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Research Article

Optical coherence tomography with angiography in the diagnosis of Alzheimer's disease

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ABSTRACT

BACKGROUND: Alzheimer's disease is becoming increasingly common and the number of patients with dementia is steadily increasing. Existing diagnostic methods (neuropsychological testing, cerebrospinal fluid examination, magnetic resonance imaging, and positron emission tomography) are either subjective, inaccessible or invasive and expensive, therefore the search for new methods of Alzheimer's disease diagnosis is necessary. The retina and the human brain share a common embryonic origin. The use of optical coherence tomography with angiography can help in the diagnosis of the disease, especially at an early stage.

AIM: To perform a comparative analysis of the vascular density of the peripapillary region of the human retina with the severity of cognitive impairment and atrophic changes according to MRI in patients with Alzheimer's disease.

MATERIALS AND METHODS: Thirty patients participated in the study: 20 with Alzheimer's disease and 10 in the control group. All patients underwent collection of complaints and history, general neurological and ophthalmological examination to evaluate inclusion and noninclusion criteria. Subsequently, neuropsychological testing, magnetic resonance imaging of the brain with assessment according to standardized neuroimaging scales, and optical coherence tomography with angiography according to a standard protocol were performed. The results were processed using the Statistica 10 software package (StatSoft, USA).

RESULTS: Assessment of retinal microvascular bed condition in Alzheimer's disease patients revealed a significant level of relative vascular density reduction in the upper half of radial peripapillary plexus of the retina due to reduction of small vessel density ($p = 0.02$). There was a direct correlation between the severity of the decrease in the FCSRT total score and changes in vascular density in the nasal sector of the retina ($r = 0.52$). There was a significant inverse relationship between vascular density in the temporal sector and the final GCA score for patients with Alzheimer's disease ($r = 0.57$). The Fazekas scale score revealed an inverse correlation between its score and the vascular density in the upper retinal half and its upper sector ($r = 0.53$).

CONCLUSION: Optical coherence tomography with angiography is a highly informative and promising method for early, including pre-diagnosis of Alzheimer's disease, which is considerably more accessible and accurate than other techniques.

Keywords: Alzheimer's disease; beta-amyloid; cognitive impairment; diagnostics; eye; optical coherence tomography with angiography; retina.

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Научная статья

Оптическая когерентная томография с ангиографией в диагностике болезни Альцгеймера

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АННОТАЦИЯ

Актуальность. Болезнь Альцгеймера становится все более распространенной, и количество пациентов с деменцией неуклонно растет. Существующие методы диагностики (нейропсихологическое тестирование, исследование цереброспинальной жидкости, магнитно-резонансная томография и позитронно-эмиссионная томография) либо субъективны, либо малодоступны, либо являются инвазивными и дорогостоящими, в связи с чем необходим поиск новых методов диагностики болезни Альцгеймера. Сетчатка и головной мозг человека имеют общее эмбриональное происхождение. Применение оптической когерентной томографии с ангиографией может помочь в диагностике заболевания, особенно на ранней стадии.

Цель исследования. Проведение сравнительного анализа сосудистой плотности перипапиллярной области сетчатки человека с выраженностью когнитивных нарушений и атрофических изменений по данным магнитно-резонансной томографии у пациентов с болезнью Альцгеймера.

Материалы и методы. В исследовании приняли участие 30 пациентов: 20 с болезнью Альцгеймера и 10 в контрольной группе. У всех пациентов произведен сбор жалоб и анамнеза, общий неврологический и офтальмологический осмотры для оценки критериев включения и невключения. В дальнейшем выполнено нейропсихологическое тестирование, магнитно-резонансная томография головного мозга с оценкой по стандартизованным нейровизуализационным шкалам и оптическая когерентная томографии с ангиографией по стандартному протоколу. Обработка полученных результатов произведена с применением программного пакета Statistica 10 (StatSoft, США).

