer's Disease by Assessing Structural and Microvasculature Changes in the Retina Using Optical Coherence Tomography Angiography – a Review of Eye Biomarkers for Alzheimer's Disease

Diagnoza choroby Alzheimera poprzez ocenę zmian strukturalnych i mikronaczyniowych w siatkówce za pomocą angiografii optycznej koherencyjnej tomografii – przegląd ocznych biomarkerów choroby Alzheimera

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Abstract: Alzheimer's disease is a chronic neurodegenerative disorder that manifests as cognitive decline and memory impairment. Diagnosis is mainly based on the assessment of cognitive functions, while neuroimaging techniques are still very expensive and difficult to access. During the embryogenesis phase, the retina and optic nerve develop as a direct extension of the diencephalon, so that abnormalities occurring in the brain can also be observed in the fundus of the eye. Using optical coherence tomography, a significant decrease in thickness of the retinal nerve fiber layer and a reduction in retinal thickness and volume in the macular area have been demonstrated. In post-mortem studies of patients with Alzheimer's disease, it has been proven that the disease, in addition to nerve cell damage, also has its cerebrovascular pathology. A potential association with the accumulation of abnormal Aβ around vascular walls, impaired blood flow and the diameter of the vessels in the retina have been identified in patients with AD. Using optical coherence tomography angiography to retinal microcirculation imaging showed a reduction in retinal vascular density compared to the control group. Unfortunately, the structural changes in the retina in patients with dementia observed by means of optical coherence tomography images may be non-specific and common to other neurodegenerative diseases, such as reduction in the thickness of the retinal nerve fiber layer in glaucoma. Nevertheless, combined measurements of retinal structural changes and microvasculature assessment in each retinal plexuses using optical coherence tomography angiography potentially increase the diagnostic ability of Alzheimer's disease.

Key words: Alzheimer's disease, retinal microvasculature, peripapillary retinal nerve fiber layer, optical coherence tomography angiography.

Abstrakt: Choroba Alzheimera jest przewlekłym zaburzeniem neurodegeneracyjnym, która objawia się spadkiem funkcji poznawczych i zaburzeniem pamięci. Diagnostyka opiera się głównie na ocenie funkcji poznawczych, a badania neuroobrazowe nadal są bardzo drogie i trudno dostępne. W fazie embriogenezy siatkówka oraz nerw wzrokowy rozwijają się jako bezpośrednie przedłużenie międzymózgowia, dlatego nieprawidłowości zachodzące w mózgu u pacjentów z chorobą Alzheimera możemy również obserwować na dnie oka. Przy zastosowaniu nowoczesnej techniki obrazowania za pomocą optycznej koherentnej tomografii wykazano znaczący spadek grubości warstwy włókien nerwowych siatkówki oraz zmniejszenie grubości i objętości siatkówki w plamce. W badaniach pośmiertnych pacjentów z demencją udowodniono, że choroba Alzheimera poza uszkodzeniem komórek nerwowych cechuje się także patologią naczyniowo-mózgową. Zidentyfikowano potencjalny związek z odkładaniem się nieprawidłowego β-amyloidu w okolicach naczyń a zaburzeniem przepływu krwi oraz średnicą naczyń w siatkówce. Zastosowanie nieinwazyjnej metody obrazowania mikrokrążenia za pomocą angiografii optycznej koherentnej tomografii wykazało zmniejszenie gęstości naczyń siatkówki w porównaniu do grupy kontrolnej. Niestety zmiany strukturalne siatkówki u pacjentów z demencją obserwowane za pomocą obrazów optycznej koherentnej tomografii mogą być niespecyficzne i wspólne dla innych chorób neurodegeneracyjnych, jak np. zmniejszenie grubości warstwy włókien nerwowych siatkówki w jaskrze. Niemniej jednak kombinowane pomiary zmian strukturalnych siatkówki oraz ocena mikrokrążenia w poszczególnych splotach siatkówki z wykorzystaniem techniki angiografii optycznej koherentnej tomografii potencjalnie mogą zwiększać zdolność diagnostyczną choroby Alzheimera.

Słowa kluczowe: choroba Alzheimera, mikrokrążenie siatkówkowe, okołotarczowa warstwa włókien nerwowych siatkówki, angiografia optyczna koherentna tomografia.

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Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia among the elderly (1). It is estimated that the prevalence of AD is about 36 million people worldwide. Due to the increase in life expectancy and the demographic ageing, the number of patients affected may double every 20 years, reaching the number of 115 million patients in 2050 (2).

