MEGA JOURNAL OF CASE REPORTS

Review Article

Compiled Date: January 27, 2023

Optical Coherence Tomography Angiography (OCTA) Applications in Early Diagnosis of Cerebral Small Vascular Disease (CSVD)

Kaiqi Ding and Yu Geng*

Department of Neurology, Center for Rehabilitation Medicine, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou, Zhejiang, China

***Corresponding author**: Yu Geng, Department of Neurology, Center for Rehabilitation Medicine, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), No.158 Shangtang Road, Hangzhou, Zhejiang Province, China, 310014, Tel: +86-13588011488; E-mail: gengy2004@126.com

Abstract

Optical coherence tomography angiography (OCTA) is a non-invasive, fast and new fundus examination without contrast agent, which can conduct three-dimensional reconstruction of fundus vascular structure by identifying the blood flow movement of retina and choroid, and present the images of fundus vessels layer by layer in the coronary plane. The central retinal artery is a branch of the internal carotid artery, and the internal carotid artery is the main blood supply artery of the intracranial blood vessels. OCTA examination can observe the retinal artery, and can be early detection method of cerebral small vessel diseases (CSVD) when patients are asymptomatic. At present, the diagnosis of CSVD mainly relies on the imaging results of brain MRI, but at this time there are already pathological changes of blood vessels. Therefore, OCTA can be used for the early diagnosis of CSVD, which is helpful for the early intervention and treatment of CSVD.

Keywords: Optical coherence tomography angiography (OCTA); Cerebral small vessel diseases (CSVD); Fundus blood vessels; Early diagnosis

Introduction of OCTA Examination

Optical Coherence Tomography (OCT) is considered an important milestone in the ophthalmic examination. It enables conduct 3D imaging of eye structures such as the cornea, Ganglion Cells (GCL), macula or optic disc, and can measure the size of the optic disc and the thickness of the retinal layers [1]. Since 2006, a new examination of OCT Angiography (OCTA) has been added to the OCT examination, which is a non-invasive examination that can visualize fundus blood flow [2]. OCTA is a new non-invasive fundus image examination, which can identify retinal blood flow movement information with high resolution, and present retinal microvascular circulation in living tissue [3]. Fundus angiography can be generated within several seconds,

which can visualize retinal capillaries based on the movement contrast of circulating blood cells. So it is widely used in the diagnosis of retinal diseases [4]. The only moving structures in the fundus are the blood cells. Repeated scanning (B-scan) of the same cross-section, through special calculation methods, to generate a contrast between static and active structures, so as to obtain blood flow signals, based on which three-dimensional vascular structure reconstruction [5].

Compared with Fluoresce in Angiography (FA) and Indocyanine Green Angiography (ICGA), OCTA does not require contrast agent, is cheaper, and has faster imaging speed. It has significant advantages and is more acceptable for patients [6]. Cerebral Small Vessel Diseases (CSVD) can be classified according to MRI images into: White Matter Hyperintensity (WMH), Enlarged Perivascular Space (ePVS), lacunar infarction, subcortical infarction, cerebral microbleeds, and cerebral atrophy. The prevalence of CSVD in older adults (over 65 years) is estimated to be 87%, about 25-50% of ischemic strokes was related with CSVD, and may lead to cognitive decline (vascular dementia), depression, abnormal gait, movement disturbance, dysphagia, and urinary incontinence [7]. Therefore, early screening of CSVD is very important to avoid the occurrence of ischemic stroke and its poor prognosis. The retina and brain have the same embryological origin [8]. And the central retinal blood vessel originates from the Internal Carotid Artery (ICA), which is a branch of the intracranial artery. OCTA parameters included focal a vascular zone area (FAZ), Retinal Nerve Fiber Layer thickness (RNFL), retinal surface capillary plexus, deep retinal capillary plexus, and Radial Peripapillary Capillary (RPC) density. Some studies have shown that the Radial Peripapillary Capillary (RPC) density is negatively correlated with the White Matter Hyperintensity (WMH) and the severity of the perivascular space [9]. There are also studies showing that RPC density is associated with CSVD [8]. In this article, we introduce the advantages and disadvantages of OCTA, as well as its imaging characteristics. In addition to the application in ophthalmology, it also applies in other neurological diseases. More importantly, it is feasible for early diagnosis of CSVD.