Результаты. При оценке состояния микрососудистого русла сетчатки глаза у пациентов с болезнью Альцгеймера было выявлено на достоверном уровне снижение относительной сосудистой плотности в верхней половине радиального перипапиллярного сплетения сетчатки за счет снижения плотности мелких сосудов (p = 0,02). Выявлена прямая взаимосвязь между выраженностью снижения суммарного балла по шкале FCSRT и изменения сосудистой плотности в носовом секторе сетчатки (r = 0,52). Получена достоверная обратная зависимость между сосудистой плотностью в височном секторе и итоговым баллом по шкале GCA для пациентов с болезнью Альцгеймера (r = 0,57). При оценке по шкале Fazekas выявлена обратная корреляция между ее результатом и сосудистой плотностью в верхней половине сетчатки и ее верхнем секторе (r = 0,53).

Заключение. Оптическая когерентная томографии с ангиографией — высокоинформативный и перспективный метод в ранней, в том числе донозологической, диагностике болезни Альцгеймера, являющийся в значительной степени более доступным и точным, чем другие методики исследования.

Ключевые слова: бета-амилоидный белок; болезнь Альцгеймера; глаз; диагностика; когнитивные нарушения; оптическая когерентная томография с ангиографией; сетчатка.

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ЭКО•ВЕКТОР

BACKGROUND

The prevalence of Alzheimer's disease (AD) and other forms of dementia is increasing, creating challenges for caregivers and their families. This increases expenditure on care and psychological support for family members, burden on the healthcare system, and socioeconomic development in general [1]. In the central nervous system (CNS), the development of dementia is believed to start several decades before the onset of cognitive impairment [2]. Specifically, extracellular plaques of beta-amyloid (Aβ) and intracellular neurofibrillary tubules of hyperphosphorylated tau protein develop in AD approximately 20 years before the initial symptoms manifest. AD [3, 4] is also associated with changes in the cerebral vasculature, such as decreased vascular density, cerebral amyloid angiopathy, altered capillary morphology, and atherosclerosis. Aβ deposition nearly reaches its peak at the onset of cognitive impairment. The acceleration of tau protein accumulation characterizes the transition period from the preclinical stage to the first clinical manifestations. However, the effect of Aβ and tau protein deposition on synaptic dysfunction and neuronal survival does not reach its peak until the moderate and severe stages [5]. Thus, timely diagnosis is crucial for developing and applying early treatment methods for AD, which can help preserve cognitive abilities or slow their decline [6]. The prevalent and easily accessible method for diagnosing AD presently is neuropsychological testing. In patients with classical Alzheimer's dementia, this test identifies a progressive deterioration of amnestic-type memory. However, diagnostics can be time-consuming and subjective and cannot provide a completely precise diagnosis. It often complements clinical interviews with patients and their relatives. Additionally, magnetic resonance imaging (MRI) is necessary for diagnosis, which reveals general cortical and selective atrophy of the mediobasal parts of the temporal lobe, accompanied by hippocampal atrophy. In 2018, experts from the American National Institute on Aging and Alzheimer's Association released revised diagnostic testing guidelines. These guidelines present a biomarker-based biological definition of AD within the amyloid, tau, neurodegeneration classification system, which was established by Jack et al. in 2016 [7]. In addition to brain MRI, several supplementary diagnostic methods are available, although they are inaccessible or expensive. A lumbar puncture can detect the level of amyloid in the cerebrospinal fluid; however, it is an invasive procedure. Additionally, positron emission tomography (PET) with "Pittsburgh substance" and fluorodeoxyglucose is an expensive option and is not widely used in hospital practice. The creation of noninvasive biomarkers that are objective, easy to measure, and widely available will boost the effectiveness of screening and diagnosing AD and other types of dementia.