Recent studies have shown that AD begins decades before it is fully clinically expressed (3–5). Before the onset of a full-blown disease, cognitive impairment progresses slowly without significant interference in daily activities. This prodromal phase is known as mild cognitive impairment (MCI) (6, 7). It is currently believed that MCI is an intermediate condition between normal aging and early dementia, in which patients may experience impairment of one or even more cognitive domains without compromising daily life performance (8). Although some MCI patients may remain stable over the life course, it is well known that the amnestic and multi-domain phase of MCI increases the risk of progression to AD (9).

Taking into consideration the fact that the diagnosis of AD remains still complicated, especially at the MCI stage, the search for new, non-invasive and inexpensive biomarkers is a promising area of research (10). In clinical practice, the diagnosis of AD is mainly based on the assessment of cognitive function, which may be unreliable in people with high cognitive reserve (11). Additionally used diagnostic techniques that include brain neuroimaging (e.g. magnetic resonance imaging (MR), positron emission tomography (PET)) or molecular measurement of protein levels in cerebrospinal fluid (CSF) (e.g. Tau and Amyloid-β (Aβ)) can be used to confirm AD diagnosis. The disadvantage of these methods are their high costs or invasiveness associated with the collection of CSF. In addition, there are still doubts as to whether they are sensitive and specific enough to allow establishing definitive diagnosis of AD (12, 13).

Since the 1990s, when optical coherence tomography (OCT) was introduced, the measurement of the peripapillary retinal nerve fiber layer (pRNFL) thickness has become a parameter commonly used in the disease diagnosis and monitoring including disorders of retina, optic nerve (CNII) and, in particular, glaucoma (14, 15). It has been noticed that damage to the retinal ganglion cells (RGC) leading to thinning of pRNFL and the retinal ganglion cell layer (GCL) thickness can also be seen in neurodegenerative diseases such as Parkinson's disease (16–18), multiple sclerosis (19, 20), dementia with Lewy bodies (21) and primarily in AD (22, 23). The optical coherence tomography angiography (OCTA) is an extension of the OCT imaging technique, which provides additional capabilities in the form of non-invasive method for the quantitative and qualitative assessment of vascularization status within the macula and optic nerve head (ONH). Post-mortem studies of patients with AD have shown that apoptosis of nerve cells in the central nervous system (CNS) is accompanied by vascular lesions in the form of amyloid angiopathy (24). Pathological changes involve not only the CNS, but also the vascular system, so using the OCTA technique for examining intraocular vessels may become a new AD biomarker (25).

An eye as a "window to the brain"

CNII consisting of RGC axons does not have the specific features of a peripheral nerve – it is basically a bunch of white matter of the brain surrounded by meninges. However, in the embryogenesis phase, the retina and CNII develop as a direct extension of the diencephalon, so we can also observe CNS abnormalities in patients with AD while performing funduscopic examination (26, 27). It is believed that RGC damage in AD may have similar pathogenesis as primary open-angle glaucoma (POAG), therefore the issue of common risk factors and mediators responsible for their emergence and development is increasingly raised (28). Both diseases are characterized by initial changes in neuronal circuits and phosphorylation of mitogen-activated protein kinases (MAPK). Propagation of neurodegenerative processes related to glial reaction, neuroinflammation, mitochondrial abnormalities with the production of reactive oxygen species and oxidative stress, etc., leads to nerve cells apoptosis (29, 30). In animal model studies, McKinnon et al. suggested that the RGC death in patients with ocular hypertension may also be due to chronic neurotoxicity caused by the accumulation of Aβ induced by an increase of intraocular pressure, and a reduced VEGF level which at the molecular level resembles AD (31). Yoneda et al. in their research on the pathogenesis of glaucoma showed a significant decrease in free Aβ which was caused by its accumulation around the retinal vessels, as well as an increase in the level of abnormal tau protein in the vitreous body (32). Similar changes in the amount of these proteins occur in the CSF of people with AD (33).