Advantages of OCTA

Fluorescein Angiography (FA) and Indocyanine Green Angiography (ICGA) are both commonly used in diagnosis in Ophthalmology department, but they are both invasive tests that require intravenous dye and imaging for up to 10-30 minutes [10]. Moreover, the above two examinations have disadvantages such as invasiveness, relatively expensive, time-consuming, dye leakage, and difficulty in locating the depth of the lesion [11]. However, they are still the gold standard for the diagnosis of choroidal and retinal neovascularization (CNV) [12]. On the other hand, Optical Coherence Tomography Angiography (OCTA) is a non-invasive technique that can obtain fundus angiographic information without the use of dyes. And multiple layers of information can be obtained. OCTA can visualize individual vascular plexuses from the Inner Limiting Membrane (ILM) to the choroid, as well as the retina, outer retina, chorionic vessels, or other regions of interest [13]. Angiography of the retina by OCTA inspection is shown in **Figure 1.**

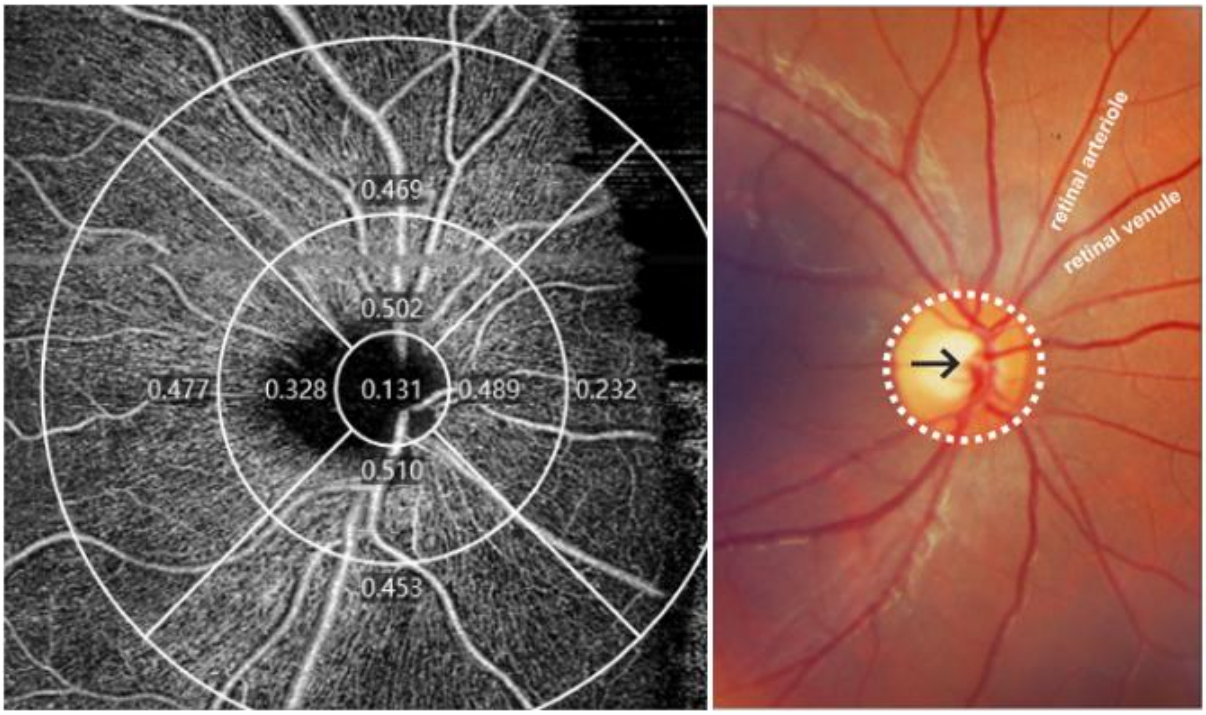

Figure 1: Retinal blood vessel in fundus. A: fundus blood vessel by OCTA, B: blood vessel map by ophthalmoscope.