The retina and brain share a common embryogenic origin, thereby exhibiting similar patterns of vascular network structure. The microvascular structure and regulatory mechanisms between these two vascular systems indicate the possibility of common pathologic degeneration markers [4,8]. Changes in retinal microcirculation similar to pathologic processes in the brain are evident in CNS diseases such as cerebral small-vessel disease and AD [9,10]. For instance, small-vessel disease is associated with dilated venules, whereas AD is associated with narrow caliber and increased tortuosity of veins [11, 12]. In addition, decreased venous blood flow velocity can be observed in earlier disease stages, as indicated by changes in quantitative parameters that assess the state of the microvascular network [13]. This is also true for diabetes and hypertension, where the retina exhibits microvascular damage such as hemorrhages, microaneurysms, perfusion loss, and arteriole narrowing, whereas the brain exhibits subcortical infarcts, lacunes, white matter hyperintensity, and microhemorrhages [14–16].

Optical coherence tomography (OCT) is a noninvasive retinal imaging method with micron resolution. Changes in the indices of the ganglion cell complex, which includes the nerve fiber layer (SNVS, retinal nerve fiber layer [RNFL]), ganglion cells, and the inner plexiform layer containing axons, cell bodies, and dendrites, are the most promising markers for identifying Alzheimer's degeneration. Several researchers reported a significant reduction in the thickness of the SNVS in OCT in the AD group compared with the control group. Thinning was reported to occur diffusely and locally in the temporal, upper, and lower quadrants [17–19]. However, reports on microcirculatory changes in this area are few, and their results are controversial. Consequently, this study aimed to evaluate the state of the retinal microvascular pool, particularly in the peripapillary area (PA).

Optical coherence tomographic angiography (OCTA) is a recent imaging technique that identifies blood cell movement in retinal capillaries without using dye [20, 21]. The primary benefit of OCTA is its capacity to visualize vessels at varying depths, similar to structural OCT. Compared with contrast angiography, OCTA details are independent of dye infiltration quality, and deeper vessels remain visible without being obstructed by superficial vessels. Few studies using OCTA in patients with AD exist, and those that are available are contentious. In 2021, a panel of authors issued a meta-analysis of 14 papers scrutinizing OCTA results in patients with AD. The research measured either area-based metrics (i.e., overall vascular area per unit retinal area), length-based metrics (i.e., overall vascular length per unit retinal area), or both. A meta-analysis revealed a noteworthy enlargement in the measurement of the foveal avascular zone (FAZ) and a considerable reduction in the density

of the surface parafoveal vessels (VD) in addition to a generally deficient capillary framework in AD. Despite this, the techniques used for data collection and processing were substantially heterogeneous among studies [22]. The Atherosclerosis Risk in Communities study found that certain uncommon retinal abnormalities may predict cognitive decline and dementia onset [23, 24]. In a recent study, quantitative OCT analysis was found to help differentiate AD from other types of dementia, and OCTA detected microvascular changes in patients with AD, representing new potential criteria for differential diagnosis [25].

MATERIALS AND METHODS

This study prospectively enrolled 20 patients with a probable diagnosis of AD and 10 cognitively normal healthy volunteers, aged 54–80 years, as determined by neuropsychological testing, with no evidence of moderate or severe cognitive impairment.

The exclusion criteria were as follows: patients with mental illness, disorders of consciousness or behavior that would prevent full participation, acute cerebral circulation disorders or related consequences affecting strategic cognitive function areas, gross motor and/or sensory impairment, and clinically significant neurological diseases such as multiple sclerosis, brain tumors, neuroinfections, and other neurodegenerative and dysmetabolic disorders. Factors to consider include the presence of comorbidities and other neurological disorders such as multiple sclerosis, brain tumors, neuroinfections, and other neurodegenerative and dysmetabolic disorders, along with concomitant somatic diseases in the decompensation stage and any retinal pathology in the macula or glaucoma, as well as any pathology that impairs transparency of the optical media (including cataracts stronger than grade 1 according to Lens Opacity Classification System scale III) and OCTA scan quality of Q6 and below.