Pathophysiological changes in AD

AD is a progressive neurodegenerative disease characterized by cognitive decline and memory impairment (34). The essence of the disease is apoptosis of nerve cells and loss of connections between neurons (35). It accounts for 60–80% of dementia cases and remains the main reason for their occurrence over the age of 60 (36). AD may occur sporadically or be genetically conditioned. The incidence of familial cases, with an autosomal dominant pattern of inheritance, is low (5–10%), associated with mutations in three different genes: amyloid precursor protein (APP), presenilin 1 (PSEN-1) and presenilin 2 (PSEN-2). Sporadic cases account for 90–95% of all cases and have multifactorial pathogenesis, consisting of a combination of genetic and environmental factors, with age as a leading risk factor (37). The main gene associated with the sporadic manifestation of the disease is the apolipoprotein E (APOE) gene located on chromosome 21. From among three isoforms, APOE 4 occurs in 50% of patients affected by AD and carries a threefold higher risk of developing the disease (38, 39). The main reason for the emergence and progression of the disease is the accumulation of abnormal proteins: extracellular Aβ arising from the APP and the formation of intracellular neurofibrillary tangles of the tau protein (40, 41). These characteristic changes are well reflected in CSF, which demonstrates abnormal levels of tau protein and Aβ (42).

In 1986, Hinton et al. were the first to describe that neurodegenerative changes in the brain of AD patients also affect CNII and retina (43). Further reports on this issue have also shown a loss of RGC leading to GCL and RNFL thinning in AD (44–46).

Koronyo-Hamaoui et al. identified post mortem Aβ deposits in the retina of AD patients. In another study, by using a modified scanning laser ophthalmoscope, they demonstrated in vivo increase in retinal fluorescence after curcumin supplementation in AD patients, which hypothetically reflected Aβ deposits. As in the case of the brain, these deposits were accumulated mainly around the blood vessels (47, 48). A potential association with the accumulation of abnormal Aβ around the retinal vessels was observed, namely impaired blood flow, increased vascular permeability and their diameter in the retina in patients diagnosed with AD (49, 50). As other researchers have not confirmed the presence of abnormal protein deposits, the incidence of Aβ in the retina of AD patients is still controversial and provides the basis for further studies in this direction (51, 52).

Visual symptoms in patients with AD

Visual symptoms are often one of the earliest manifestations in people with AD, with visual impairment affecting most patients, contributing to reduced quality of life.

Pathological changes in the visual function mainly concern disturbances in the visual field (most often the lower hemisphere is damaged), abnormal electrophysiological tests, incorrect perception of colours and contrast sensitivity, disturbances in perception of depth and movement sensitivity (53, 54). More complex symptoms such as visual memory deficits and visual hallucinations may appear earlier, even before other AD symptoms arise (55, 56). In addition, abnormalities in eye movements were observed in patients with AD and MCI. Smooth pursuit and saccadic movements become slower and less precise as a result of the disease (57, 58).

Visual symptoms in AD are not only caused by damage to the associative visual areas, but there is more and more evidence that the involvement of retina and CNII is also a contributing factor of developing visual symptoms, which raises the interest of ophthalmologists in the search for new AD biomarkers in the retina (59–62).

The appearance of the retina and optic disc in AD patients

Morphometric studies in vivo using non-invasive diagnostic techniques have provided evidence of the involvement of retina, CNII and choroid in neurodegenerative processes occurring in patients with AD.

Fundus photography is the oldest, classic technique for documenting and imaging the retina and optic disc. Examination of patients with AD on the basis of fundus photographs showed abnormalities in the RNFL (images using a green filter), as well as changes in the appearance of optic disc. It has been found that in patients with AD there is an increase in the volume of optic nerve disc cup, an increased cup-to-disc (C/D) ratio and decreased area of the neuroretinal rim, which may correlate with the duration of the disease (23, 63).

In recent years, some efforts have been made to use fundus photographs to analyze changes in the retinal blood vessels. By measuring qualitatively and quantitatively microcirculation parameters, the fractal dimension, caliber, as well as the tortuosity and branching patterns of the retinal vessels have been analyzed. Studies have shown that patients with AD have an altered retinal microvascular network (narrower veins, increasing variability of vessel width, attenuate complexity of branching characteristic, reduced optimality of the branching geometry and less tortuous venules) compared to the control group. These changes in retinal microvasculature may reflect similar pathophysiological processes in brain microvasculature in AD patients. (64–67).

Application of OCT in AD diagnostics

OCT is a high-resolution, non-invasive imaging technique for retina based on the principle of low coherence interferometry, which is commonly used to assess morphological changes in the retina of the macular and optic disc area (14).