There are several OCTA devices around the world. In the United States and Europe, Carl Zeiss Meditec (AngioPlexTM) and Optovue (AngioVueTM) have both received FDA and European approval for the clinical use of SD-OCT technology **[14].** Now I take AngioPlexTM as an example to introduce the content of different layer of OCTA imaging, as shown in **Figure 2.**

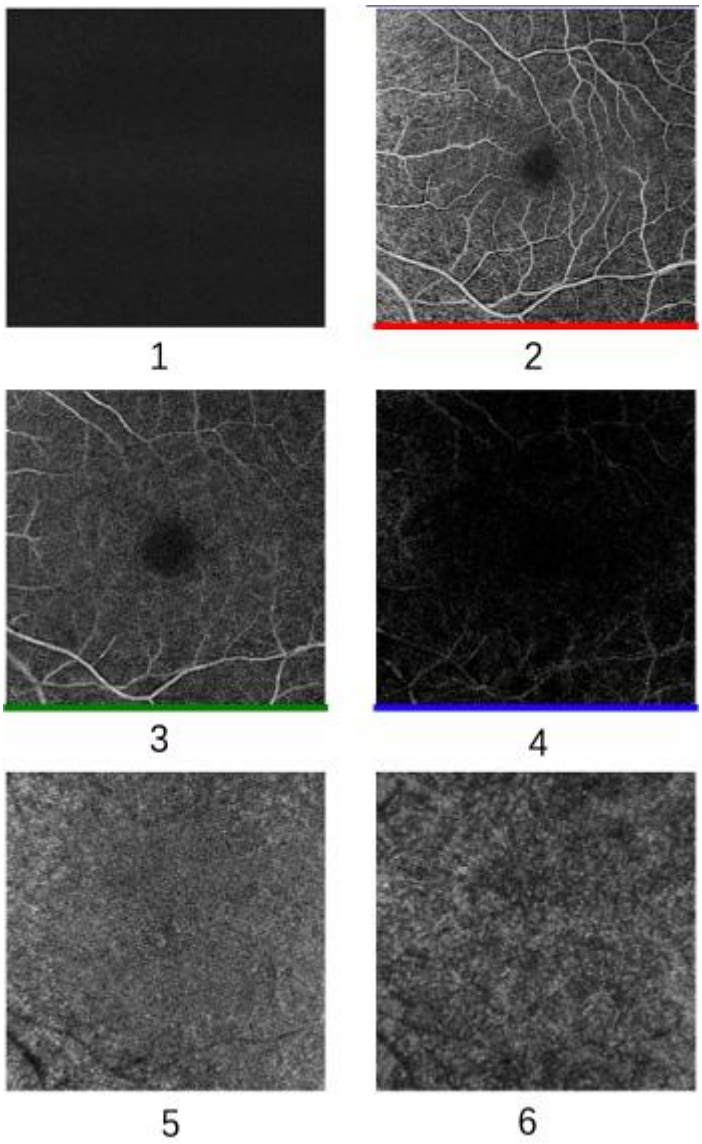

Figure 2: The en-face of retina by OCTA. A: Vitreoretinal interface (300 um below ILM to ILM), B: Superficial retina (ILM to IPL), C: deep retina (IPL to OPL, D: Avascular zone (OPL to EZ, E: Choroidal capillaries, F: Choroid.

The Blood Supply of Retina

We can observe the vascular density and perfusion of the retina through the non-invasive examination of Optical Coherence Tomography Angiography (OCTA). So why can we know the condition of intracranial blood vessels by observing the retinal blood condition? This starts with the origin of retinal blood vessels **[15].** The central retinal artery penetrates into the center of the optic nerve at 10-12 mm behind the eyeball, travels forward to the optic nerve head, and is divided into superior nasal, inferior nasal, superior temporal, and inferior temporal arteries to nourish different layers of retinal tissue. Moreover, the central retinal artery is a terminal artery without collateral anastomosis, the blockage of the central retinal artery can cause retinal ischemia in the corresponding area, resulting in loss of function. The central retinal artery originates from the ophthalmic artery, and the ophthalmic artery is the main branch of the C7 segment of the Internal Carotid Artery (ICA). A few variants originate from Middle Cerebral Artery (MCA). The bilateral Internal Carotid Arteries (ICA) originate

from the common carotid arteries and supply 2/3 of the brain. The other 1/3 is supplied by the vertebral-basilar artery. The retinal vascular blood supply of the human eye can be divided into four layers from the anterior border of the retina to the posterior axis position, namely the Superficial Capillary Plexus (SCP), the Intermediate Capillary Plexus (ICP), the Deep Capillary Plexus (DCP) and Radial Capillary Plexus (RPC) **[16].** Each individual capillary plexus has specific morphological characteristics **[17].** The vessels in each plexus are closely connected, but these interconnected vessels are sparse. Currently, OCTA is nuclearized by OCT B-scan and can replace Fluorescein Angiography (FA) in most cases **[18].** The different layers of OCTA are shown in Figure 3.