All patients underwent neuropsychological testing, including the mini-mental state examination (MMSE), free and cued selective reminding test (FCSRT), clock drawing test, and clinical dementia rating (CDR) assessment. Brain MRI was performed on all participants to confirm the diagnosis and identify patients meeting the exclusion criteria. Patients then underwent further assessment using atrophy scales, including Fazekas, Koedam, global (diffuse) cortical atrophy (Pasquier scale, GCA), and medial temporal lobe atrophy.

The RTVue-XR Avanti tomograph (Optovue Inc., USA) was used for OCT, employing the 3D PAR algorithm to eliminate projection artifacts and provide analytical measurement of capillary network density. This was done to evaluate the state of the retinal microvasculature using the Angio Retina 3 mm and Angio Disc 4.5-mm scanning protocols. The Angio Retina 3-mm protocol, centered on the macula, was used to assess vascular density. Analytical parameters for OCTA were automatically generated using the tomography software as a heat map showing vascular density. Areas on the heat map that are low enough to be classified as colder than green within the vascular density color scale would indicate reduced vascular density. An HD Angio disk scan measuring 4.5 × 4.5 mm with a resolution of 400 × 400 pixels was conducted within the optic disk area (ODA) and PA. The EnFace mode was used to isolate the superficial nerve fiber layer. The radial peripapillary capillary (RPC) plexus was then analyzed. For analysis, the RPC was divided into upper and lower halves and four distinct sectors (Fig. 1). The vascular density (VD) percentage was measured within the ODA and the indicated PA in each sector. Then, an average was obtained for both PA and their combined total area. The analysis conducted with Angio Analytics software revealed the VD of the entire network of both the PA and ODA. In addition, it indicated the relative density of capillaries excluding large or small vessels. The results were analyzed using nonparametric statistical methods, specifically the Mann–Whitney *U*-test for two independent samples. Correlation interdependencies were evaluated using Spearman rank correlation.

RESULTS

The study included 30 patients (58 eyes), and no significant differences were observed between the two groups regarding sex and age. The AD group displayed lower neuropsychological testing scores than the control group, as was anticipated (Table 1). Brain MRI data showed signs of atrophy in the temporal cortex (middle, basal, and lateral) and parietal cortex (medial and lateral) in the main group. Table 2 presents the data obtained during MRI evaluation using neuroimaging scales. Tables 3–5 exhibit the results of the performed OCTA in the two groups, along with its comparison and the search for correlation with neuropsychological testing data and evaluation of neuroimaging scales.

DISCUSSION AND CONCLUSIONS

Neuropsychological testing revealed that 19 patients diagnosed with typical AD and one patient with the atypical logopenic variant of primary progressive aphasia participated in this study. The primary group included older patients with AD, most of whom showed only mild dementia according to the CDR scale. Considering the development of cortical section atrophy within the mediobasal area with primary involvement of the hippocampus in patients with AD, this group experienced atrophy in the medial sections of the temporal lobe ($p = 0.001$). During the assessment of the retinal microvascular bed

Table 1. Comparison of the results of different neuropsychological techniques in patients with AD and controls

Groups	FCSRT	MMSE	CDT	CDR
Patients with AD	27.95 ± 12.51	21.95 ± 5.15	4.21 ± 2.64	1.20 ± 0.41
Controls	47.50 ± 0.76	29.38 ± 1.19	10.00 ± 0	0
Significance of differences ($p < 0.05$)	0.001	0.001	0.001	0.001

Table 2. Comparison of MRI assessment results using the neuroimaging scales in the study groups

Groups	Fazekas	Koedam	MTA	GCA
Patients with AD	1.33 ± 0.49	1.07 ± 0.88	2.20 ± 1.15	17.53 ± 8.73
Controls	0.67 ± 0.82	0.67 ± 0.82	0.20 ± 0.45	9.33 ± 3.21
Significance of differences ($p < 0.05$)	0.079	0.381	0.001	0.250