According to post-mortem studies in AD patients, a significant decrease in pRNFL thickness was confirmed using in vivo OCT imaging, as well as changes in retinal thickness and volume of the macula. In 2001 Parisi et al. are the first using the Stratus OCT 3 examined people with diagnosed AD disease. They found a significant reduction in pRNFL thickness in each of the 4 quadrants evaluated (68). Some analyzes have shown that statistically significant changes occur only in the superior (69–71) or both superior and inferior quadrants (72, 73). It has been suggested that the probable reason for the differences in the results of the above tests may be the severity of the disease assessed on the basis of the Mini-Mental State Examination (MMSE) test. Kelser et al. have shown a correlation between MMSE results and a reduction in pRNFL thickness, which suggests that retinal nerve fiber degeneration and CNS damage happen simultaneously (73). In studies, where patients obtained low results in the MMSE, statistically significant reduction in pRNFL thickness involved all quadrants (68, 74). In contrast, in the trials conducted by Berish et al. and Paquet et al., in which patients with AD obtained high MMSE results, there was a reduction in pRNFL thickness only in the superior quadrants, postulating that this is the area of the earliest RGC axonal damage in AD patients (75, 76).

Recently, the OCT technique has evolved from older generations, i.e. time domain OCT (TD-OCT) to spectral domain OCT (SD-OCT) and swept source OCT (SS-OCT), which have faster scanning speeds, higher axial resolution and smaller measurement variation (77). Thanks to the progress in OCT technology, it is possible to precisely assess the individual retinal layers in which RGCs are located (78). Macular lesions in the form of damage to the ganglion cell complex (GCC) consisting of three inner layers of the retina: RNFL, GCL and the inner plexiform layer (IPL) are also sensitive markers of neurodegenerative disease (79). Macula contains more than 50% of all RGCs, whose cell body size is 10 to 20 times the diameter of their axons, therefore lowering the thickness of GCL and IPL may be more sensitive to pathological changes in AD than lowering the thickness of pRNFL (80). In addition, individual variability has less effect on GCL and IPL thickness compared to pRNFL thickness (81). In studies where the thickness of individual retinal layers in the macula was assessed in patients with AD, it was confirmed that lowering the thickness of GCL-IPL complex may be a new marker for detecting nerve cell damage in MCI and AD which is associated with the process of neurodegeneration (80, 82–84).

SD-OCT with the use of enhanced depth imaging (EDI SD--OCT) is a technique that allows visualization of deeper struc-

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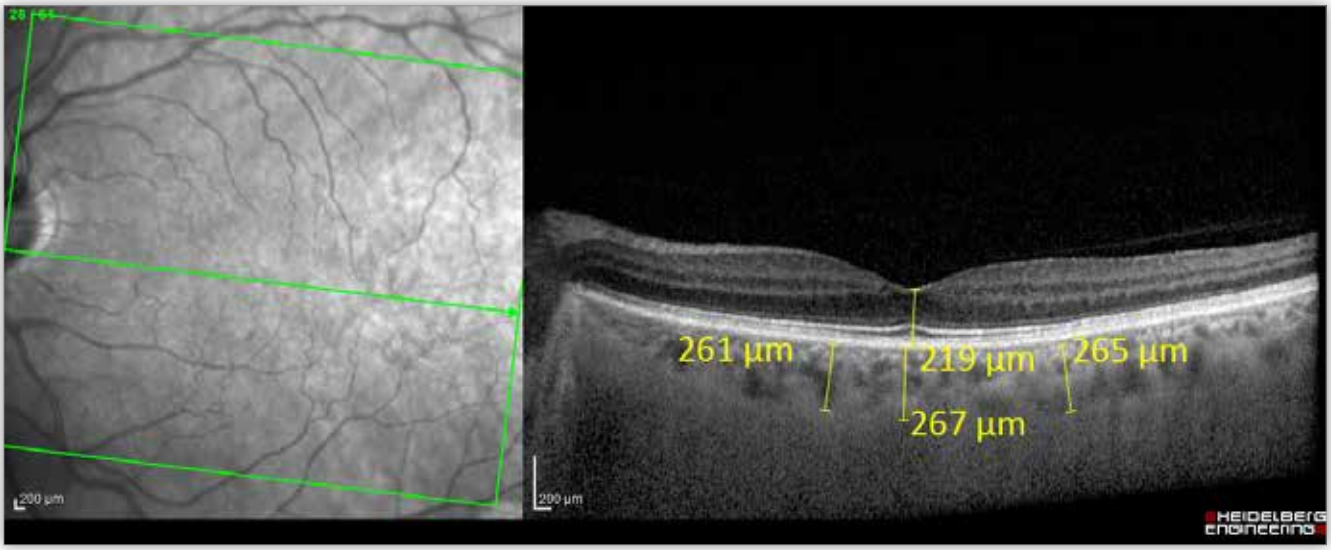

Fig. 1. Measurements of retinal thickness in the fovea and choroidal thickness in the subfoveal, nasal and temporal regions as assessed with enhanced depth imaging optical coherence tomography in a patient with Alzheimer's disease (authors' archives).