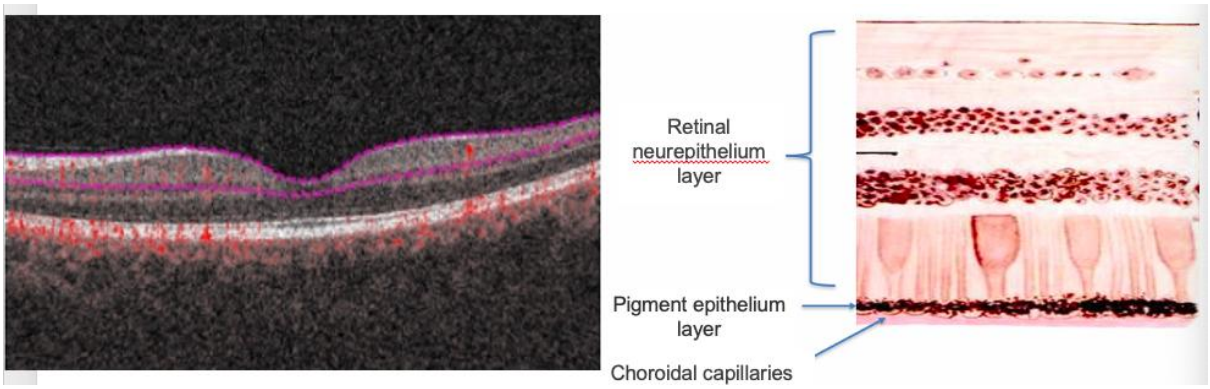

Figure 3: The cross-sectional view of the retina under OCTA, which can be divided into neuroepithelial layer, pigment epithelial and choriocapillary layer.

Current Clinical Application of OCTA

Optical Coherence Tomography Angiography (OCTA) has been widely used in Ophthalmology, such as Diabetic Retinopathy (DR), age-related macular degeneration, glaucoma, etc. **[19].** Diabetic retinopathy is typically characterized by micro-angiomas, intraretinal hemorrhages, intraretinal microvascular abnormalities, hard exudates, and neovascularization. The gold standard imaging technique for assessing macular perfusion is Fluorescein Angiography (FA), which is able to show leaky microaneurysms and non-perfused capillaries **[20].** However, it only produces two-dimensional images, especially when the dye leaks, where the fluorescent signals of the surface and deep capillary networks overlap and are difficult to distinguish **[21].** In this context, OCTA is a useful imaging technique for assessing retinal vessels in different capillary networks. OCTA also has huge potential applications in neurological diseases. At present, many studies have shown that many neurological diseases have pathological changes in the retina and optic nerve. Such as neurodegenerative diseases, Multiple Sclerosis (MS), migraine, etc **[1].** The main risk factors for neurodegenerative diseases are old age and cardiovascular disease **[22].** There is increasing evidence that a decline in capillary number and density with age is observed in both humans and rodents. Common ophthalmic signs and symptoms of Alzheimer's Disease (AD) are visual field changes and decreased vision **[23].** Additionally, other retinal changes, such as changes in macular RNFL thickness, have been associated with early changes in AD patients **[24].** Multiple Sclerosis (MS) is a chronic demyelinating inflammatory disease. At autopsy, 99% of patients had evidence of demyelination within the optic nerve **[25].** Optic neuritis occurs in 25% of patients and about 50% patients will suffer from it during disease progression **[26].** Visual impairment is also common in Parkinson's Disease (PD) patients, which is related to the reduction of dopamine, and the severity of PD is related to the

thickness of retinal nerve fiber layer near the optic papilla. In migraine, RNFL thickness was reduced, especially in migraine patients with aura **[27].**

Introduction of Cerebral Small Vessel Diseases (CSVD)