Table 3. Evaluation of the VD in ODA and PA projections

VD area		AD	Controls	Significance of differences ($p < 0.05$)
Small vessels	Total area	48.76 ± 1.58	49.91 ± 1.48	0.07
	ODA	49.31 ± 6.06	52.58 ± 6.73	0.20
	PA	51.04 ± 2.05	52.24 ± 1.66	0.24
	Upper half	50.78 ± 2.05	52.76 ± 1.50	0.02
	Lower half	53.67 ± 11.37	51.63 ± 2.09	0.75
	Temporal sector	53.05 ± 2.82	53.38 ± 1.77	0.47
	Upper sector	50.25 ± 3.16	53.25 ± 2.31	0.03
	Nasal sector	47.55 ± 3.33	47.63 ± 3.42	0.90
	Lower sector	53.95 ± 3.07	56.00 ± 4.04	0.17
All vessels	Total area	55.11 ± 1.83	56.20 ± 1.10	0.15
	ODA	58.94 ± 5.19	60.94 ± 5.39	0.33
	PA	57.08 ± 1.90	58.44 ± 1.08	0.11
	Upper half	57.06 ± 1.90	58.98 ± 1.08	0.01
	Lower half	57.10 ± 2.09	57.88 ± 1.27	0.44

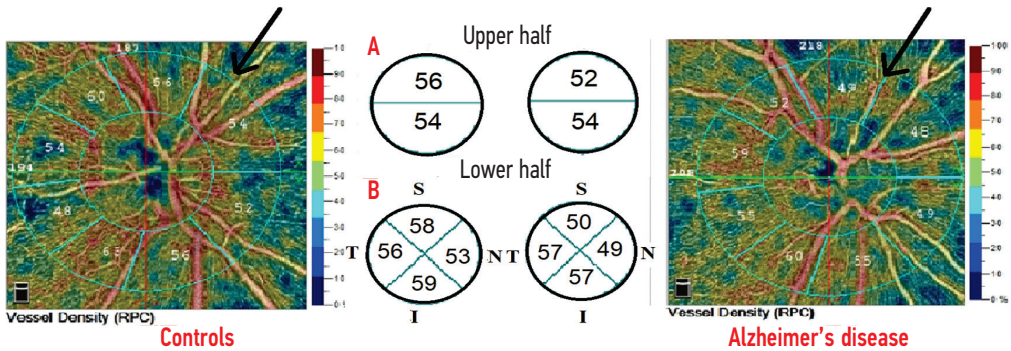

Figure 1. The arrows on the heatmap indicate a decrease in vascular density in the upper region of the radial peripapillary plexus in the AD group compared with the control group. The retina is divided into the upper and lower parts (A) and further subdivided into sectors (B), denoted by abbreviations (S for upper, I for lower, T for temporal, and N for nasal). The vascular density decreased in a patient with AD in the retinal upper region and upper sector compared with that in a healthy volunteer

in patients with AD, a significant decrease in the relative VD in the upper half of the radial retinal RPC plexus was found. The cause for this is the decline in the density of small vessels when compared with the control group; however, the numerical values themselves fall within the normal range for their age. Additionally, the thickness of the RNFL, which topographically corresponds to the PA, is reduced in patients with AD, as previously mentioned. Most likely, the degeneration of the SNVS in AD is caused by the axonal death of ganglion cells, in addition

Table 4. Correlation analysis between neuropsychological testing results and VD in the ODA and PA projection for patients with AD (Spearman correlation coefficient (r) values $p < 0.5$)