Ryc. 1. Pomiary grubości siatkówki w dołeczku oraz naczyniówki w okolicy poddołeczkowej, w nosowej i skroniowej za pomocą optycznej koherencji tomografii o zwiększonej głębokości obrazowania u pacjenta z chorobą Alzheimera (materiał własny).

tures of the eye such as choroid. The thickness of the choroid (CT) varies depending on the location of the examination – the thickest is under the fovea, and the thinnest in the nasal part of the retina (85). The results obtained with EDI SD-OCT confirmed that CT is thinning with age. In addition, it has been shown that CT is significantly reduced in all regions in patients with AD (fig. 1) (86–88).

Interpreting the result obtained using by OCT should always be aware of other neurodegenerative diseases, which can also lead to damage of the RGC. In the study in which we were analyzing the thickness of pRNFL, we found that OCT may be an auxiliary technique in the diagnosis of AD. Analysis of pRNFL thickness showed that AD patients had significantly reduced pRNFL thickness compared to healthy subjects, but this thickness was higher than for POAG patients. However, we found no difference in pRNFL thickness between the group of patients with AD and preperimetric glaucoma, i.e. in which there were no changes in the Visual field (fig. 2) (89).

The use of OCTA in the diagnosis of AD

Post-mortem studies of patients with Alzheimer's dementia have shown that the disease has cerebrovascular pathology. Although small brain vessel abnormalities are involved in the creation and development of MCI and AD, microvasculature in the CNS remains difficult to investigate in vivo (90). Brain and retinal blood vessels share a common embryological origin and show similarity in anatomical features and physiological properties, therefore retinal vascular examination may be valuable in providing new information on AD (91). The study conducted by Berish et al. with the use of laser Doppler has shown that AD patients have narrower retinal veins and lower venous blood flow in comparison to healthy controls (75). A potential association with the accumulation of abnormal Aβ around vascular walls, impaired blood flow and the diameter of the vessels in the retina have been identified in patients with AD (92–94).

The introduction of a modern and non-invasive imaging technique OCTA to visualisation of the vascular network of the retina enables qualitative and quantitative measurements of vessels at various retinal depths. OCTA is a technique that uses motion contrast for imaging, generating high-resolution angiographic images in a few seconds. OCTA compares the decorrelation signal (differences in the intensity or amplitude of the backscattered OCT signal) between successive b-scans made in exactly the same cross-section to create a blood flow map (95, 96). The first commercially used software versions of OCTA devices did not allow the measurement of capillary network parameters in the optic disc scan, therefore researchers determined the total number of black pixels which corresponded to the total area of capillaries (97).

Some studies using OCTA to assess microvascular network in AD patients have shown that retinal vascular density is significantly reduced in comparison to a healthy control group. Bulut et al. were the first to use the OCTA technique to analyze vascular lesions only in the superficial vascular plexus (SVP) of the retina in AD patients. They found that the density of vessels in SVP was lower in patients with AD than in the control group, which correlated with the results obtained in MMSE, while the area of the foveal avascular zone (FAZ) increased. They suggested that this may have been associated with reduced angiogenesis due to VEGF binding and blocking by Aβ deposits (98). In addition, Aβ deposits, which build up inside the walls of blood vessels, probably lead to occlusion and reduce blood flow, which was also emphasized in previous reports (99). Further scientific reports have also confirmed that in patients with AD there is a decrease in the density of vessels in each retinal plexus. Analysis of vascular lesions in the white matter of the brain expressed with the Fazekas scale has shown a significant correlation with reduced vascular network density in the superficial retinal OCT angiogram. However, no significant relationship were found between the retinal microcrovasculature density and the level of Aβ, tau protein or MMSE result (100). In turn, Jiang et al. with the use of OCTA, by means of fractal analysis (box counting, Dbox) to assess the density of vascular network in SVP and deep vascular plexus (DVP), examined the relationship between microvascula-