Cerebral Small Vessel Disease (CSVD) refers to a series of clinical, imaging, and pathological syndromes caused by various etiologies affecting cerebral arterioles and their distal branches, arterioles, capillaries, venules, and venules **[28].** It may develop in the early stages of the disease for many years because it remains asymptomatic **[29].** Anatomically, small vessels include arterioles (100-400 um) and their distal branches (less than 200 um), capillaries, and venule diseases. At present, it is believed that CSVD mainly refers to cerebral arteriole, and the diameter of the diseased blood vessel is 50-400 um. The central retinal artery is also small blood vessel, and its diameter is about 160 um **[30].** Common causes of CSVD include arteriosclerosis, Cerebral Amyloid Angiopathy (CAA), hereditary small vessel disease, inflammatory and immune-mediated small vessel disease, and venous collagen disease **[31].** Including 25% of ischemic stroke and 45% of dementia may be related to CSVD **[32].** Among them, arteriosclerosis and Cerebral Amyloid Angiopathy (CAA) is the most common **[33].** According to Standards for Reporting Vascular changes on Neuroimaging (STRIVE), CSVD can be classified according to MRI images as: White Matter Hyperintensity (WMH), Enlarged Perivascular Space (EPVS), lacunar infarcts, subcortical infarcts, cerebral microbleeds, and cerebral atrophy [34]. The MRI classification of cerebral small vessel disease is shown in **Figure 4.**

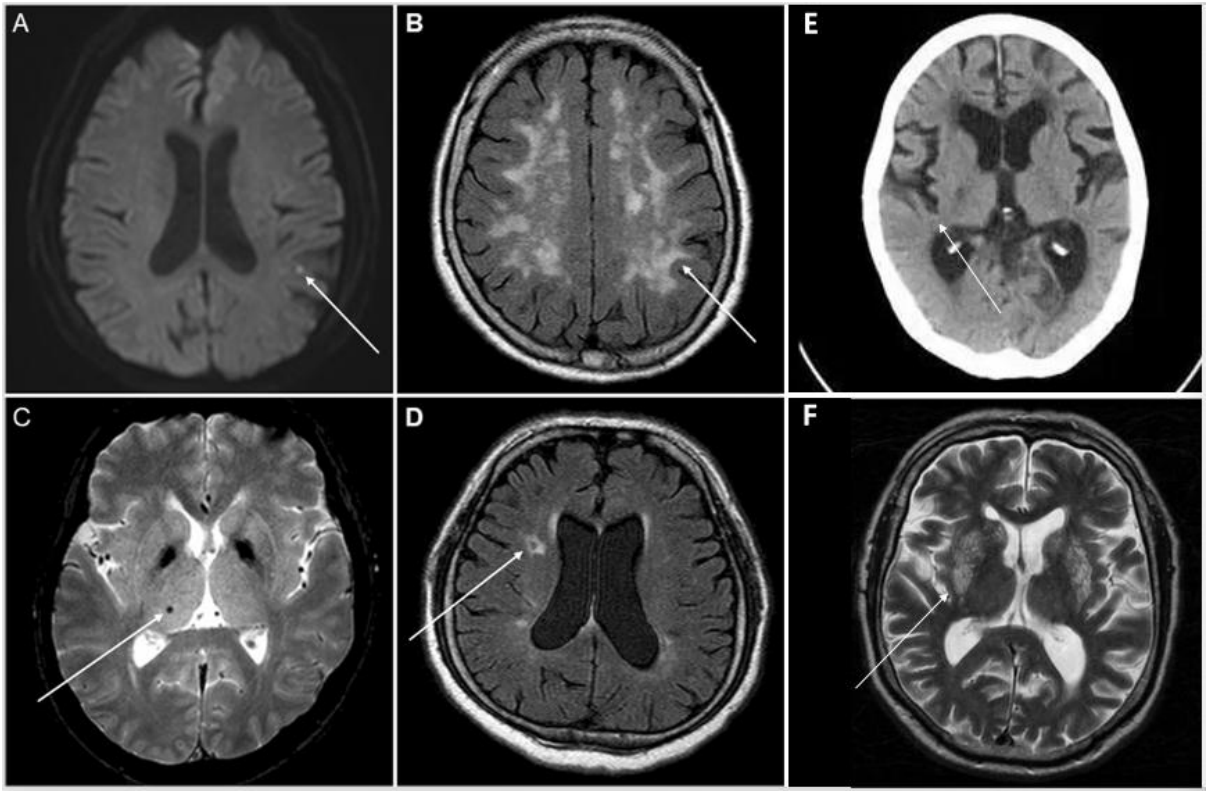

Figure 4: Several classifications of cerebral Small Vessel Disease (CSVD) on MRI images, A: subcortical infarction, B: White Matter Hyperintensity (WMH), C: cerebral microhemorrhage, D: lacunar infarction, E: brain atrophy, F: Enlarged Perivascular Space (ePVS).