VD area		FCSRT	MMSE	CDT	CDR
Small vessels	Total area	0.30	–0.20	–0.07	–0.11
	ODA	0.29	0.27	–0.18	–0.04
	PA	0.16	–0.23	0.18	–0.25
	Upper half	0.09	–0.45	0.15	–0.08
	Lower half	0.25	–0.03	0.31	–0.35
	Temporal sector	–0.05	–0.28	0.05	–0.27
	Upper sector	–0.02	–0.59	0.24	–0.09
	Nasal sector	0.52	–0.13	0.39	–0.13
	Lower sector	–0.06	–0.08	0.09	–0.14
All vessels	Total area	0.37	–0.19	0.06	–0.11
	ODA	0.20	0.26	–0.20	0.00
	PA	0.21	–0.21	0.35	–0.20
	Upper half	0.15	–0.42	0.15	–0.08
	Lower half	0.14	–0.22	0.37	–0.18

Table 5. Correlation analysis between data obtained by MRI and VD in the ODA and PA projection for patients with AD (Spearman correlation coefficient (r) values, $p < 0.5$)

VD area		Fazekas	Koedam	MTA	GCA
Small vessels	Total area	–0.13	–0.04	–0.32	–0.07
	ODA	–0.03	0.04	–0.05	0.34
	PA	–0.39	–0.36	–0.39	–0.32
	Upper half	–0.20	–0.31	–0.31	–0.35
	Lower half	–0.53	–0.38	–0.35	–0.34
	Temporal sector	–0.18	0.03	–0.43	–0.57
	Upper sector	–0.17	–0.36	–0.03	–0.24
	Nasal sector	–0.22	0.01	–0.21	–0.22
	Lower sector	–0.48	–0.47	–0.39	–0.16
All vessels	Total area	–0.10	–0.02	–0.39	–0.28
	ODA	0.03	0.04	–0.07	0.26
	PA	–0.30	–0.36	–0.31	–0.44
	Upper half	–0.16	–0.33	–0.30	–0.44
	Lower half	–0.31	–0.34	–0.28	–0.43

to retrograde degeneration caused by the loss of cortical neurons [17]. The timing of microcirculation disruption in this region requires further investigation. Ganglion cell death and blood flow disturbance in the capillary network appear to be parallel. A correlation analysis was conducted to determine the degree of change in the VD of capillaries in the projection of the ODA and PA and its relationship to the outcome of neuropsychological tests in patients with AD. The analysis revealed a reliable inverse relationship between the decrease in the MMSE score and the change in the VD in the upper sector of the retinal RPC plexus. Further analysis of individual test responses with an assessment of the "amnestic" component is necessary to interpret the obtained result. The FCSRT test, with direct reproduction, is highly sensitive in AD diagnosis. A correlation was directly found between the decrease in the FCSRT score and the change in the retinal VD in the nasal sector ($r = 0.52$; $p < 0.05$). Furthermore, a significant correlation was observed between the scores on the scales measuring neurodegeneration and OCTA data. The GCA scale quantitatively evaluates cerebral atrophy in 13 brain regions separately for each hemisphere,

with the total score being the summation. The study identified a noteworthy negative correlation between the VD in the temporal region and the final GCA score among patients with AD ($r = -0.57$, $p < 0.05$). These findings provide additional evidence of the potential usefulness of OCTA data. The Fazekas score revealed a negative correlation between the outcome and VD in the retinal inferior half and sector ($r = -0.53$, $p < 0.05$). Nonetheless, this study has certain limitations. For instance, although the diagnosis was developed based on the neuropsychological testing and brain MRI results, biomarker studies in the cerebrospinal fluid, let alone PET, were not conducted, which may have constrained the accuracy of our diagnosis. Second, no significant age differences were observed between the two groups; however, the control group participants were still younger ($p = 0.08$). Third, the study excluded individuals with glaucoma; however, we cannot completely rule out glaucoma with pseudonormal pressure or patients with latent diabetes mellitus. Finally, OCTA imaging protocols are not standardized, which may lead to inconsistent clinical practice. Thus, enlarging the patient pool, performing further analysis of the VD in the FAZ, and conducting correlation analysis between SNVS thickness, glucocorticosteroids, and VD are recommended to enhance the reliability of the results. However, we believe that OCTA is promising as a method for AD diagnosis.

ADDITIONAL INFORMATION

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