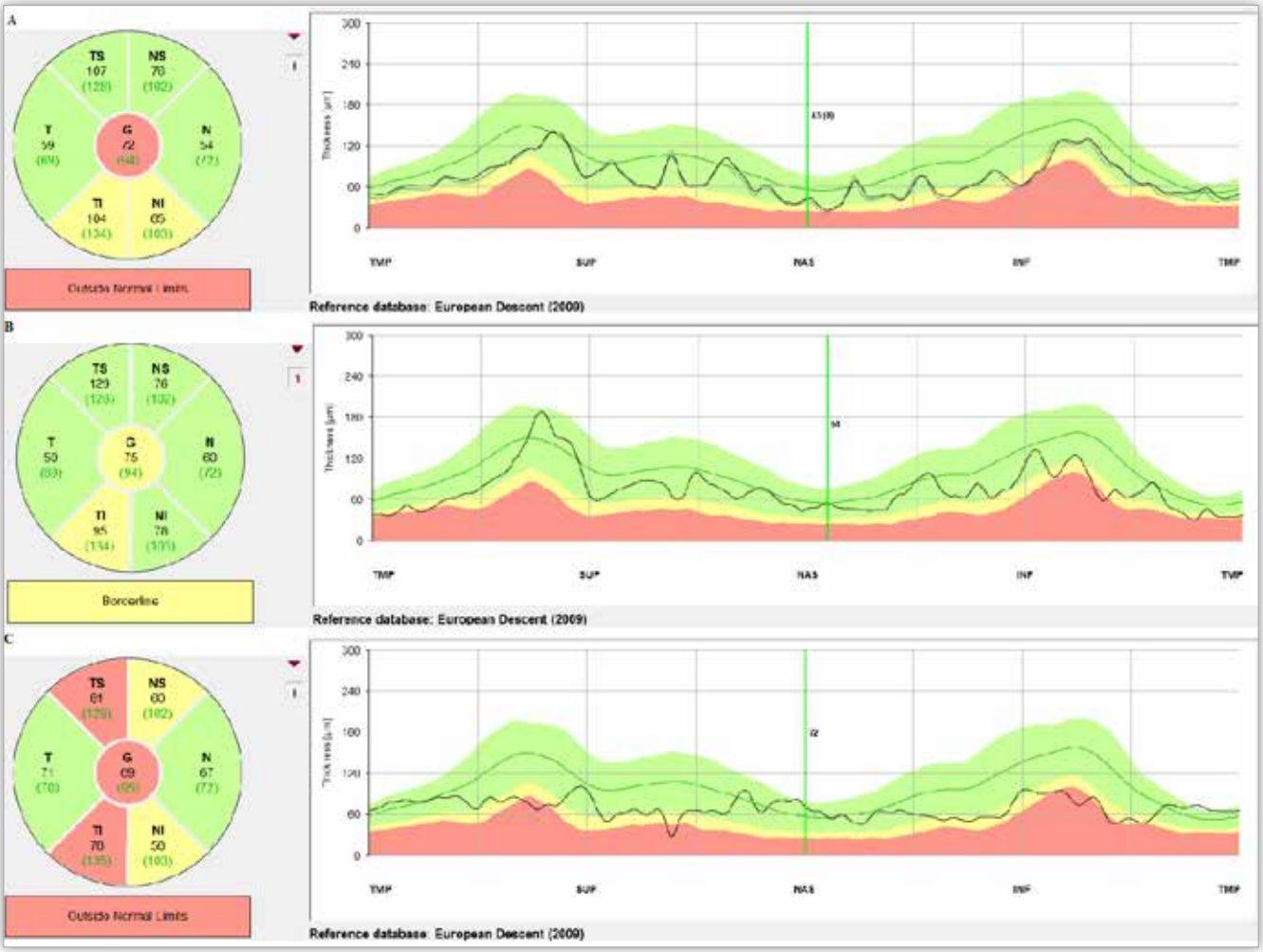

Fig. 2. Measurements of the peripapillary retinal nerve fiber layer thickness in patients with Alzheimer's disease (A), preperimetric glaucoma (B) and primary open-angle glaucoma (C) using optical coherence tomography. Reduction of the peripapillary retinal nerve fiber layer thickness to the borderline in a patient with Alzheimer's disease in the inferior sectors (A) while in a patient with preperimetric glaucoma, only mild reduction of the thickness in the peripapillary retinal nerve fiber layer in inferior temporal sector compared to the normative database is visible. Significant reduction of the preipapillary retinal nerve fiber layer thickness in superior and inferior sectors of a patient with primary open-angle glaucoma where red color indicates significant difference in respect to normative database (C) (authors' archives).