Brain atrophy is a condition in which neurons and the connections between them are lost, which leads to a decrease in brain volume [35]. The consequences of the disease manifest in cognitive and neurological problems. Brain atrophy affects specific regions of brain tissue, manifested by corresponding dysfunction in associated areas of the brain. A reduction in brain tissue volume is associated with cognitive decline [36]. White Matter Hyperintensities (WMH) were introduced by Hachinski, Potter, and Merskey in 1987 for bilateral periventricular hypodense white matter areas seen on CT images, and periventricular and subcortical white matter in T2-weighted and FLAIR images on MRI high signal. Histologically, axonal atrophy was observed along with reduction in the number of myelin sheaths. This may be due to insufficient blood supply of the deep white matter due to vascular pathology [37]. Makedonov et al. [38] reported that WMHs were less perfused than normal white matter as assessed by SPECT and MRI. CMBs appear as small, oval or round hypointense lesions on T2 sequences in the brain, due to the degenerative state of small blood vessels and the subsequent breakdown of hemoglobin released from erythrocytes [39]. Cerebral Perivascular Space (cPVS), also known as V-R space (VRS). Enlarged Perivascular Space (ePVS) is also one of the imaging manifestations of CSVD. It manifests as well-circumscribed round, oval, linear, and tubular structures on brain MRI, consistent with the course of perforating vessels. ePVS is easily confused with lacunar infarction. Lacunar infarction is hyperintensity in acute phase and hypointensity in chronic phase on DWI image sequence, while ePVS is on the contrary [40]. Recent Subcortical Infarction (RSSI), often presenting as acute-onset specific compartment syndrome, the classic 5 syndromes include pure sensory stroke, pure motor hemiplegia, ataxic hemiparesis, dysarthria-hand Clumsy syndrome and sensorimotor stroke, and they generally have a good prognosis [41]. Lacunar infarcts, typically small cavities in brain tissue that remain after removal of necrotic tissue from subcortical infarcts, are caused by occlusion of small perforated arteries, and they account for approximately 20% of ischemic strokes [31].

The Early Diagnostic Value of OCTA in Cerebral Small Vessel Diseases (CSVD)

Because the central retinal artery is a continuation of the Internal Carotid Artery (ICA), which is part of the intracranial artery, and the central retinal artery belong to small blood vessel. By observing the central retinal artery, we can directly observe the small intracranial arteries and provide a window forusto diagnosis cerebral small vessel disease (CSVD) [42]. The retinal vessel is a potential marker of cerebrovascular disease because it shares same origin with the intracranial blood circulation [43]. Both the retina and brain exhibit microvascular disease in the context of vascular risk factors such as diabetes and hypertension. Diabetic retinopathy, for example, is characterized by microaneurysms and flame spot hemorrhages in non-proliferative retinopathy. In proliferative diabetic retinopathy, it is characterized by the growth of new blood vessels and edema of retinal tissue [44]. In hypertensive retinopathy, it is characterized by narrowing of arterioles and altered light reflection in the center of arterioles (copper wire and silver wire arterioles). Late hypertensive retinopathy resembles non-proliferative diabetic retinopathy as well as focal retinal ischemia, which causes retinal whitening (cotton hair spots) [45].

Conclusion

Because our cranial cavity is a closed structure, it is difficult to obtain pathological specimens. At present, the diagnosis of cerebral small vessel disease depends on clinical and MRI imaging manifestations, such as White

Matter Hyperintensity (WMH), Enlarged Perivascular Space (ePVS), lacunar infarcts, subcortical infarcts, cerebral microbleeds, and cerebral atrophy. Fundus structures are regarded as the only window to observe intracranial conditions, such as papilledema in patients with intracranial hypertension. Optical Coherence Tomography Angiography (OCTA) is a convenient and non-invasive ophthalmic examination, through which we can observe the retinal artery and its branches. Both the retinal artery and the intracranial artery originate from intracranial artery. We can directly display the small cerebral vessels by observing the retinal artery, which provides a basis for early diagnosis of Cerebral Small Vessel Disease (CSVD) before appearance of clinical symptoms and radiographic changes.