Ryc. 2. Badanie grubości okołotarczowej warstwy włókien nerwowych siatkówki u pacjentów z chorobą Alzheimera (A), jaskrą preperymetryczną (B) oraz jaskrą pierwotnie otwartego kąta (C) przy pomocy optycznej koherentnej tomografii. Zmniejszenie grubości warstwy włókien nerwowych siatkówki u pacjenta z chorobą Alzheimera do wartości granicznej w sektorach dolnych (A) natomiast u pacjenta z jaskrą preperymetryczną widoczne jest jedynie niewielkie zmniejszenie grubości okołotarczowej warstwy włókien nerwowych siatkówki w sektorze dolno-skroniowym w porównaniu z normatywną bazą danych. Znaczące zmniejszenie grubości okołotarczowej warstwy włókien nerwowych siatkówki w sektorach górnych i dolnych u pacjenta z rozpoznaniem jaskry pierwotnej otwartego kąta gdzie kolor czerwony wskazuje znaczącą różnicę w stosunku do normatywnej bazy danych(C) (materiał własny).

ture and GCL-IPL thickness in patients with AD and MCI. They found a reduction in vascular density in each retinal plexus in AD patients, with a significant correlation between density in DVP and retinal thickness of GCL-IPL (101).

In years 2017–2018, our study group conducted the research in which retinal microvasculature in the macular area and optic disc was compared in patients with AD, POAG and a healthy control group. Using the OCTA technique, we revealed that the density of vessels in each retinal plexuses between the examined groups showed significant differences. Patients with AD had a significantly reduced density in DVP and an enlarged area of FAZ in comparison to the other groups. In addition, we observed that the SVP also occur slight decrease in vessel density in comparison to healthy controls, while injury of this plexus was significantly lower than in patients with POAG. In POAG, the reduction in vascular density affected all retinal vascular plexuses, but significant changes, unlike the results obtained in patients with AD, occurred only in the RPC layer and in SVP, which correlated with the loss of pRNFL thickness. We found no correlation between MMSE result, pRNFL thickness, and retinal vascular density in AD patients (fig. 3) (102).

Summary

The discovery of AD biomarkers, in PET imaging or analysis of CSF composition, has enabled a better understanding of the disease. These biomarkers are crucial for monitoring and recruiting AD patients for clinical trials, however, their widespread implementation remains a challenge due to their difficult availability, high costs and invasiveness in regard to CSF sample collection.