References

1. Wylęgała A. Principles of OCTA and Applications in Clinical Neurology. Curr Neurol Neurosci Rep. 2018;18(12):96.
2. Makita S, Hong Y, Yamanari M, Yatagai T, Yasuno Y. Optical coherence angiography. Opt Express. 2006;14(17):7821.
3. Wylęgała A, Teper S, Dobrowolski D, Wylęgała E. Optical coherence angiography: A review. Medicine. 2016;95(41):e4907.
4. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous. 2015;1:5.
5. Tan ACS, Tan GS, Denniston AK, et al. An overview of the clinical applications of optical coherence tomography angiography. Eye. 2018;32(2):262-86.
6. Fu W, Zhou X, Wang M, et al. Fundus Changes Evaluated by OCTA in Patients With Cerebral Small Vessel Disease and Their Correlations: A Cross-Sectional Study. Front Neurol. 2022;13:843198.
7. Li Q, Yang Y, Reis C, et al. Cerebral Small Vessel Disease. Cell Transplant. 2018;27(12):1711-22.
8. Lee JY, Kim JP, Jang H, et al. Optical coherence tomography angiography as a potential screening tool for cerebral small vessel diseases. Alzheimers Res Ther. 2020;12(1):73.
9. Lee JY, Kim JP, Jang H, et al. Optical coherence tomography angiography as a potential screening tool for cerebral small vessel diseases. Alz Res Therapy. 2020;12(1):73.
10. Novotny HR, Alvis D. A method of photographing fluorescence in circulating blood of the human eye. Tech Doc Rep SAMTDR USAF Sch Aerosp Med. 1960;60-82:1-4.
11. Novotny HR, Alvis D. A method of photographing fluorescence in circulating blood of the human eye. Tech Doc Rep SAMTDR USAF Sch Aerosp Med. 1960;60-82:1-4.
12. Do DV, Gower EW, Cassard SD, et al. Detection of new-onset choroidal neovascularization using optical coherence tomography: the AMD DOC Study. Ophthalmology. 2012;119(4):771-8.
13. Matsunaga D, Yi J, Puliafito CA, Kashani AH. OCT angiography in healthy human subjects. Ophthalmic Surg Lasers Imaging Retina. 2014;45(6):510-5.
14. Sun Z, Yang D, Tang Z, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: an updated review. Eye (Lond). 2021;35(1):149-61.
15. Yiu G, Mukkamala L. Branch Retinal Artery Ischemia. Retina. 2018;38(8):e61-e62.
16. Schwartz DM, Fingler J, Kim DY, et al. Phase-variance optical coherence tomography: a technique for noninvasive angiography. Ophthalmology. 2014;121(1):180-7.

17. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1-55.
18. Agemy SA, Scripsema NK, Shah CM, et al. Retinal Vascular Perfusion Density Mapping Using Optical Coherence Tomography Angiography In Normals And Diabetic Retinopathy Patients. Retina. 2015;35(11):2353-63.
19. Johannesen SK, Viken JN, Vergmann AS, Grauslund J. Optical coherence tomography angiography and microvascular changes in diabetic retinopathy: a systematic review. Acta Ophthalmol. 2019;97(1):7-14.
20. Gass JD. A fluorescein angiographic study of macular dysfunction secondary to retinal vascular disease. V. Retinal telangiectasis. Arch Ophthalmol. 1968;80(5):592-605.
21. Marmor MF, Ravin JG. Fluorescein angiography: insight and serendipity a half century ago. Arch Ophthalmol. 2011;129(7):943-8.
22. Turski GN, Schmitz-Valckenberg S, Holz FG, Finger RP. Retinale Bildgebung von Makula und Papille bei neurodegenerativen Erkrankungen. Ophthalmologe. 2017;114(2):114-19.
23. Pelak VS, Hills W. Vision in Alzheimer's disease: a focus on the anterior afferent pathway. Neurodegenerative Disease Management. 2018;8(1):49-67.
24. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. Neurology. 2009;73(11):862-8.
25. Mastropasqua R, Agnifili L, Borrelli E, et al. Optical Coherence Tomography Angiography of the Peripapillary Retina in Normal-Tension Glaucoma and Chronic Nonarteritic Anterior Ischemic Optic Neuropathy. Current Eye Res. 2018;43(6):778-84.
26. Spain RI, Liu L, Zhang X, et al. Optical coherence tomography angiography enhances the detection of optic nerve damage in multiple sclerosis. Br J Ophthalmol. 2018;102(4):520-4.
27. Ascaso FJ, Marco S, Mateo J, Martínez M, Esteban O, Grzybowski A. Optical Coherence Tomography in Patients with Chronic Migraine: Literature Review and Update. Front Neurol. 2017;8:684.
28. Litak J, Mazurek M, Kulesza B, et al. Cerebral Small Vessel Disease. Int J Mol Sci. 2020;21(24):9729.
29. Mustapha M, Nassir CMNCM, Aminuddin N, Safri AA, Ghazali MM. Cerebral Small Vessel Disease (CSVD) - Lessons From the Animal Models. Front Physiol. 2019;10:1317.
30. Banerjee G, Wilson D, Jäger HR, Werring DJ. Novel imaging techniques in cerebral small vessel diseases and vascular cognitive impairment. Biochim Biophys Acta. 2016;1862(5):926-38.
31. Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. Adv Clin Exp Med. 2021;30(3):349-56.
32. Bath PM, Wardlaw JM. Pharmacological Treatment and Prevention of Cerebral Small Vessel Disease: A Review of Potential Interventions. Int J Stroke. 2015;10(4):469-78.
33. Bridges LR, Andoh J, Lawrence AJ, et al. Blood-Brain Barrier Dysfunction and Cerebral Small Vessel Disease (Arteriolosclerosis) in Brains of Older People. J Neuropathol Exp Neurol. 2014;73(11):1026-33.
34. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822-38.

35. Ogata J, Yamanishi H, Ishibashi-Ueda H. Pathology of cerebral small vessel disease. In: Pantoni L, Gorelick PB, eds. Cerebral Small Vessel Disease. 1st ed. Cambridge University Press; 2014:4-15.
36. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689-701.
37. Young VG, Halliday GM, Kril JJ. Neuropathologic correlates of white matter hyperintensities. Neurology. 2008;71(11):804-11.
38. Markus HS, Hunt B, Palmer K, Enzinger C, Schmidt H, Schmidt R. Markers of Endothelial and Hemostatic Activation and Progression of Cerebral White Matter Hyperintensities: Longitudinal Results of the Austrian Stroke Prevention Study. Stroke. 2005;36(7):1410-14.
39. Yakushiji Y. Cerebral Microbleeds: Detection, Associations and Clinical Implications. In: Toyoda K, Anderson CS, Mayer SA, eds. Frontiers of Neurology and Neuroscience. Vol 37. S. Karger AG; 2016:78-92.
40. Kim YD, Kim JY, Park YJ, et al. Cerebral magnetic resonance imaging of coincidental infarction and small vessel disease in retinal artery occlusion. Sci Rep. 2021;11(1):864.
41. Chen X, Wang J, Shan Y, et al. Cerebral small vessel disease: neuroimaging markers and clinical implication. J Neurol. 2019;266(10):2347-62.
42. Patton N, Aslam T, MacGillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anatomy. 2005;206(4):319-48.
43. Moss HE. Retinal Vascular Changes are a Marker for Cerebral Vascular Diseases. Curr Neurol Neurosci Rep. 2015;15(7):40.
44. Kwa VIH, van der Sande JJ, Stam J, Tijmes N, Vrooland JL. Amsterdam Vascular Medicine Group. Retinal arterial changes correlate with cerebral small-vessel disease. Neurology. 2002;59(10):1536-40.
45. Cheung CY lui, Tay WT, Ikram MK, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study. Stroke. 2013;44(9):2402-8.

Citation of this Article

Ding K and Geng Y. Optical Coherence Tomography Angiography (OCTA) Applications in Early Diagnosis of Cerebral Small Vascular Disease (CSVD). Mega J Case Rep. 2023; 6: 2001-2010.

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