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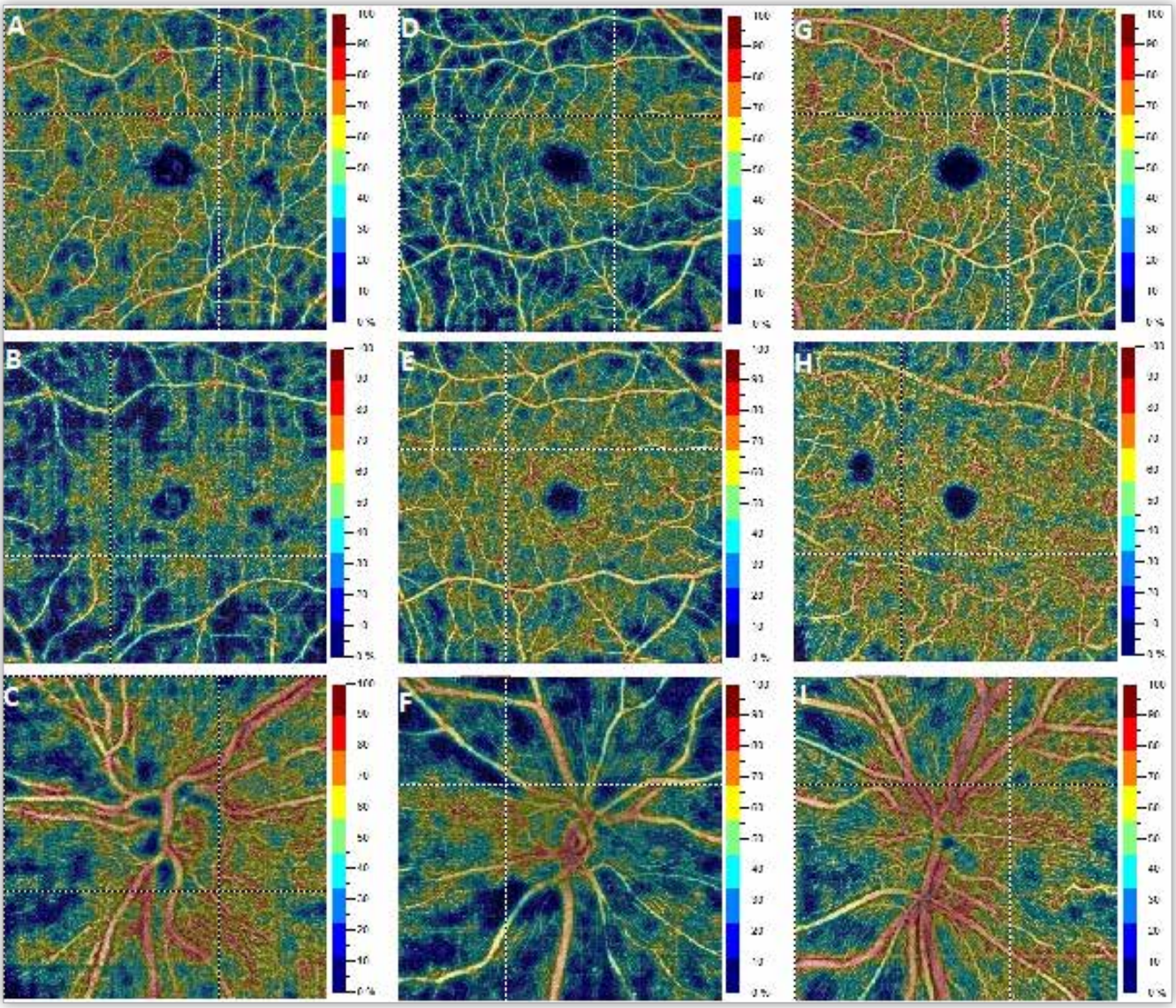

Fig. 3. Comparison of vessels density in angiograms (6 x 6 mm^2) of patient with Alzheimer's disease (A, B, C), primary open-angle glaucoma (D, E, F) and healthy control (G, H, I) in the superficial retinal vascular plexuses (A, D, G), deep retinal vascular plexuses (B, E, H) and in the radial peripapillary capillary (C, F, I). Patient with Alzheimer's disease shows a significant reduction in the density of vessels in the deep vascular plexus (B) compared to patient with primary open-angle glaucoma (E) and control group (H). Patient with primary open-angle glaucoma has a reduced vascular density in the superficial vascular plexus (D) and in the radial peripapillary capillary (I) compared to other groups (authors' archives).

Ryc. 3. Angiogramy (6 x 6 mm^2) pacjenta z chorobą Alzheimera (A, B, C), jaskrą pierwotną otwartego kąta (D, E, F) oraz osoby zdrowej (G, H, I) porównujące gęstość naczyń w powierzchownych splotach naczyniowych siatkówki (A, D, G), splotach naczyniowych głębokich siatkówki (B, E, H) oraz w warstwie radialnej okołotarczowych kapilar (C, F, I). Pacjenci z chorobą Alzheimera wykazują znaczne zmniejszenie gęstości naczyń w splocie głębokim (B) w stosunku do pacjentów z jaskrą pierwotnie otwartego kąta (E) oraz grupy kontrolnej (H). Pacjenci z jaskrą pierwotnie otwartego kąta mają zmniejszoną gęstość naczyń w splocie naczyniowym powierzchownym (D) oraz w warstwie radialnej okołotarczowych kapilar (I) w porównaniu do pozostałych grup (materiał własny).

Currently, growing high hopes are attached to AD eye biomarkers. The most promising appear to be structurally changes in the retina and its microvasculature that can be directly related to the deposition of Aβ. New technologies such as OCT and OCTA contribute to the progress of knowledge in AD diagnostics. Unfortunately, structural lesions found at optic disc in patients with AD assessed with OCT images may be non-specific and common to other neurodegenerative diseases, such as reduced pRNFL thickness in glaucoma. Nevertheless, combined measurements of retinal structural changes using the OCT technique and microvasculature assessment in each retinal plexus using the OCTA technique can potentially increase diagnostic ability and be a valuable approach in predicting development of AD. Further research addressing this issue is required so that these methods can become sensitive and specific enough to be useful in everyday practice.

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